Substituent Chemical Shifts (SCS) in NMR, Part 6[*]
A Model for the Calculation of Proton Chemical Shifts in Substituted Alkanes.

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A development of a previous calculation of partial atomic charges (CHARGE3) is given which allows the prediction of the proton chemical shifts in a variety of substituted alkanes.

This is accomplished by identifying the effects of substituents at the α, β, γ and the more distant protons. The hydrogen electronegativity is changed to a value close to the Pauling value, the γ (H.C.C.X) SCS is shown to be a function of the polarisability of X rather than the electronegativity and the problem of multi-substitution of electronegative substituents is overcome by an explicit correction for oxygen and fluorine substituents. These amendments allow the proton chemical shifts of $CH_{4-n}X_n$ and $CH_3CH_{3-n}X_n$ (n=1-3, X=H, NH_2, OH, F, Cl, Br, I, SH) to be predicted generally to 0.1 ppm apart from some of the Br and I compounds.

The method has also been tested on a variety of cyclic alkanes, including substituted cyclohexanes and norbornanes, cis and trans decalin, bicyclo(2,2,2)octane, perhydrophenalene and anthracene and some t-butyl methanes, providing a wide variety of steric interactions and strain energies, and also on fluoro and chloro substituted cyclohexanes and norbornanes.

For these compounds the orientation dependence of the γ methyl SCS is considered both explicitly and as a result of steric effects. In contrast the effects of fluorine and chlorine SCS's at the γ (i.e. vicinal) proton are non-orientational.

The long range effects of proton-proton interactions are *shielding* at the protons but the long range effects of C, F and Cl *de*shield the affected protons. For H, C and Cl an r^{-6} distance dependence was found but fluorine steric effects were better reproduced with an r^{-3} distance dependence. The calculations reproduced the observed proton chemical shifts of the compounds studied to 0.17 ppm. It was not necessary to invoke in these calculations either the magnetic anisotropy or the electric field effects of the fluorine and chlorine substituents, and the implication of these results on present theories of proton chemical shifts is discussed.

* For part 5, see ref. 1.

INTRODUCTION

The most important single experimental parameter in nmr spectroscopy is the chemical shift, and proton chemical shifts have been compiled and interpreted for many years[2]. Despite this considerable effort, there is still no calculation of proton chemical shifts sufficiently accurate to be of use to the practising chemist, who has to rely on the various data collections of proton chemical shifts which often cannot be extrapolated to an unknown structure. This is generally explained as due to the number of interactions which may contribute to proton chemical shifts. In his pioneering study, Zurcher[3] considered the magnetic anisotropy, the electric field and Van-der-Waals effects of the substituents in order to estimate proton chemical shifts in steroids. Unfortunately at that time the only accurate data was that of the methyl protons in the steroids and the averaging of the proton shifts over the three methyl protons obscured any orientational effects. Further studies by Apsimon et al[4] using a similar formalism did not give a definitive result on the factors influencing proton chemical shifts.

The explanation in terms of the electric field and magnetic anisotropy of the substituent becomes questionable when the proton chemical shifts of saturated hydrocarbons are considered. These range over >2 ppm., which is 20% of the usual range of proton chemical shifts, yet these molecules possess neither magnetically anisotropic nor polar substituents. Clearly there are other important factors determining proton chemical shifts.

Recent studies[5-10] have begun to provide an insight into these factors. Li and Allinger [5] observed a correlation between the steric interaction energy experienced by the hydrogen atoms in a variety of cyclohexanols with the chemical shift and also that the sensitivity of the hydrogen chemical shift differed for methine, methylene and carbinol hydrogens. Danneels and Anteunis[6] in a study of the proton chemical shifts of methyl substituted cyclohexanes, noted that the influence of a vicinal methyl group on the proton chemical shift was a function of the C.C.C.H. dihedral angle. This is approximately a $\cos\theta$ function, shielding (- 0.5 ppm) at 0° and deshielding (+ 0.25 ppm) at 180°. Fisher and Gradwell[7] analysed the proton spectra of some methyl norbornanes and adamantanes and confirmed these trends. Boaz[8] assigned the

proton spectra of some cyclic hydrocarbons and interpreted the observed shieldings as due to electron density changes plus the influence of parallel β C-H bonds. Curtis et al[9] in a study of methylcyclohexanes using ^{2}D NMR obtained good agreement with the observed shifts using an additive scheme with no less than 14 parameters with separate parameters for axial and equatorial hydrogens and four different gauche (C.C.C.H) effects.

In principle, quantum mechanical calculations of proton chemical shifts should be able to quantify these results. But until recently they have had very limited success. The gauge independent GIAO calculations have been successfully applied to calculate the chemical shifts of the heavier nuclei, but not protons[11]. The commercial HyperNMR package[12] using SCF theory with semi-empirical wave functions[13] we have found to be of considerable utility (see later).

The most promising approach to the prediction of proton chemical shifts has been the semi-empirical calculations of partial atomic charges in molecules which have given surprisingly good correlations with proton chemical shifts[14,15,16]. In particular Gasteiger and Marsili[15] (henceforth GM) showed that the partial atomic charges calculated by their electronegativity equalisation approach gave a good correlation with the proton chemical shifts of a variety of substituted simple alkanes. More recently Abraham and Grant[16] also obtained a good correlation of charge versus proton chemical shifts for a similar set of molecules using the CHARGE3 scheme which is based on experimental dipole moments. There were, however notable deficiencies in both of these schemes. The slope of the chemical shift versus charge differed markedly for different substitution patterns, a serious deficiency in any predictive scheme. Also these schemes were not applied to more complex molecules in which orientational and steric effects were present. Thus it was of some interest to determine whether the CHARGE3 scheme could be developed to be a predictive calculation of proton chemical shifts whilst at the same time retaining the ability to give accurate molecular dipole moments. We shall show that this is indeed possible and give here a development of the CHARGE3 routine which allows the prediction of the proton chemical shifts of a variety of saturated

simple acyclic and cyclic alkanes and their fluoro and chloro derivatives. A preliminary account of part of this work has been given.[17]

THEORY

As the theory has been presented earlier[16] only a brief summary is given here. The CHARGE3 scheme is essentially a classical calculation of inductive and resonance contributions to give partial atomic charges, and molecular dipole moments. 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; an α effect from atom J, a β effect from atom K, and a γ effect from atom L.

The charge (q_i) on atom I resulting from atom J is given by Equation 1, where E_j and E_i are the electronegativities of atoms I and J and A(I,J) is a constant dependent on the exchange and overlap integrals for the bond I-J. In CHARGE3 there is a set of parameters A(I,J) for all the bonding pairs under consideration.

$$q_i(\alpha) = (E_j - E_i)/A(I,J) \qquad (1)$$

The β effect is the influence of atom K on I and is proportional to both the electronegativity of atom K and the polarisability of atom I. Taking the electronegativity of hydrogen as a base, the β effect is defined in Equation 2 where c is a constant. In order to account for the variation of polarisability with charge, the β effect calculation is carried out iteratively, according to Equation 3, where P_i is the polarisability of atom I with charge q_i, and $P_i°$ and $q_i°$ are the corresponding initial values. For S, Cl, Br and I the beta effect was enhanced by a factor of 1.54.

$$q_i(\beta) = (E_K - E_H)\, P_i/c \qquad (2)$$

$$P_i = P_i°(1.0 + 3.0\,(q_i° - q_i)) \qquad (3)$$

The γ effect was assumed to be proportional to the β effect and is given by Equation 4. For S, Cl, Br and I the γ effect was multiplied by two.

