# Substituent Chemical Shifts in NMR Spectroscopy. Part 7.†
## C-C Anisotropy and the Methyl Effect

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A previous model for the calculation of proton chemical shifts in substituted alkanes based upon partial atomic charges and steric interactions has been modified to include C-C anisotropy contributions and an orientation dependent methyl $\gamma$ effect (i.e. Me.C.C.H).

The ring inversion in 1,1-dimethylcyclohexane and cis-decalin has been slowed at low temperature and the individual proton chemical shifts assigned, along with those for 5$\alpha$-androstane.

The new scheme (CHARGE4) predicts the proton chemical shifts of a variety of acyclic, cyclic and polycyclic hydrocarbons over 188 data points spanning 2ppm to within 0.11ppm, a 40% improvement over the previous model. Systems considered include substituted cyclohexanes and norbornanes, cis- and trans- decalin, perhydrophenalene and anthracene, adamantane and androstane, as well as methyl-butanes and t-butyl-methanes.

## Introduction

In the previous paper in this series[1] a model for the calculation of the proton chemical shifts in substituted methanes and ethanes ( RX, R= Me, Et; X= F, Cl, Br, I, OH, $NH_2$, SH) and of a number of more complex hydrocarbons including the ring systems of cyclohexane, norbornane, decalin, perhydrophenalene, perhydroanthracene and adamantane was given. This model was based on a semi-empirical calculation of the partial atomic charges of the protons in these molecules (CHARGE3) together with specific long range effects. These were H-H steric effects which were shielding at the protons, and H-C steric effects which were deshielding, both proportional to $r^{-6}$. The ubiquitous orientation dependent $\gamma$ methyl effect ( H.C.C.Me) was considered both explicitly and as a direct consequence of the steric effects. Both models gave the first accurate prediction of the proton chemical shifts of these compounds ( r.m.s. error 0.16 ppm over 139 shifts spanning 7 ppm).

Two common mechanisms postulated to account for proton chemical shifts, i.e. magnetic anisotropy and electric field effects were not included in these calculations and we now wish to

† For Part 6, see Ref. 1.

consider their importance. The electric field effect cannot be investigated rigorously in hydrocarbons as the low polarity of the C-C and C-H bonds makes this a minor (but not insignificant ) contribution to the proton chemical shifts. This will be dealt with subsequently when the proton shifts of polar molecules ( RX, X= F, Cl ) are considered[2]. Here we wish to consider the magnetic anisotropy contributions and in particular the effect of C.C anisotropy on the calculated proton chemical shifts of a variety of hydrocarbons.

The shielding of a nucleus in the liquid state ($\sigma_N$ ) due to the magnetic anisotropy of a substituent group (G) with axial symmetry was given by McConnell[3] (eqn. 1 ).

$$\sigma_N = \Delta\chi^G ( 1 - 3 \cos^2 \phi) / 3 L_0 R^3 \qquad (1)$$

where $L_o$ is Avogadro's number, R is the distance from the perturbing group to the nucleus of interest , $\phi$ is the angle between the vector R and the symmetry axis, and $\Delta\chi^G$ is the anisotropy of the molar susceptibility of the group.

$$\Delta \chi^G = \chi^G_{\parallel} - \chi^G_{\perp} \qquad (2)$$

where $\chi_{\parallel}^G$ and $\chi_{\perp}^G$ are the susceptibilities parallel and perpendicular to the symmetry axis respectively.

For hydrocarbons the magnetic anisotropy effects were initially ascribed solely to the C-C bonds and McConnell's equation then becomes

$$\delta = \Delta\chi^{C\text{-}C} ( 1 - 3 \cos^2 \phi) / 3 L_0 R^3 \qquad (3)$$

where $\Delta\chi^{C\text{-}C}$ is the molar anisotropy of the C-C bond. Bothner-By et al.[4] noted that a value of the C-C bond anisotropy of about 3.3 × $10^{-6}$ $cm^3$ $mol^{-1}$ would explain the observed chemical shift difference between cyclopentane and cyclohexane and Sheppard et al.[5] found the observed difference between the axial and equatorial protons in cyclohexane could be accounted for similarly. However, extending this approach[5-8] to larger molecules gave values of $\Delta\chi^{C\text{-}C}$ ranging from 3.9 to 15.0 × $10^{-6}$ $cm^3$ $mol^{-1}$ in contrast to the value of 1.21 × $10^{-6}$ $cm^3$ $mol^{-1}$ calculated by variational methods[9]. Narasimhan et al.[10] suggested that the C-H bond anisotropy should also be included and they obtained values of $\Delta\chi^{C\text{-}C}$ in the range 1.5 to 3.0 × $10^{-6}$ $cm^3$ $mol^{-1}$ and $\Delta\chi^{C\text{-}H}$ 0.2 to 1.5 × $10^{-6}$ $cm^3$ $mol^{-1}$ [10,11]. However attempts to explain the chemical shifts in alkyl derivatives[12], effects on methyl groups[13] and effects from the methyl group in methylcyclohexanes[14] clearly demonstrated that other factors were important.