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$$q_i(\gamma) = \beta_{il}/10.0 \qquad\qquad (4)$$

The total charge is given by Equation 5.

$$q_i = q_i(\alpha) + q_i(\beta) + q_i(\gamma) \qquad\qquad (5)$$

In order that an element may be included in the scheme, it is necessary to obtain values for the electronegativity and polarisability of that element in the appropriate hybridisation state. The electronegativities were originally taken from the values given by GM[15] except for Cl, Br and I which were taken directly from the proton chemical shifts of the MeX compounds.

RESULTS

The CHARGE3 scheme arbitrarily breaks down the influence of substituents into α, β and γ effects and it is convenient to consider the changes to be made in this order.

The α and β effects.

In previous investigations[15,16] the calculated proton chemical shift for methane was anomalous. This can only be due to the electronegativity difference (E_C-E_H) in equation 2 as changing E_C-E_H or the factor A(C,H) in equation 1 will give the same effect for all C-H protons. A related anomaly in CHARGE3 was that the slope of the proton chemical shift vs charge plot for alkanes (CH_4, CH_3R, CH_2R_2, CHR_3) differed from that of CH_3X (X=H, C, N, O, F) and again this is a function of the hydrogen electronegativity (equation 2). Furthermore GM noted that the cumulative beta effect of substituents is not a linear function of the number of the substituents as would be predicted from equations 2 and 3, but a curved plot. The curvature ranges from a gentle slope for Me and Cl to a sharp bend for F (see Figure 1A). The problem is how to modify CHARGE3 to overcome these deficiencies.

FIGURE 1: A, $\delta(CH_{4-n}X_n)$ and **B** $,\delta(CH_3CH_{3-n}X_n)$ vs. the number of substituents (n).
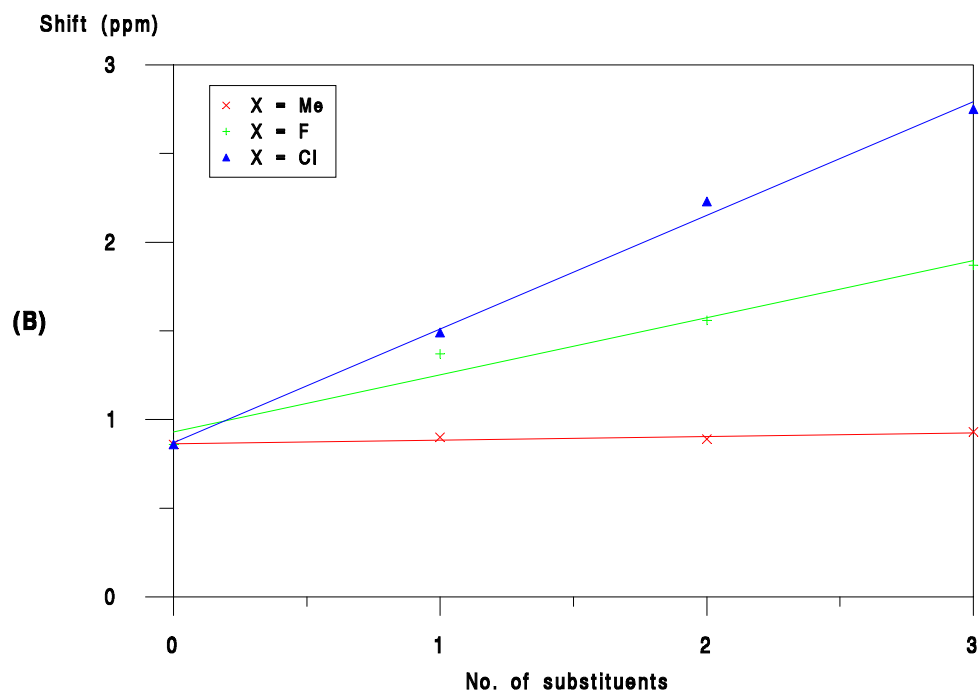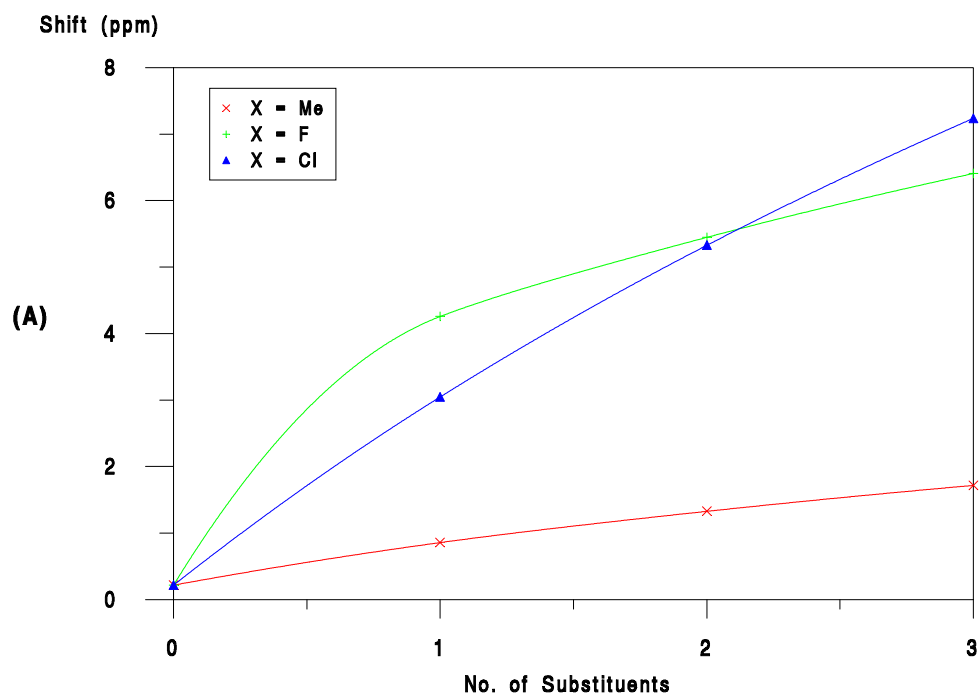
We first noted that the experimental points for the δ (CH_nX_{4-n}) vs n plot (figure 1A) are well reproduced by an exponential function (equation 6) with different values of the curvature parameter b for the different substituents.

$$\delta_i = \delta_0 + A (1 - \exp (-bq)) \qquad (6)$$

Also the electronegativity of hydrogen in both the GM and CHARGE schemes[15,16] was given from the orbital electronegativities compiled by Hinze and Jaffe based on the Mulliken scale[18]. This was used rather than the more common Pauling scale[19] because the orbital electronegativity as opposed to the atomic electronegativity can be obtained. Thus the electronegativity of C(sp3) < C(sp2)< C(sp). The disadvantage of this scale is that the hybridisation of an atom is often not known and also the atomic ionisation potentials and electron affinities required are not always known accurately . The value of E_H of 7.17 given corresponds to a value of 2.4 on the Pauling scale, which is rather high. Thus values of E_H which were more consistent with the Pauling value (2.20) and which would give a unified slope for the δ vs q plot were considered. Simultaneously equation 3 was replaced for $q_i > q_i^\circ$ with an exponential curve similar to equation 6. One that satisfies the boundary conditions is equation 7.

$$P_i = P_i^\circ \exp (-b (q_i - q_i^\circ)) \qquad (7)$$

The calculations gave optimum values of E_H 6.9, b 10.0 and A(C,H) 25.0. Taking the observed shifts of methane, ethane, CH_2Me_2, $CHMe_3$, CH_3X and CH_3CH_2X (X=NH_2, OH, F, Cl) equation 8 was obtained relating charge to the proton chemical shift with a correlation coefficient of 0.999 and rms error of 0.059 ppm. The observed and calculated chemical shifts are given in table 1. The value of E_H is equivalent to 2.3 on the Pauling scale which is close to the accepted value and the charge on the hydrogen of methane is 43.2 me corresponding to a C-H bond dipole of 0.22D.

$$\delta = 160.84 q - 6.68 \qquad (8)$$

The coefficient of 160 ppm/electron compares very reasonably with other shift vs charge equations where values from 130 to 180 have been given[20,21].