In a seminal paper, Bothner-By and Pople[15] reviewed this early work and also obtained a limiting value of the C-C anisotropy since:

$$\Delta\chi^{C\text{-}C} = \chi_{\parallel}^{C\text{-}C} - \chi_{\perp}^{C\text{-}C} \tag{4}$$

and

$$\chi^{C\text{-}C} = (\chi_{\parallel}^{C\text{-}C} + 2\chi_{\perp}^{C\text{-}C}) / 3 \tag{5}$$

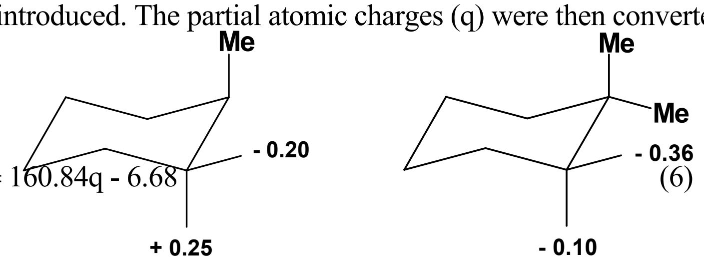
where $\chi^{C\text{-}C}$ is the mean molar susceptibility and $\chi_{\parallel}^{C\text{-}C}$ and $\chi_{\perp}^{C\text{-}C}$ are the susceptibilities parallel and perpendicular to the C-C bond. To avoid the bond being paramagnetic in the longitudinal direction, the C-C anisotropy must be less than one and half times the mean susceptibility. Using a value of 3.0 × $10^{-6}$ $cm^3$ $mol^{-1}$ for the mean susceptibility from crystal data a limiting value of 4.5 × $10^{-6}$ $cm^3$ $mol^{-1}$ for $\Delta\chi^{C\text{-}C}$ was obtained.

A modified McConnell equation to account for shorter distances more precisely was proposed by ApSimon et al.[16] From studying data on substituted cyclohexanes and borneols ApSimon deduced values for $\Delta\chi^{C\text{-}C}$ of 8.42 × $10^{-6}$ $cm^3$ $mol^{-1}$ and $\Delta\chi^{C\text{-}H}$ of 6.62 × 10-6 $cm^3$ $mol^{-1}$, well in excess of the limit suggested by Bothner-By and Pople. Indeed further studies questioned whether the correction term produced better results than the simple eqn. 3. [17,18].

Zürcher[19] included the magnetic anisotropy, van der Waals (i.e. steric) and electric field effects in the calculation of proton chemical shifts in steroids and bornanes. However, the only reliable data available at that time were the shifts of methyl groups (and some methine protons adjacent to substituents) which obscured the effects under consideration. Later work by Tribble et al.[20] using a similar approach found van der Waals and magnetic anisotropy contributions to give the best results, even over combinations including C-H electric field effects and more parameters. Their published values of $\Delta\chi^{C\text{-}C}$ and $\Delta\chi^{C\text{-}H}$ were 9.93 and 0.84 × $10^{-6}$ $cm^3$ $mol^{-1}$ respectively, much larger than Bothner-By and Pople's limit.

**Theory**

The CHARGE3 scheme[1] calculates the effects of atoms α, β and γ on the partial atomic charge of the atom under consideration, based upon classical concepts of inductive and resonance contributions. In CHARGE3A the carbon γ effect ( i.e. C.C.C.H) is proportional to the carbon polarisability , whereas in CHARGE3B an orientational dependence ($\cos\theta \times \text{abs} \cos\theta$, where $\theta = \angle$C.C.C.H) was introduced. The partial atomic charges (q) were then converted to shift values using eqn. 6.




$$\delta = 160.84q - 6.68 \quad (6)$$

The effects of more distant atoms were considered to be steric ($r^{-6}$ term), where H..H interactions were shielding and X..H ( X = C, F, Cl) interactions deshielding. Further, any X..H steric contributions on a methylene or methyl proton resulted in a push-pull effect (shielding) on the other proton(s) on the attached carbon. These contributions were then added to the calculated shifts of eqn. 6.

The C-C anisotropy was included in the present calculations using eqn. 3 with the magnetic vector pointing along the C-C bond and acting at the mid-point. This calculation was performed for all the C-C bonds in the molecule, except for those immediately adjacent to the proton considered (i.e. $H\text{-}C_{\alpha}\text{-}C_{\beta}$ ). The point dipole approximation breaks down at close distances[15], and including this bond would simply give a constant term for all methyl, methylene and methine protons. The calculated shift is thus given by:

$$\delta_{total} = \delta_{charge} + \delta_{steric} + \delta_{anisotropy} \quad (7)$$

where the value of the C-C anisotropy should be less than the limit of $4.5 \times 10^{-6}$ $cm^3$ $mol^{-1}$ ( i.e. 7.47 ppm $Å^3$ /molecule ).

*The Methyl Effect*. Neither the C-C anisotropy nor any of the previous mechanisms can explain the substituent chemical shift (SCS) of the methyl group in cyclohexanes[21,22] (figure 1). In particular the SCS of an equatorial methyl on $H_{2e}$ is -0.03 ppm but on $H_{2a}$ is -0.31 ppm yet the orientation of the methyl group is symmetrical to both protons and the H...H distances virtually identical. These SCS are well documented , reproducible and additive[22].

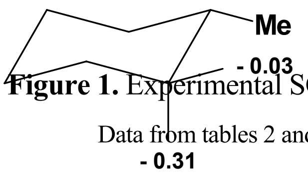



**Figure 1.** Experimental SCS of the methyl group on the gamma protons in methylcyclohexanes**.**

Data from tables 2 and 3.

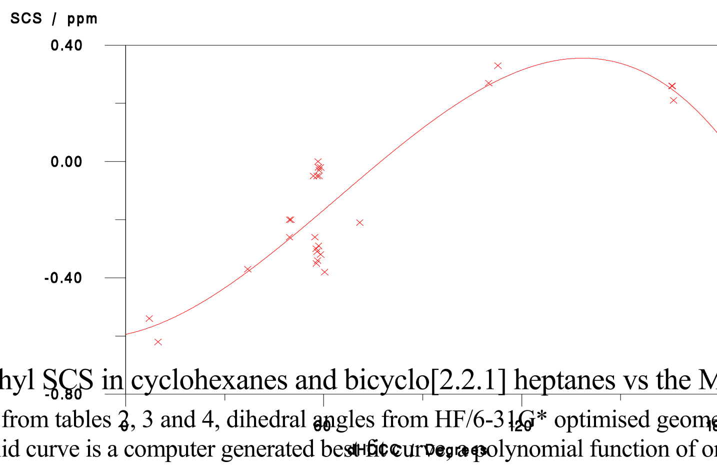



**Figure 2.** Methyl SCS in cyclohexanes and bicyclo[2.2.1] heptanes vs the Me-C-C-H angle.

Data from tables 2, 3 and 4, dihedral angles from HF/6-31G* optimised geometries, Ref. 23.

The solid curve is a computer generated best-fit curve, a polynomial function of order 3.

We note also that the methyl SCS in $CH_3$.CH.CH and $CH_3$.CH.$CH_2$ fragments are very similar. E.g. the SCS for the CH proton in trans 1,2-dimethylcyclohexane vs. methylcyclohexane is -0.38 ppm, compared to the 2a proton in methylcyclohexane of -0.31ppm (Figure 1).

The methyl effect can be visualised somewhat differently as follows. In figure 2 the methyl SCS on the γ protons in some methyl-cyclohexanes and norbornanes are plotted against the Me-C-

C-H dihedral angle. It can be seen that for a dihedral angle of ca $60^0$ there is the same anomaly as noted above which means that the data cannot be fitted by any curve which is simply a function of the Me-C-C-H dihedral angle. In order to fit the data one must also take account of the different C-Me anisotropy effects, as well any H..H shielding from the protons on the methyl group to the ring protons. The former effect is shielding at a dihedral angle of 180° and deshielding at 60° while the H..H shielding effects are large at 0°, significant at 60°, but minimal beyond 90°.

For all the data in figure 2 the fragments under consideration are $CH_3$.CH(C).CH(C) or $CH_3$.CH(C).$CH_2$(C). While the 2a and 2e protons are both gauche to the methyl carbon (see figure 3) the 2a proton is also gauche to the ring carbon attached to the beta carbon (see (a)), but the 2e proton is trans (see (b)). With this distinction noted, all the data in Figure 2 can be fitted with a carbon gamma effect for the $CH_3$.CH.CH and $CH_3$.CH.$CH_2$ fragments which is a function of the two dihedral angles ($\theta$ and $\phi$). The approximation chosen is a simple $\cos\theta.\sin\phi$ function (eqn. 8).

$$q_H = A_1 \cos\theta.\sin\phi + k \qquad 0 < \theta < 90° \qquad (8)$$

$$q_H = A_2 \cos\theta.\sin\phi + k \qquad 90 < \theta < 180°$$

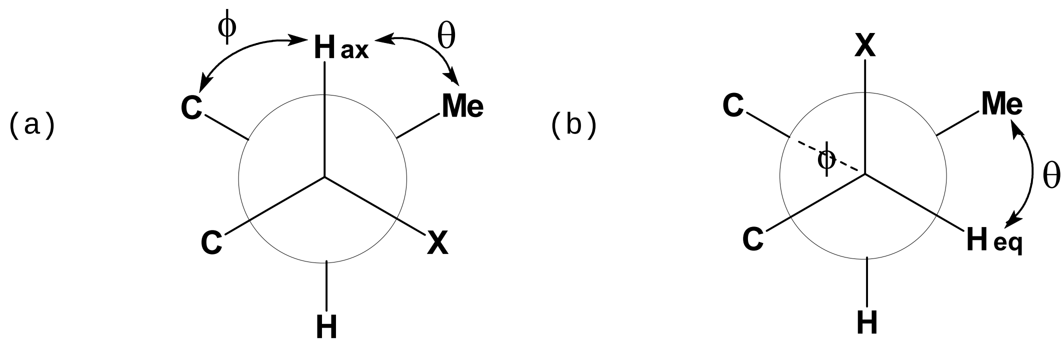



**Figure 3.** Definition of dihedral angles chosen to distinguish equatorial and axial gamma protons relative to an equatorial methyl substituent.