There remains the problem of fluorine (and oxygen) beta substitution. The non-linear effect of multiple fluorine substitution was so great that GM did not attempt to calculate the proton shifts of the multi fluorosubstituted methanes and ethanes. This non-linear effect is well known in quantum mechanical calculations of fluoro compounds. The geminal fluorine atoms strongly interact with each other, and the F.C.F angle is much less than tetrahedral and the CF bond dramatically shortened in the CF_2 and CF_3 groups[22]. Similar effects occur for multiple oxygen substitution[23]. The CHARGE3 scheme was modified to take explicit account of these effects by reducing the beta fluorine and beta oxygen effects by the appropriate factor. This minor change gave excellent agreement with both the observed proton shifts and dipole moments of the fluoro and oxygen substituted methanes (table 1).

The γ (H.C.C.X) effect.

In CHARGE3 the γ effect of a substituent was taken as the β effect divided by 5 or 10 (see above). The γ effect could not be refined by recourse to the experimental dipole moments as it is only a small perturbation ($<$ 0.1 D) of the dipole moment. However the γ effect of substituents on the proton chemical shift is often large and easy to measure thus it is possible to examine this in more detail. Figure 1B shows the chemical shift of the methyl protons in substituted ethanes as a function of the number of substituents. There are some similarities to that of beta substitution (figure 1A) in that the plot for fluorine is again curved but in contrast those for Cl and Me including the origin are accurately linear. More significantly there is no relation between the electronegativity of the substituent and the γ SCS which is in the order $I > Br > Cl > F > OH > NH_2$ (table 2). The order is roughly proportional to the polarisability of the substituent. Thus the γ effect is now given by equation 9 which replaces equation 4.

$$q_i (\gamma) = 0.0050\ P_i\ P_X{}^\circ \qquad\qquad (9)$$

The γ effect of sulphur is much less than predicted from eqtn 9 using the value of the sulphur polarisation of 1.748^{16}. The sulphur polarisation was therefore reduced to 1.10, similar to that of carbon. Also further inspection showed that the γ effect was reduced for methylene and methine compared to methyl protons (see table 2). Presumably the methylene and methine protons are increasingly shielded from external perturbation by the attached carbon atoms. The γ effect is roughly proportional to the number of attached hydrogen atoms thus for methylene and methine hydrogens equation 9 is multiplied by 2/3 and 1/3 respectively. Finally, as in the case of beta substitution, the γ effects for CX_2 and CX_3 (X=F, O) are reduced by the appropriate factors .

These simple amendments to the CHARGE3 scheme provide a comprehensive calculation of the proton chemical shifts of a variety of methyl and ethyl derivatives (table 1), whilst at the same time giving calculated dipole moments essentially unchanged from those given by CHARGE3. The results in table 1 will be discussed later.

TABLE 1: Observed and Calculated Proton Chemical Shifts (δ) of Substituted
Methanes and Ethanes.

System \ X	H	NH$_2$	OH	F	Cl	Br	I	SH
CH$_3$X								
obs[a]	0.22[b]	2.46[b]	3.38	4.26	3.05	2.68	2.16	2.08[c]
calc	0.27	2.34	3.34	4.26	3.12	2.79	2.21	2.09
C*H*$_3$CH$_2$X								
obs[d]	0.86	1.11	1.24	1.37	1.49	1.71	1.85	1.33
calc.	0.80	1.30	1.22	1.20	1.49	1.65	1.88	1.31
CH$_3$C*H*$_2$X								
obs[d]	0.86	2.75	3.71	4.51	3.57	3.47	3.20	2.56
calc.	0.80	2.76	3.71	4.60	3.51	3.19	2.63	2.48
CH$_2$X$_2$								
obs[e]		---	4.90[f]	5.45	5.33	4.94	3.90	---
calc.		---	4.90	5.52	5.27	4.74	3.79	---
CHX$_3$								
obs[e]		---	4.98[g]	6.41	7.24	6.82	4.91	---
calc.		---	4.99	6.44	7.00	6.34	5.12	---
CH$_3$C*H*X$_2$								
obs.[e]		---	5.23[f]	5.94[h]	5.87	5.86	---	---
calc.		---	5.21	5.81	5.57	5.06	---	---
C*H*$_3$CHX$_2$								
obs.[e]		---	1.33[f]	1.56[h]	2.23	2.47	---	---
calc.		---	1.33	1.50	2.12	2.41	---	---
CH$_3$CX$_3$								
obs.[e]		---	1.44[g]	1.87[h]	2.75	---	---	---
calc.		---	1.44	1.84	2.72	---	---	---

a) ref. 25, b) this work, c) Me$_2$S ref. 25, d) ref. 24, e) ref. 15, f) in D$_2$O this work, g) OMe this work, h) ref. 1.

TABLE 2: Proton γ SCS (H.C.C.X) ppm of Substituted Ethanes and Butanes.

System \ X	NH$_2$	OH	F	Cl	Br	I	SH
CH_3.CH$_2$X[a]	0.25	0.38	0.51	0.64	0.86	0.99	0.48
Et.CH_2.CH$_2$X[b]	0.16	0.30	0.42	0.49	0.59	0.55	0.34[d]
Me$_2$CH.CH$_2$X[c]	-0.14	0.06	-	0.26	0.26	0.02	0.03

a) from ethane (0.855 ppm). ref. 24

b) from butane (CH$_2$ 1.260 ppm). ref. 26.

c) from isobutane (CH 1.715 ppm, ref. 24), shifts from this work.

d) this work.

Long range Effects.

Although the modified CHARGE3 scheme gives reasonable values of the proton chemical shifts of substituted methanes and ethanes (table 1) in more complex compounds long range effects and possible orientational effects may be present. E.g. the hydrogens of cyclohexane have very different chemical shifts (table 4), yet on CHARGE3 they are calculated as having identical atomic charges and therefore shifts. Clearly other mechanisms must be included in order to obtain a more general scheme.

There are almost as many interpretations as investigations for these long range effects (see earlier) and the central problem is how to define the various contributions. We used the commercial HyperNMR[12] programme which is based on FPT/INDO theory[13] to identify some of these trends. In order to identify the H..H steric contribution the proton chemical shifts of the methylene protons of trans-butane were calculated as a function of the rotation of the distant methyl group (figure 2) and a similar calculation was performed for the individual methyl protons in propane. In these calculations the only nuclei altering their position are the methyl protons, and figure 3 shows the calculated shifts as a function of the closest H..H distance. We note that the proton chemical shift *de*creases as the H..H distance decreases and the calculated curves are well reproduced by an r^{-6} function (the curves in figure 3). These

results are of interest as it has been generally assumed that increasing steric repulsion gives rise to low-field shifts of the affected hydrogen atoms[27]. Also the trans (anti) hydrogen atom in propane is *not* affected by the change in the H..H distance, i.e. there is no push-pull effect for H..H interactions (see later). An alternative explanation of these results is C-H bond anisotropy but trial calculations gave negligible shifts compared to those of figure 3. Thus this interpretation was not pursued further.