This function cannot be applied to the $CH_3.C_q.CH$ or $CH_3.C_q.CH_2$ fragments where $C_q$ is a quaternary carbon as the β carbon no longer possesses two different substituent atoms, hence a simpler function of θ only was used and this was taken as Bcosθ ( $\theta < 90°$ ) and Ccosθ ($\theta > 90°$ ).

These simple amendments were then included into the CHARGE scheme which was then paramaterised and tested on the observed proton chemical shifts of all the hydrocarbon data in ref. 1 plus a number of previously uncharacterised molecules of specific interest which were assigned in this work.

**Experimental.**

1,1-Dimethylcyclohexane, cis-decalin, 2,2-dimethylbutane, 2,3-dimethylbutane and 2,2,3-trimethylbutane were obtained from Aldrich Ltd. and a sample of 5α-androstane was kindly supplied by Glaxo Wellcome. 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 solutions and with a probe temperature of ca. 25 °C, and referenced to TMS. Typical conditions for proton spectra were 64 transients, spectral width 3,100 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. A 600 MHz $^1$H spectra of 5α-androstane in $CDCl_3$ and a HMQC plot of cis-decalin in $d_5$-pyridine at -40°C were both run on a Varian Unity 600 NMR Spectrometer.

*Assignments*. The proton chemical shifts of 2,2-dimethyl, 2,3-dimethyl and 2,2,3-trimethylbutane were obtained immediately by first order analysis and are given in table 1. The vicinal couplings to the methyl group in 2,2-dimethyl and 2,2,3-trimethylbutane were 7.52 and 6.85 Hz. respectively.

*1,1-Dimethylcyclohexane*. The $^1$H spectrum was run in a 50:50 mixture of $CFCl_3$:$CDCl_3$ and at 0°C the (average) shifts for the methyls and the 2H, 3H and 4H protons were immediately obtained as δ 0.879, 1.222, 1.430, and 1.371 respectively . At -80°C the ring inversion is in slow exchange and the individual shifts resolved with no further change observed to -90°C. The assignment of the axial or equatorial protons was made on the basis of the splitting patterns. Both the equatorial and axial methyl groups appeared as a single line at δ 0.871. The $H_{2a}$ pattern was distinctive with two large couplings ($^2J_{2a2e}$ and $^3J_{2a3a}$) and one small coupling ($^3J_{2a3e}$) in contrast to the $H_{3a}$ and $H_{4a}$ more complex multiplets. The $H_{4a}$ and $H_{4e}$ chemical shifts were distinguished by integration. The remaining $H_{2e}$ and $H_{3e}$ assignment was based upon a DQF-COSY[24] correlation run at -85°C. These assignments are given in table 2 and were confirmed by comparison with the average shifts of the room temperature spectrum.

*Cis-decalin.* The proton chemical shifts for cis-decalin used previously[1] were taken from the results of Grant et al.[25] . These investigations obtained $^2H$ spectra at room temperature which were averages of the shifts in the axial and equatorial positions due to rapid ring inversion. The assignments were based upon a regression analysis.

The proton shifts for a fixed conformation were obtained from the low temperature spectrum. In chloroform solution at room temperature the proton spectrum consists of three broad peaks at ca δ 1.65, 1.53 and 1.31 of intensity 1:4:4. On cooling to -40°C the spectrum was resolved and no further change was noted to -50°C. The axial and equatorial protons are distinguishable by their splitting patterns. This assignment was further helped by obtaining the spectrum in $d_5$-pyridine at -40°C. The low temperature 13-C spectrum has been completely assigned[26,27] thus the assignment was confirmed by a HET-CORR[24] experiment (400 MHz) and an HMQC plot (600 MHz.). The assignment is given in table 2 and the numbering used based upon that of Abraham et al.[26] shown in Figure 4.

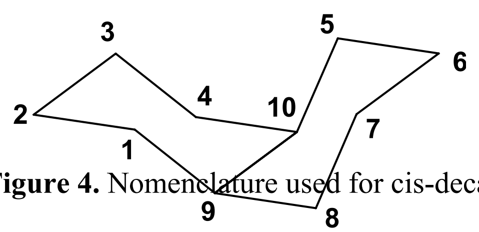



**Figure 4.** Nomenclature used for cis-decalin

The H(1a/5a) protons are to the low-field of the value in cyclohexane by about 0.4 ppm, probably because of their unusual 1,3 interactions to two axial $-CH_2-$ groups (C5 and C7). Conversely, the 1e,5e protons suffer a corresponding shielding effect of about 0.5 ppm due to the 'push-pull' effect. This assignment is unequivocal as observation of the low temperature spectra in pyridine solution show the 1-equatorial proton clearly resolved as a large doublet at δ 1.048, in contrast to the 1-axial multiplet at δ 1.586 shown in chloroform solution.

The 2a,6a and 2e,6e protons are close to the values in cyclohexane, and the 3a,7a to the three position in axial-methylcyclohexane[1] although the 3e,7e is unexpectedly shielded. The 4a,8a and 4e,8e protons could not be separated even in $d_5$-pyridine at 600 MHz. Indeed simple additive methyl SCS effects in cyclohexane[1] would suggest a shift difference of only about 0.03 ppm.

When the data for cis-decalin obtained here are averaged by the ring inversion process and these figures compared with the assignment of ref. 25 (adjusted to the numbering given in Figure 4) it is found that the assignments for 1,5a/4,8e, 1,5e/4,8a and the 9,10 (CH) protons are in agreement, but the assignment of ref. 25 for the 2,6/3,7 protons are now reversed.

*5α-Androstane.* HET-CORR correlations were used to determine the relative position of the protons based upon the 13-C assignments of Blunt et al.[28]. The 16α and β protons were thus distinguished, although the 4α, β/6α,β protons were indeterminate with only three correlations at δ 1.194, 1.229 and 1.258 resolved of the expected eight. The assignment of α or β position was based upon examination of the 1-D spectra (400 and 600MHz) and the DQF-COSY and COSY-LR[24] (mixing delay of 130 and 230ms) spectra.

The only clearly resolved protons at 400 MHz are the18-Me (δ 0.685, (t) J=0.80 Hz), 19-Me (δ 0.782, (d) J=0.73 Hz) and 9-CH (δ 0.678, (d,d,d) J=4.20, 10.50 and 12.38 Hz) protons. At 600 MHz the 5-CH (δ 1.024, complex multiplet); 12α (δ 1.09, (d,t) J=3.88, ca. 12.7 Hz); 8-CH (δ 1.28, (d,q) J=4.03, ca. 10.6 Hz); 17β (δ 1.39, (m)); 2β (δ 1.41, (d,d,d) J=1.96, 8.45, 11.82 Hz); 2α (δ 1.48, eq pattern); and 12β (δ 1.70, (d,d,d) J=2.78, 4.03, 12.31 Hz) protons are also distinguishable.

Both the assignments and the proton shifts obtained agree with those of Schneider et al.[29] ( table 5) . Further details of all the assignments plus spectra are given in ref. 30, along with full details of the geometry optimisations[23] at the RHF/6-31G* level.

## Results.

The above amendments to the theory were then tested on the data set of all the hydrocarbon shifts given in tables 1-5, a total of 188 shifts spanning 2.0 ppm.

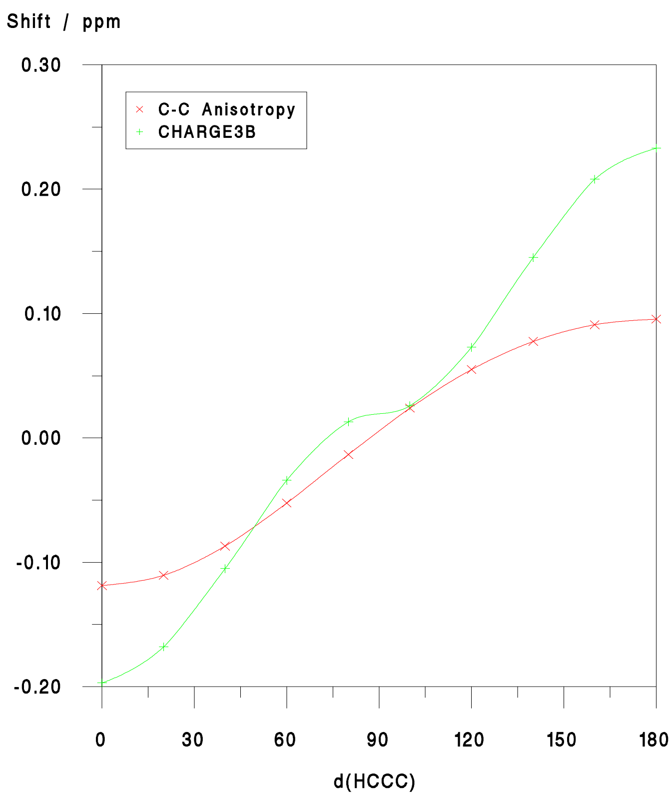



**Figure 5.** The shift contributions of the CHARGE3B carbon γ effect and the C-C anisotropy term for the methyl protons in propane as a function of the HCCC dihedral angle (θ)**.**

*The C-C anisotropy*. Paramaterisation of the anisotropy within the CHARGE3A scheme gave a ca. 15% improvement in the overall fit with a value of $\Delta\chi^{C\text{-}C}$ of 4.98 ppm $Å^3$ / molecule ($3.0 \times 10^{-6}$ $cm^3$ $mol^{-1}$). This value is in agreement with the results of Bothner-By et al.[4] and well within the limit specified by Bothner-By and Pople[15]. In contrast the CHARGE3B scheme showed no improvement with any value of $\Delta\chi^{C\text{-}C}$. On closer examination the improvement with CHARGE3A was found to be due mainly to the $C_\beta$-$C_\gamma$ bond contributions, with no change in the fit if the more distant C-C bonds were excluded. This explains why the CHARGE3B scheme shows no improvement since a $\cos\theta \times \text{abs} \cos\theta$ carbon $\gamma$ effect is implicit.