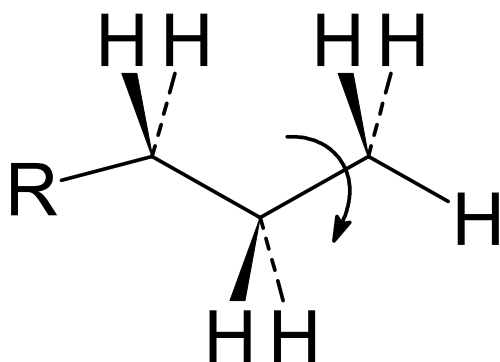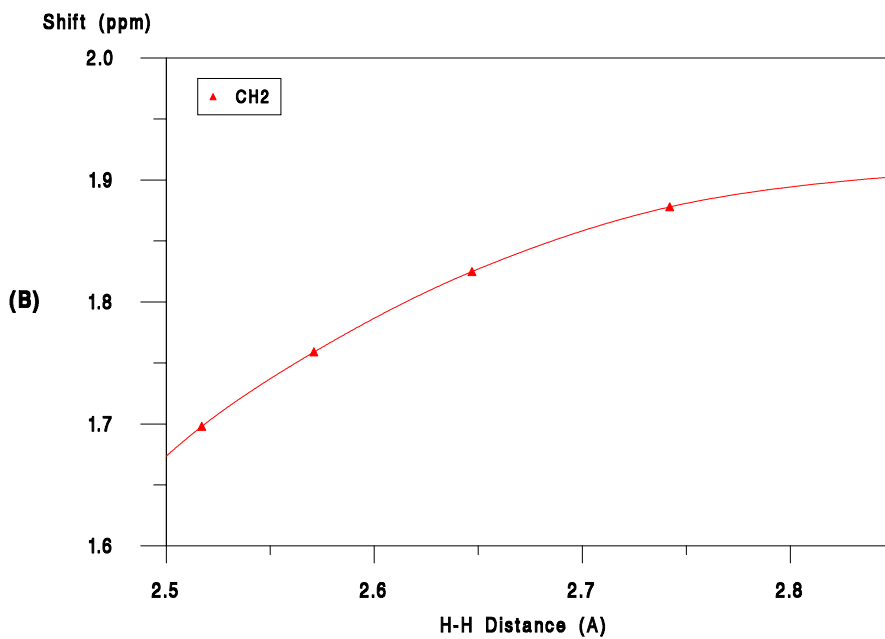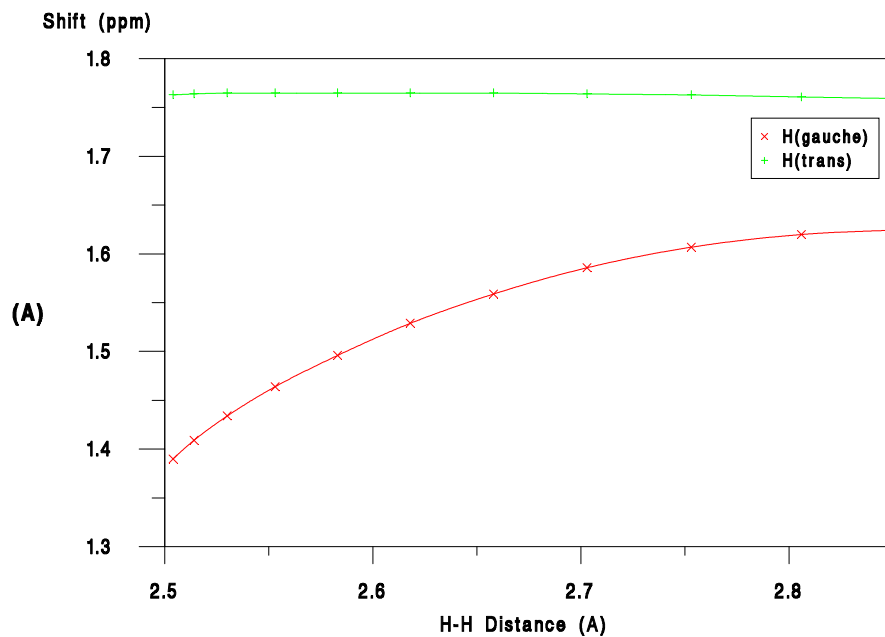**FIGURE 2:** Methyl Protons Rotated in Propane and Trans-butane (R=H, CH_3).

FIGURE 3: The Effect of Rotating a Methyl Group on (A) the Proton Chemical Shifts of the other Methyl Protons in Propane and (B) the delta CH_2 Protons of trans Butane.

We first followed Li and Allinger[5] in calculating the H..H steric interaction from the non-bonded steric potential[17]. As the r^{-6} function is simpler and has now been shown to have a sound theoretical basis we use this henceforth with a cut-off at the Van-der-Waals minimum (equation 10, where a_s is a shielding constant). This is mainly for computational convenience as this removes a large number of very small H..H interactions.

$$\delta_{steric} = a_s (1/r^6 - 1/r_{min}^6) \qquad (10)$$

In contrast to the H..H steric interaction, the steric effects of other substituents on proton chemical shifts can be observed experimentally and figure 4 and table 3 show the SCS of protons experiencing steric interactions with substituents in the cyclohexane and norbornane systems. These SCS are clearly steric effects, as the SCS of the same protons when the CHX atoms are interchanged, i.e. over the same number of bonds are all very much smaller (usually < 0.1 ppm , cf. table 5).

FIGURE 4: Sterically Perturbed Hydrogen atoms in Cyclohexane and Norbornanes.
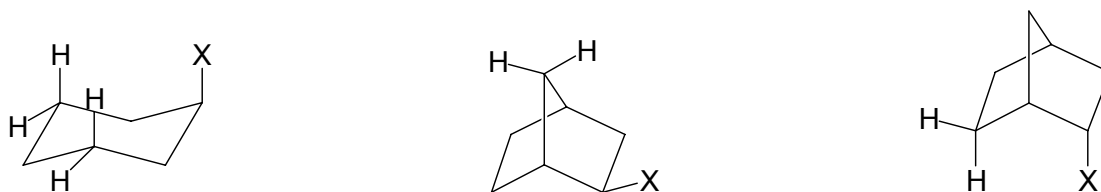
Two immediate conclusions can be made from the above results. There are sizeable low-field proton shifts due to the proximity of these substituents to the proton in question and in all cases except fluorine there is a compensating upfield shift of the methylene proton which is not experiencing the steric interaction[*]. This we term the push-pull effect.

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[*] One referee drew our attention to possible confusion over the use of the terms 'steric' and 'Van der Waals' to explain our long range effects. The former is considered short range and repulsive and the latter long range and attractive. However, since equation 10 contains both repulsive and attractive regions of the non-bonded potential[17], both terms are applicable. The distinction is made that all H...H interactions are *shielding*, while all X...H interactions considered are *deshielding*.

TABLE 3: SCS (ppm) of Close Substituents in Cyclohexane and Norbornane Systems.[a]

Substituent Position	1-AXIAL		2-EXO		2-ENDO	
X	H_{3ax}	H_{3eq}	H_{7syn}	H_{7ant}	H_{6en}	H_{6exo}
F	0.44	0.07	0.51	0.16	0.65	0.04
OH	0.46	-0.20	0.39	-0.06	0.72	-0.11
Cl	0.65	-0.18	0.59	0.06	0.84	-0.15
Br	0.68	-0.13	0.68	0.11	0.84	-0.07
Me	0.13	-0.15	0.15	-0.15	0.39	-0.20

a) data from ref. 28.