A comparison of the CHARGE3B carbon $\gamma$ effect and the C-C anisotropy term (Figure 5) shows that the former is much larger, although the shifts around a HCCC dihedral angle (θ) of 60° (the gauche orientation) and 120° are similar. In contrast the CHARGE3B $\gamma$ effect is more shielding in the eclipsed orientation ( $\theta = 0°$), and more deshielding for the trans or anti arrangement ( $\theta = 180°$).

*The methyl function*. The methyl functions as outlined in the last section were added to the CHARGE3A scheme with the C-C anisotropy term and all the parameters varied. For the $CH_3.CH(C).CH/CH_2$ fragment eqn. 8 gave good results for methylcyclohexanes and methylnorbornanes with values of $A_1$ of -0.38ppm, $A_2$ of -0.13ppm and k of 0.09ppm. However the effects from the isopropyl groups in the dimethyl and trimethyl butanes were not improved possibly due to the conformational averaging in these molecules. Thus the effects from isopropyl groups were left unchanged from the CHARGE3A scheme.

The $CH_3.C_q.CH/CH_2$ fragment cosθ function gave an optimised value for B ( $\theta < 90°$) approaching zero, with C of -0.29ppm ( $\theta > 90°$) deshielding as expected. Closer analysis revealed that for $\theta < 90°$ the $CH_3.C_q.CH$ fragment data points were shielding as expected, but the $CH_3.C_q.CH_2$ points deshielding. However, the limited data set precluded increasing the parameter set, and thus B was set to zero. The sum of the interactions for $\theta < 90°$ will invariably be shielding as the protons of the carbon connected to $C_\beta$ are delta to the protons under consideration, and thus there will be an H...H steric shielding contribution.

This function when applied to the effects from t-butyl groups ( t-Bu.CH and t-Bu.$CH_2$ fragments) produced erratic results. It is possible that the strain and resulting deformation of the acyclic t-butyl compounds (di-t-butylmethane, tri-t-butylmethane etc.) obscure the smaller methyl effect under consideration. Consequently, the carbon $\gamma$ effect from t-butyl was left unchanged.

The calculated proton chemical shifts from this modified scheme ( henceforth CHARGE4) of a number of acyclic and cyclic hydrocarbons are given in Tables 1 and 2, with the methyl SCS in cyclohexanes and bicyclo[2.2.1]heptanes in Tables 3 and 4. These calculated values include C-H electric field effects. The electric field calculations follow Zurcher's approach[19] but use the partial atomic charges given by CHARGE4 to directly calculate the substituent electric field at the proton. These are given in detail elsewhere[2] for fluorine SCS in which the electric field contribution is predominant but we note that the inclusion of these effects in the present calculations does not affect the fit of the data, but simply reduces the H...H steric contribution. The calculated shifts are compared also with those calculated by CHARGE3A.

**Table 1.** Observed vs. calculated proton chemical shifts (δ) of acyclic alkanes**.**

| Molecule | | Experimental[A] | CHARGE3A | CHARGE4 |
|---|---|---|---|---|
| Methane | $CH_4$ | 0.22 | 0.27 | 0.27 |
| Ethane | $CH_3$ | 0.86 | 0.80 | 0.80 |
| Propane | $CH_2$ | 1.30 | 1.30 | 1.30 |
| | $CH_3$ | 0.90 | 0.85 | 0.86 |
| Iso-butane | CH | 1.74 | 1.77 | 1.77 |
| | $CH_3$ | 0.89 | 0.95 | 0.90 |
| n-Butane[B,C] | $CH_2$ | 1.29 | 1.29 | 1.28 |
| | $CH_3$ | 0.89 | 0.85 | 0.89 |
| 2-Methylbutane[B,D] | CH | 1.45 | 1.72 | 1.62 |
| | $CH_2$ | 1.20 | 1.26 | 1.30 |
| | $CH_3$ (Et) | 0.86 | 0.85 | 0.87 |
| | $CH_3$ (iPr) | 0.87 | 0.90 | 0.90 |
| 2,2-Dimethylbutane[E] | $CH_2$ | 1.20 | 1.23 | 1.33 |
| | $CH_3$ | 0.82 | 0.85 | 0.83 |
| | $^t$Bu | 0.85 | 0.95 | 0.91 |
| 2,3-Dimethylbutane[E,F] | CH | 1.41 | 1.69 | 1.60 |
| | $CH_3$ | 0.83 | 0.90 | 0.88 |
| 2,2,3-Trimethylbutane[E] | CH | 1.38 | 1.60 | 1.48 |
| | $CH_3$ | 0.83 | 0.90 | 0.85 |
| | $^t$Bu | 0.83 | 0.95 | 0.89 |
| 2,2,3,3-Tetramethylbutane[G] | $^t$Bu | 0.87 | 0.95 | 0.87 |
| Neo-pentane | $CH_3$ | 0.93 | 0.95 | 0.92 |
| Di-t-butyl-methane | $CH_2$ | 1.23 | 0.90 | 1.26 |
| | $^t$Bu | 0.97 | 0.95 | 0.89 |
| 1,1-Di-t-butyl-ethane | CH | 1.18 | 1.39 | 1.20 |
| | $CH_3$ | 0.86 | 0.90 | 0.77 |
| | $^t$Bu | 0.98 | 0.95 | 0.87 |
| 2,2-Di-t-butyl-propane | $CH_3$ | 0.83 | 0.95 | 0.79 |
| | $^t$Bu | 0.99 | 0.95 | 0.83 |
| Tri-t-butyl-methane | CH | 1.38 | 1.15 | 0.94 |
| | $^t$Bu | 1.22 | 0.95 | 0.83 |

[A] Data from Ref. 1 except where stated. [B] Ref. 31. [C] Calculated from weighted trans:gauche butane, Ref. 32. [D] Gauche conformer. [E] Shifts this work. [F] Weighted , Ref. 33. [G] Ref. 34.

**Table 2.** Observed vs. calculated proton chemical shifts (δ) of cyclic alkanes.

| Molecule | | Experimental[A] | CHARGE3A | CHARGE4 |
|---|---|---|---|---|
| Cyclopentane | $CH_2$ | 1.51 | 1.56 | 1.49 |
| Cyclohexane | ax | 1.19 | 1.10 | 1.11 |
| | eq | 1.68 | 1.64 | 1.69 |
| Norbornane | 1,4 (CH) | 2.19 | 2.07 | 1.92 |
| | endo | 1.16 | 1.26 | 1.30 |
| | exo | 1.47 | 1.53 | 1.50 |
| | 7a,s | 1.18 | 1.45 | 1.30 |
| Bicyclo[2.2.2]octane | | | | |
| | CH | 1.50 | 2.07 | 2.02 |
| | $CH_2$ | 1.50 | 1.42 | 1.44 |
| Trans-decalin | | | | |
| | 1,4,5,8a | 0.93 | 0.88 | 1.02 |
| | 1,4,5,8e | 1.54 | 1.39 | 1.63 |
| | 2,3,6,7a | 1.25 | 1.16 | 1.17 |
| | 2,3,6,7e | 1.67 | 1.64 | 1.75 |
| | 9,10 (CH) | 0.88 | 0.88 | 0.87 |
| Cis-decalin[B] | | | | |
| | 1,5a | 1.59 | 0.96 | 1.13 |
| | 1,5e | 1.18 | 1.03 | 1.24 |
| | 2,6a | 1.19 | 1.11 | 1.13 |
| | 2,6e | 1.70 | 1.64 | 1.69 |
| | 3,7a | 1.32 | 1.03 | 1.20 |
| | 3,7e | 1.38 | 1.49 | 1.60 |
| | 4,8a | 1.45 | 1.30 | 1.36 |
| | 4,8e | 1.45 | 1.31 | 1.58 |
| | 9,10 (CH) | 1.64 | 1.51 | 1.52 |
| Perhydro-phenalene | | | | |
| | 1,3,4,6,7,9a | 0.95 | 0.86 | 1.03 |
| | 1,3,4,6,7,9e | 1.57 | 1.38 | 1.66 |
| | 2,5,8a | 1.29 | 1.21 | 1.20 |
| | 2,5,8e | 1.65 | 1.64 | 1.78 |
| | 10-12 (CH) | 0.96 | 0.96 | 0.90 |
| | 13 (CH) | 0.32 | 0.38 | 0.39 |
| Perhydro-anthracene | | | | |
| | 1,4,5,8a | 0.95 | 0.89 | 1.05 |
| | 1,4,5,8e | 1.56 | 1.39 | 1.65 |
| | 2,3,6,7a | 1.23 | 1.16 | 1.19 |
| | 2,3,6,7e | 1.67 | 1.64 | 1.77 |
| | 9,10a | 0.72 | 0.66 | 0.93 |
| | 9,10e | 1.43 | 1.14 | 1.56 |
| | 11-14 (CH) | 0.91 | 0.89 | 0.92 |