PROCEDURE

It is clearly essential to include the above effects in any comprehensive calculation of proton chemical shifts. In our model the computational procedure was simplified by calculating the steric shifts due to these interactions directly, rather than as partial atomic charges. These steric shifts are then added to the proton shifts calculated earlier using equation 8. Note also that the steric shifts are excluded for the α, β and γ substituents as the effect of these on the proton has already been evaluated.

A central problem in these calculations is the mechanism of the orientation dependence of the methyl γ SCS. I.e. is the observed dihedral angle dependence due to an intrinsic angular dependence of the carbon γ effect (C.C.C.H) plus a steric contribution, or is it due to a non-orientation dependant γ effect plus a somewhat larger steric contribution? This problem was addressed by evaluating both possibilities.

The observed proton chemical shifts of a variety of cyclic and acyclic alkanes (table 4) were calculated by including the following interactions into the CHARGE3 scheme.

1) An H..H steric interaction (equation 10) giving an upfield shift with *different* coefficients depending on the types of the two protons involved: CH, CH_2 and CH_3.

2) A push-pull routine for the proton of a methylene or methyl group other than the proton which is experiencing a C..H steric shift.

3) An explicit carbon gamma effect given by A) a simple through bond shift and B) a $\cos\theta \times$ abs($\cos\theta$) effect.

4) A C..H steric interaction using equation 10 but giving a *low-field* shift for the affected protons.

It was immediately apparent that the calculations of the steric effects experienced by a methyl group could not be performed accurately, as the push-pull effect on the methyl protons combined with the averaging of their shifts due to rapid rotation of the methyl group means that all steric effects average to zero. Indeed this may be the reason for the lack of variation of the methyl group chemical shift. In all the hydrocarbons examined here except methane and the t-butyl compounds, the methyl shift is 0.85-0.95δ. The H..H steric shifts experienced by the methyl protons were thus put at zero. In one case, tri-t-butyl methane the rotation of one of the t-butyl methyl's becomes so slow at -160^0 C that the three protons of the methyl group are non-equivalent.[29] The resulting large changes in the methyl proton chemical shifts (table 4) support the above thesis and were of considerable use in the subsequent C..H steric shift parametrisation.

TABLE 4: Observed vs calculated proton chemical shifts (δ) of hydrocarbons without (A) and with (B) an explicit γ.carbon dihedral angle dependence.

Molecule.		Expt.[a]	Calculated [b]	
			A	B
Propane	CH_3	0.90	0.85	0.86
	CH_2	1.33	1.30	1.30
Iso-butane	CH_3	0.89	0.90	0.91
	CH	1.74	1.77	1.77
Neo-pentane	CH_3	0.93	0.95	0.97
Di-t-butyl-methane[c]	^tBu	0.97	0.95	0.96
	CH_2	1.23	0.90	1.03
Di-t-butyl-ethane [c]	^tBu	0.98	0.95	0.96
	CH_3	0.86	0.90	0.89
	CH	1.18	1.39	1.38
Di-t-butyl-propane [c]	^tBu	0.99	0.95	0.96
	CH_3	0.83	0.95	0.94
Tri-t-butyl-methane[c]	^tBu	1.22	0.95	0.95
	CH	1.38	1.15	1.14
-160°C: (CH_3) [d]	$CH_3(a)$ 0.63		0.58	0.55
	$CH_3(b)$ 1.25		0.59	0.60
	$CH_3(c)$ 1.67		1.67	1.67
Cyclic Systems:				
Cyclobutane[e] CH_2		1.96	1.96	1.47
Cyclopentane				
	CH_2	1.51	1.56	1.43
Cyclohexane[f] Ax.		1.19	1.10	1.10
Eq.		1.68	1.64	1.71
Norbornane[f] 7a,s		1.18	1.45	1.49
(1) 1,4 (CH)		2.19	2.07	2.17
endo		1.16	1.26	1.32
exo		1.47	1.53	1.48
Bicyclo[2.2.2]octane [g]				
(2) CH_2		1.50	1.42	1.42
CH		1.50	2.07	2.21

Trans-decalin [g,h]

(3)	9,10 (CH)	0.88	0.88	0.86
	1,4,5,8a	0.93	0.88	0.95
	2,3,6,7a	1.25	1.16	1.12
	1,4,5,8e	1.54	1.39	1.55
	2,3,6,7e	1.67	1.64	1.71

Cis-decalin [h]

(4)	1,5a/4,8e	1.30	1.16	1.32
	2,6a/3,7e	1.33	1.33	1.45
	1,5e/4,8a	1.54	1.13	1.36
	2,6e/3,7a	1.56	1.30	1.36
	9,10 (CH)	1.62	1.48	1.59

Perhydro-phenalene [g]

(5)	13 (CH)	0.32	0.38	0.38
	10-12 (CH)	0.96	0.96	0.97
	1,3,4,6,7,9a	0.95	0.86	0.95
	2,5,8a	1.29	1.21	1.13
	1,3,4,6,7,9e	1.57	1.38	1.55
	2,5,8e	1.65	1.64	1.71

Perhydro-anthracene [g]

(6)	9,10a	0.72	0.66	0.81
	11-14 (CH)	0.91	0.89	0.90
	1,4,5,8a	0.95	0.89	0.95
	2,3,6,7a	1.23	1.16	1.12
	9,10e	1.43	1.14	1.39
	1,4,5,8e	1.56	1.39	1.55
	2,3,6,7e	1.67	1.64	1.71

Tertiary butylcyclohexane [j, i]

	1a	0.94	1.08	1.10
	1e (^{t}Bu)	0.83	0.95	0.96
	2,6a	0.91	0.73	0.88
	2,6e	1.75	1.55	1.73
	3,5a	1.19	1.11	1.10
	3,5e	1.75	1.64	1.71
	4a	1.08	1.09	1.10
	4e	1.64	1.64	1.71

Trans-cis-1,3,5-trimethylcyclohexane [i]

(7)	1a (Me)	0.97	0.90	0.91
	1e	2.02	1.97	2.05
	2,6a	1.02	1.14	1.15
	2,6e	1.43	1.45	1.41
	3,5a	1.61	1.62	1.63
	3,5e (Me)	0.83	0.90	0.91

4a	0.48	0.86	0.82
4e	1.60	1.51	1.46
Adamantane [f] CH	1.87	2.07	2.21
CH$_2$	1.75	1.22	1.44

a. data from ref. 15 and 25 except where stated.

b. all geometries were optimised at the RHF/6-31G* level using Gaussian92 .(ref. 31).

c. ref. 32, d. ref. 29, e. ref. 33, f. ref. 34, g. ref. 8, h. ref. 9, i. ref. 6, j. ref. 35.

FIGURE 5:

(1)   **(2)**   **(3)**

(4)   **(5)**

(6)   **(7)**
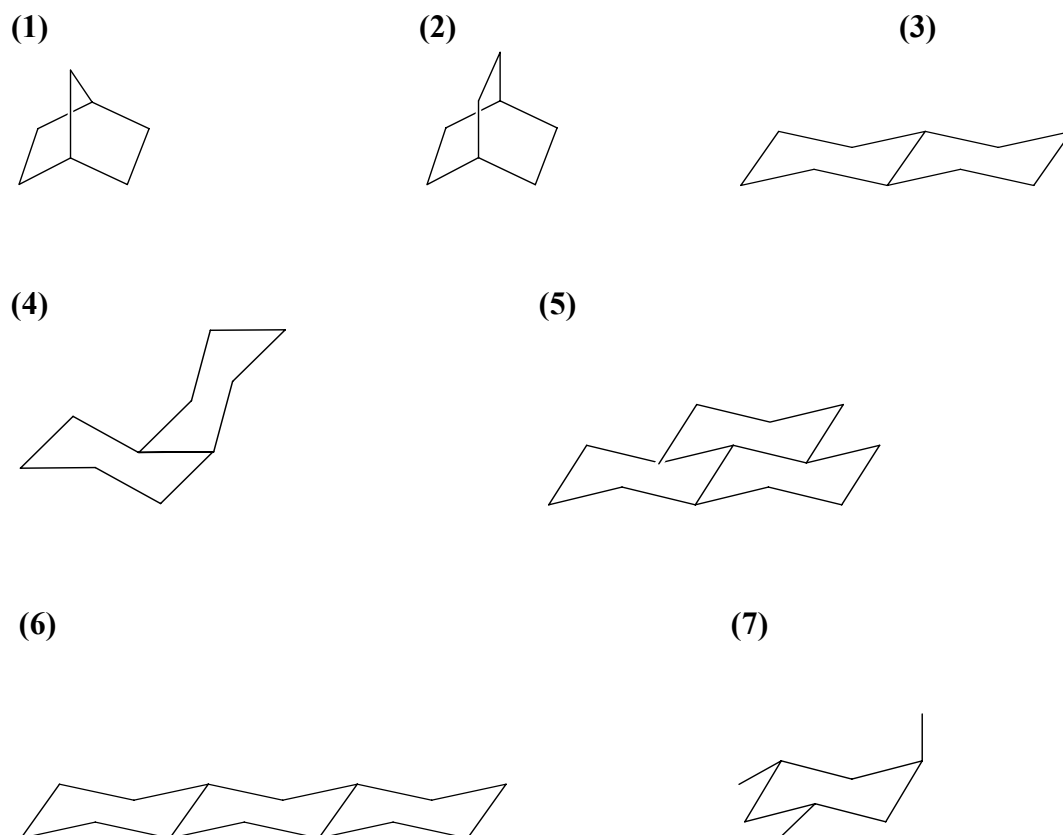
X..H Steric Shifts.

The protons in the data set which experience C..H steric shifts are those given in table 3 plus the di- and tri-tert-butyl methanes and some methyl substituted alkanes (e.g. trans, cis-1,3,5-trimethyl cyclohexane, methyl adamantane etc.). These provide sufficient information to

test the validity of equation 10 when applied to C..H steric shifts. It was found that equation 10 did give good agreement with the observed results with a C..H R_{min} of 3.35 A with different coefficients for CH, CH_2 and CH_3 protons.

Finally all the parameters used in the calculations were iteratively refined using the complete data set for hydrocarbons of tables 4, 5 and 6 to give the lowest rms error. It should be noted here that the analysis is over-determinate, i.e. there are many more proton shifts than coefficients thus the extent of the agreement between the observed and calculated shifts is considerable support for the validity of the above analysis. The observed and calculated hydrocarbon shifts are given in table 4 and the methyl SCS in cyclohexanes and norbornanes in tables 5 and 6, the calculated shifts both without (A) and with (B) the explicit dihedral angle dependence . These will be discussed later.

In a similar manner, the observed SCS in chloro and fluoro cyclohexanes and norbornanes were used to determine the validity of this model for these SCS. Preliminary results for the fluoroalkanes have been given previously[1]. The observed SCS are given in tables 5 and 6 and inspection clearly shows that there is no obvious dihedral angle dependence of the γ (X.C.C.H) SCS. Thus the analysis given earlier for the substituted ethanes may be used without any modification. The only additional interaction is the direct steric term for fluorine and chlorine. Detailed analysis of the steric interactions shows that whilst the chlorine steric effect is well reproduced by an r^{-6} function, that of fluorine is better fitted by an r^{-3} function. In both cases it was not found necessary to include a cut-off at the Van-der Waals minimum. Also the available data, which is less comprehensive than that for methyl substitution, did not suggest any sub-division of the steric shift coefficients into CH, CH_2 and CH_3 groups. The observed and calculated SCS for methyl, fluorine and chlorine in cyclohexanes and norbornanes are given in tables 5 and 6.

TABLE 5: Observed and calculated SCS (ppm) for substituted cyclohexanes without (A) and with (B) a γ carbon dihedral angle dependence.

				Substituent					
Proton	Methyl				Fluoro			Chloro	
Equatorial Substituents									
	obs[a]	calc			obs[b]	calc		obs[c]	calc
		A	B			A	B		A	B
H-1a	0.15	0.26	0.23		3.30	3.44	3.50	2.63	2.36	2.38
H-2e	-0.03	-0.07	-0.13		0.47	0.24	0.25	0.53	0.42	0.43
H-2a	-0.31	-0.09	-0.13		0.23	0.19	0.19	0.33	0.39	0.42
H-3e	0.00	0.00	0.00		0.18	0.02	0.07	0.10	0.00	0.01
H-3a	0.02	0.06	0.02		0.09	0.12	0.12	0.12	0.09	0.06
H-4e	0.01	0.00	0.00		-0.03	0.01	0.04	-	0.00	0.00
H-4a	-0.08	0.00	0.00		-0.07	0.03	0.07	-	0.02	0.03
Me[d]	0.86	0.90	0.91							
Axial Substituents									
H-1e	0.33	0.29	0.34		3.26	3.40	3.46	2.83	2.36	2.42
H-2e	-0.20	-0.11	-0.17		0.35	0.24	0.25	0.40	0.42	0.43
H-2a	0.25	0.14	0.19		0.24	0.27	0.27	0.45	0.40	0.44
H-3e	-0.26	-0.16	-0.20		0.07	0.03	0.10	-0.18	-0.12	-0.13
H-3a	0.27	0.25	0.16		0.44	0.37	0.39	0.65	0.58	0.59
H-4e	-0.02	0.00	0.00		-0.10	0.03	0.08	-	0.01	0.02
H-4a	-0.06	-0.03	-0.01		0.09	0.05	0.09	-	0.00	0.02
Me[d]	0.93	0.90	0.91							

a) ref. 6.   b) ref. 1.   c) ref. 28.   d) Methyl shift.

TABLE 6: Observed and calculated[a] SCS (ppm) for substituted bicycloheptanes without (A) and with (B) a γ carbon dihedral angle dependence.

	Methyl			Fluoro			Chloro		
	Substituent								
Proton	obs[b]	calc		obs[c]	calc		obs[d]	calc	
		A	B		A	B		A	B
2-exo substituent									
H-1	-0.37	-0.07	-0.22	0.16	0.12	0.12	0.20	0.20	0.21
H-2n	0.33	0.11	0.11	2.53	3.33	3.34	2.71	2.20	2.27
H-3x	-0.54	-0.27	-0.34	-	0.23	0.25	0.33	0.40	0.42
H-3n	0.26	0.18	0.05	-	0.30	0.27	0.75	0.46	0.45
H-4	-0.03	0.01	0.01	-	0.03	0.09	0.12	0.02	0.04
H-5x	-0.03	0.00	0.00	-0.03	-0.01	0.04	0.00	-0.02	0.00
H-5n	-0.06	0.06	0.01	0.00	0.02	0.08	-0.09	0.05	0.04
H-6x	0.01	-0.03	-0.01	0.08	0.04	0.07	0.14	-0.01	0.00
H-6n	-0.02	0.03	0.02	-0.01	0.26	0.16	-0.02	0.14	0.08
H-7s	0.15	0.14	0.12	-	0.38	0.40	0.59	0.53	0.55
H-7a	-0.15	-0.17	-0.11	-	0.04	0.10	0.06	-0.13	-0.11
Me[e]	0.86	0.90	0.91						
2-endo substituent									
H-1	-0.21	0.03	-0.08	0.30	0.12	0.12	-	0.20	0.21
H-2x	0.42	0.05	0.15	2.50	3.33	3.40	2.68	2.15	2.27
H-3x	0.27	0.19	0.04	-	0.23	0.25	0.75	0.45	0.45
H-3n	-0.63	-0.21	-0.33	-	0.27	0.25	0.22	0.41	0.41
H-4	-0.08	0.00	-0.01	-	0.02	0.07	0.08	0.02	0.02
H-5x	0.01	-0.01	0.01	0.09	0.03	0.07	0.04	-0.02	-0.01
H-5n	-0.08	-0.08	-0.03	0.09	0.05	0.15	0.14	-0.01	0.08
H-6x	-0.20	-0.36	-0.23	-0.22	0.04	0.11	-0.15	-0.22	-0.22
H-6n	0.39	0.55	0.35	0.55	0.71	0.58	0.84	1.03	0.94
H-7s	0.15	-0.02	0.00	-	0.03	0.07	-	0.04	0.05
H-7a	0.07	-0.04	-0.01	-	0.11	0.12	-	-0.02	0.00
Me[e]	0.93	0.90	0.95						

a) Calculated SCS cf. 2-substituted norbornanes. b) ref. 7. c). expt. SCS cf. 3-exo- and 3-endo-fluorocamphor, ref. 30. d) expt. SCS cf. 2-exo-chloro-norbornane and 2-endo-chloro-bornane, ref. 28. e) Methyl shift.

DISCUSSION

The results of tables 1, 4, 5 and 6 are encouraging in that the simple extension to the CHARGE3 scheme proposed has given calculated proton chemical shifts for a wide range of molecules in generally good agreement with the observed shifts. Using all the hydrocarbon shifts in these tables (a total of 109 shifts spanning a range of 2 ppm.) both the options A and B gave identical rms errors for the observed vs. calculated shifts of 0.17 ppm. This value may be compared with the corresponding rms error of 0.30 ppm given by HyperNMR using the recommended TNDO/2 option[12] and also the value of 0.34 ppm obtained using fixed average values of the shifts of CH, CH_2 and CH_3 of 1.57, 1.32 and 0.90 δ. The charge routine with the amendments outlined here thus gives the most accurate prediction to date of the proton chemical shifts of saturated hydrocarbons. The HyperNMR calculated shifts are not significantly better than those given by averaging the methyl, methylene and methine values, though it should be noted that the parametrisation of HyperNMR used a much smaller data base than the one given here and this could have affected the result.

It is of some interest to note that proton chemical shifts now have a simple chemical explanation. E.g. the decrease in shielding on going from $CH_4 \rightarrow CH_3 \rightarrow CH_2 \rightarrow CH$ is simply due to the increased electronegativity of carbon *versus* hydrogen and the effects of the electronegativity of the β substituent are clearly demonstrated in table 1 for a range of substituent groups. The agreement between the observed and calculated shifts is very good except for the very polarisable bromine and iodine substituents. In these cases further substitution directly affects the halogen atoms and a more complex iteration procedure would be necessary to accommodate their substituent effects.

It is not possible on the basis of the above results to distinguish between the two options A and B, i.e. whether carbon has an intrinsic orientation dependent γ effect or not. Although the two schemes give very different results in certain cases (cf. table 4) the overall rms errors were identical. It is possible that option B is implicitly including in the dihedral angle term the effect of C-C bond anisotropy, and it may be pertinent to note in this respect that fluorine and

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chlorine do not have any intrinsic γ orientation substituent effect. The C-C bond is the only homopolar bond in these molecules. Further calculations and investigations with oxygen and nitrogen compounds which are in progress may help to clarify these possibilities.

Also of note are the different interpretations of the cyclohexane chemical shifts in the two schemes. In option B the orientation dependence of the carbon γ effect produces a deshielding of the equatorial protons due to the ring carbon atoms in a trans (anti) orientation, whereas the axial protons are in a gauche orientation wrt the ring carbon atoms, producing a shielding effect. In option A the difference between the axial and equatorial protons is solely due to H..H steric shifts shielding the axial protons.

One of the most intriguing aspects of these results is the absence of any explicit magnetic anisotropy or electric field effects, which have been considered in the past to dominate proton chemical shifts[3]. The absence of significant magnetic anisotropy effects may have been anticipated, as the groups considered here are not very anisotropic (though one previous explanation for the axial-equatorial difference in cyclohexane was C-C bond anisotropy[36]). It is hoped to include magnetically anisotropic groups e.g. C=O, C=N etc. in the charge scheme subsequently.

The linear and quadratic electric field effects of substituents on proton chemical shifts are well documented theoretically [1,36,37]. However the absence of any significant linear electric field effect is clearly evident merely from comparison of the experimental fluorine and chlorine SCS in tables 1,5 and 6. The CF and CCl bonds have very similar dipole moments (1.86 and 1.89 D for MeF and MeCl res.) but both the γ effect and the steric shift for chlorine are much greater than that of fluorine. This is very strong support for the absence of any significant linear electric field effect. In contrast the quadratic electric field effect is closely related to the Van-der-Waals (i.e. steric) shifts and these steric shifts are clearly identified   in the above treatment.

The push-pull effect (table 3) may indeed be a reflection of the steric interaction of two neighbouring C..X atoms (X=C, Cl etc.) in which the effect of this interaction on the attached

hydrogen atoms depends on the H-C..X angle. This more complex calculation could in principle have been performed, but due to the lack of extensive data for these steric shifts the simpler push-pull routine was used. There is some evidence in the option A parametrisation for CH polarisation shifts as suggested by Boaz[8], in that the coefficients of the interacting CH, CH_2 and CH_3 groups are very different whereas this is not the case for the affected proton. I.e. a CH proton has a similar effect on a CH or CH_2 group but the reverse is not the case. This trend is not observed in option B where the coefficients in the steric H..H matrix are much smaller and show no clear pattern.

There are a number of areas where it is clear that a more complex treatment would be needed to better reproduce the observed results. For example the γ effect of an equatorial methyl group in cyclohexane (table 5) is -0.03 ppm on H_{2e} and -0.31 ppm on H_{2a}, yet the orientation of the methyl group is identical to both protons and the distance of the interacting methyl protons to H_{2e} and H_{2a} also virtually identical. Thus no treatment will reproduce this effect which does not explicitly distinguish the axial and equatorial protons in cyclohexane. Indeed Grant and co-workers[9] did this in their successful additive scheme. The problem with this type of treatment is that it is not easy to extend it to non perfectly staggered alkanes (e.g. norbornanes etc.). But a more accurate representation of the methyl SCS would give a significant increase in the accuracy of the above scheme. Also the methine protons of norbornane (2.19δ), adamantane (1.87δ) and bicyclooctane (1.50δ) cover a range of 0.7 ppm, yet there are no steric effects on these protons and the γ carbon atoms are in a trans (anti) orientation in all the compounds. It is possible that the methine proton chemical shift is a function of the adjoining C.C.C angles. This could easily be included in the scheme, but a more definitive analysis would be required first.

There are other isolated anomalies in the scheme. For example the bridge protons of norbornane, the CH_2 protons of adamantane and the t-butyl compounds. The norbornane bridge proton chemical shifts may reflect the steric strain at the bridge carbon atom, in which the C.C.C angle is only 95.3^0 but steric effects are less significant in adamantane. There

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appears to be a possible link with the C.C bond length as all these compounds have anomalously long C.C bonds due to steric effects. In all cases the geometry used was obtained from GAUSSIAN92 using the recommended 6-31G* basis set[38]. The significance of any geometry changes was estimated by repeating the calculations using geometries from PCMODEL[39]. In all cases the difference in the calculated shifts was <0.1 ppm. This was encouraging and also provides an upper limit of the accuracy of the calculations. However, "standard geometries e.g. adding a standard methyl group to an unstrained cyclohexane to give axial methyl cyclohexane, gave differences of ca 0.5 ppm and this demonstrates the requirement for reasonably accurate geometries in these calculations.

In summary, we show that a simple extension of the CHARGE 3 scheme can give an accurate prediction of the proton chemical shifts of a variety of hydrocarbons, and this suggests that an extension of such methodology could provide a simple method of predicting the proton chemical shifts of a wide variety of organic compounds.

EXPERIMENTAL

Isobutanol, isobutylamine, isobutyl chloride, bromide and iodide and isobutyl and butyl mercaptan were obtained from Aldrich Chem. Co. ^{1}H n.m.r. spectra were obtained on a Bruker AMX 400 spectrometer operating at 400.14 MHz for protons. Spectra were of 10 mg/ml solutions in $CDCl_3$ with a probe temperature of ca. 25° C and referenced to TMS. Typical conditions were; proton spectra 128 transients with a spectral width of 3,300 Hz with 32K data points, giving an acquisition time of 5 seconds and zero filled to 128K to give a digital resolution of 0.025 Hz.

The ^{1}H spectra were analysed on a first order basis. The proton chemical shifts and couplings of n-butyl mercaptan are CH_3 0.914, J=7.34 Hz , γ CH_2 1.415, β CH_2 1.601, α CH_2 2.534 , SH 1.331, J=7.75 Hz. Those for the isobutyl compounds are given in table 7.

TABLE 7: Proton Chemical Shifts (δ) and Proton-Proton Couplings (Hz.) in $Me_2.CH.CH_2X$ Compounds.

Substituent	Chemical Shifts			Couplings	
	Me	CH	CH$_2$	Me.CH	CH.CH$_2$
NH$_2$	0.899	1.578	2.997	6.66	6.53
OH	0.922	1.770	3.410	6.70	6.49
Cl	1.011	1.972	3.388	6.68	6.18
Br	1.030	1.978	3.307	6.63	6.05
I	1.011	1.732	3.148	6.58	5.91
SH[a]	0.981	1.741	2.421	6.65	6.43

a. J (CH$_2$.SH) 8.22 Hz.

REFERENCES

1   R.J.Abraham, M.Edgar, L.Griffiths and R.L.Powell, *J. Chem. Soc. Perkin Trans. 2*, 561 (1995).

2   R.J. Abraham, J. Fisher and P. Loftus, "Introduction to NMR Spectroscopy", **Chapter 2**, J. Wiley & Sons, Chichester, U.K. (1988).

3   R.F. Zurcher, *Prog. Nuc. Mag. Res. Spect.*, **2**, 205 (1967).

4   J. W. Apsimon and H. Beierbeck, *J. Canad. Chem.*, **49**, 1328 (1971).

5   S. Li and N.L. Allinger, *Tetrahedron*, **44**, 1339 (1988).

6   D. Danneels and M. Anteunis, *Org. Mag. Res.*, **6**, 617 (1974).

7   J. Fisher and M.J. Gradwell, *Mag. Res. Chem.*, **30**, 338 (1992).

8   H. Boaz, *Tetrahedron Lett.*, **55** (1973).

9   a) J.Curtis, D.M.Grant and R.J.Pugmire, *J. Am. Chem. Soc*., **111**, 7711 (1989).

      b) J.Curtis, D.K.Dalling and D.M.Grant, *J. Org. Chem*., **51**, 136 (1986).

10   E. Pretsch and W. Simon, *Helv. Chim. Acta*., **52,** 2133 (1969).

11   H.M.Sulzbach, P.V.R.Schleyer and H.F.Schaefer, *J. Am. Chem. Soc.*, **116**, 3967 (1994).

12   HyperNMR, Hypercube Inc., 419 Phillip St., Waterloo, Ontario, Canada.

13   a) A.C.Blizzard and D.P.Santry, *J. Chem. Phys*., **55**, 950 (1971).

      b) J.A.Pople and D.V.Beveridge, Approximate Molecular Orbital Theory,
       McGraw-Hill, NY (1970).

14   R.J. Abraham and B.D. Hudson, *J. Comp. Chem.*, **6**, 173, (1985).

15   J. Gasteiger and M. Marsili, *Org. Mag. Res.*, **15**, 353, (1981).

16   R.J. Abraham and G.H. Grant, *J. Comp. -Aid. Mol. Des.*, **6**, 273,(1992).

17   R.J.Abraham, M.Edgar, L.Griffiths and R.L.Powell, *J. Chem. Soc. Chem. Comm.*, 1544 (1993) .

18   a) J. Hinze and H. H. Jaffe, *J. Phys. Chem*., **67**, 1501 (1963).

       b) R. S. Mulliken, *J. Chem. Phys*, **2**, 782 (1934).

19   M.L.Huggins, *J. Am. Chem. Soc*., **75**, 4123 (1953).

20   R. J. Abraham, G.H. Grant, I.S.Haworth and P.E.Smith, *J. Comp-Aid. Mol. Des*., 5,21 (1991).

21   H. Gunther, "NMR Spectroscopy", **Chapter 4**, J. Wiley , Chichester, U.K. (1973).

22   R.J.Abraham, E.J.Chambers and W.A.Thomas, *J. Chem. Soc. Perk. Trans*. 2, 949 (1994).

23   F.C.Mijlhoff, H.J.Geise and E.J.M.Van Schaick, *J. Mol. Struct*., **20**, 393 (1974).

24   C. Altona, J.H.Ippel, A.J.A.Westra Hoekzema, C.Erkelens, M.Groesbeek and L.A.Donders,
      Mag. Res. Chem., **27**, 564, (1989).

25   J. Emsley, J. Feeney, L.H. Sutcliffe, "High Resolution NMR Spectroscopy", **2**, Appendix B, Pergamon Press, Oxford, 1996.

26   R.J.Abraham, L.Griffiths and P.Loftus, *J. Comp. Chem*., **3**, 407 (1982).

27   ref 21, page 89.

28   R. J. Abraham, A. P. Barlow and A. E. Rowan, *Mag. Res. Chem*., **27**, 1074 (1989).

29   J.E.Anderson , private communication.

30   C.R.Kaiser,R.Rittner and E.A.Basso, *Mag. Res. Chem*., 32, 503 (1994).

31   Gaussian 92, Revision F.4, M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. M. W. Gill,
          M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Replogle,
          R. Gomperts, J. L. Andres, K.Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox,
          D. J.Defrees, J. Baker, J. J. P. Stewart, and J. A. Pople, Gaussian Inc., Pittsburgh PA, 1992.

32   S.Hellmann, H.D.Beckhaus and C.Ruchardt, *Chem. Ber*. **116**, 2219 (1983).

33   K. B Wiberg and B. J. Nist, *J. Am. Chem. Soc*., **83**, 1226 (1961).

34   R.J. Abraham and J. Fisher, *Mag. Res. Chem.*, **23**, 856 (1985).

35   R.J.Abraham, E.J.Chambers and W.A.Thomas, *J. Chem. Soc. Perkin Trans. 2*, 1061 (1993).

36   ref. 25, vol 1, ch 4.

37   M.Grayson and W.T.Raynes, *Mag. Res. Chem*., *33*, 138 (1995)

38   J.B.Foresman and A. Frisch, Exploring Chemistry with Electronic Structure Methods,
          Gaussian Inc., Pittsburgh, USA. (1993).

39   PCMODEL(4.0). Serena software, PO Box 3076, Bloomington, Indiana, USA.