| | | | | |
|---|---|---|---|---|
| Adamantane | CH | 1.87 | 2.07 | 1.98 |
| | $CH_2$ | 1.75 | 1.22 | 1.35 |
| | | | | |
| Bornane[C] | 2n | 1.23 | 0.90 | 0.97 |
| | 2x | 1.49 | 1.52 | 1.53 |
| | 3n | 1.13 | 0.84 | 1.09 |
| | 3x | 1.71 | 1.68 | 1.80 |
| | 4 (CH) | 1.60 | 2.12 | 1.75 |
| | 7,8-$CH_3$ | 0.83 | 0.95 | 0.82 |
| | 10-$CH_3$ | 0.83 | 0.95 | 0.99 |
| | | | | |
| Tertiary-butylcyclohexane | | | | |
| | 1a (CH) | 0.94 | 1.08 | 1.00 |
| | 1-$^t$Bu | 0.83 | 0.95 | 0.93 |
| | 2,6a | 0.91 | 0.73 | 0.90 |
| | 2,6e | 1.75 | 1.55 | 1.85 |
| | 3,5a | 1.19 | 1.11 | 1.09 |
| | 3,5e | 1.75 | 1.64 | 1.70 |
| | 4a | 1.08 | 1.09 | 1.13 |
| | 4e | 1.64 | 1.64 | 1.72 |
| | | | | |
| Cis-4-$^t$Butyl-methylcyclohexane[D] | | | | |
| | 1a-$CH_3$ | 0.86 | 0.90 | 0.83 |
| | 1e (CH) | 1.90 | 1.97 | 2.00 |
| | 2,6a | 1.45 | 1.25 | 1.37 |
| | 2,6e | 1.49 | 1.53 | 1.55 |
| | 3,5a | 1.17 | 0.98 | 1.09 |
| | 3,5e | 1.49 | 1.38 | 1.70 |
| | 4a (CH) | 0.93 | 1.03 | 1.00 |
| | 4e-$^t$Bu | 0.84 | 0.95 | 0.93 |
| | | | | |
| Trans-4-$^t$Butyl-methylcyclohexane[D] | | | | |
| | 1a (CH) | 1.24 | 1.35 | 1.36 |
| | 1e-$CH_3$ | 0.86 | 0.90 | 0.99 |
| | 2,6a | 0.93 | 1.02 | 0.79 |
| | 2,6e | 1.73 | 1.58 | 1.59 |
| | 3,5a | 0.93 | 0.79 | 0.94 |
| | 3,5e | 1.73 | 1.55 | 1.87 |
| | 4a (CH) | 0.95 | 1.06 | 1.01 |
| | 4e-$^t$Bu | 0.84 | 0.95 | 0.94 |
| | | | | |
| 1,1-Dimethylcyclohexane[B] | | | | |
| | 1a-$CH_3$ | 0.87 | 0.95 | 0.82 |
| | 1e-$CH_3$ | 0.87 | 0.95 | 0.99 |
| | 2,6a | 1.09 | 1.02 | 1.17 |

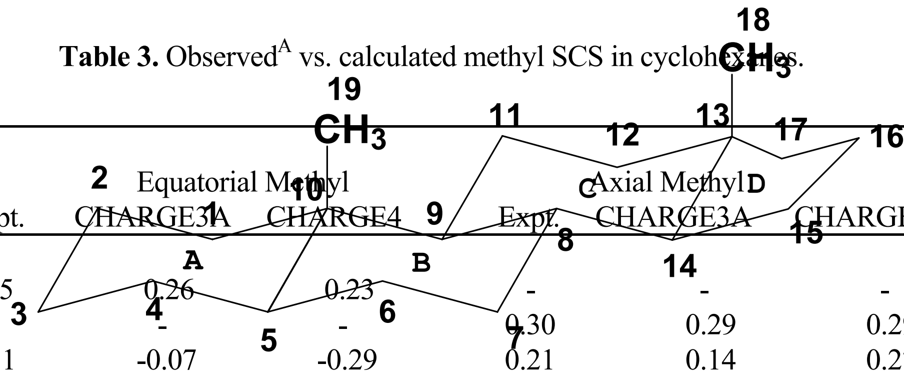
| | | | | |
|---|---|---|---|---|
| | 2,6e | 1.32 | 1.48 | 1.29 |
| | 3,5a | 1.36 | 1.33 | 1.37 |
| | 3,5e | 1.48 | 1.45 | 1.54 |
| | 4a | 1.04 | 1.07 | 1.13 |
| | 4e | 1.65 | 1.64 | 1.71 |
| Trans-1,2-dimethylcyclohexane[D] | | | | |
| | 1,2a (CH) | 0.94 | 1.30 | 1.09 |
| | 1,2e-$CH_3$ | 0.88 | 0.90 | 0.93 |
| | 3,6a | 0.88 | 1.07 | 0.84 |
| | 3,6e | 1.63 | 1.48 | 1.55 |
| | 4,5a | 1.21 | 1.16 | 1.17 |
| | 4,5e | 1.66 | 1.64 | 1.74 |
| Cis-1,3-dimethylcyclohexane[D] | | | | |
| | 1,3a (CH) | 1.34 | 1.40 | 1.38 |
| | 1,3e-$CH_3$ | 0.86 | 0.90 | 0.98 |
| | 2a | 0.54 | 0.93 | 0.53 |
| | 2e | 1.63 | 1.49 | 1.45 |
| | 4,6a | 0.76 | 1.02 | 0.84 |
| | 4,6e | 1.63 | 1.58 | 1.61 |
| | 5a | 1.25 | 1.21 | 1.17 |
| | 5e | 1.69 | 1.64 | 1.74 |
| Trans-1,4-dimethylcyclohexane[D] | | | | |
| | 1,4a (CH) | 1.26 | 1.01 | 1.24 |
| | 1,4e-$CH_3$ | 0.86 | 0.90 | 1.00 |
| | 2,3,5,6a | 0.90 | 0.90 | 0.80 |
| | 2,3,5,6e | 1.65 | 1.55 | 1.57 |
| Cis,cis-1,3,5-trimethylcyclohexane[D] | | | | |
| | 1,3,5a (CH) | 1.39 | 1.36 | 1.37 |
| | 1,3,5e-$CH_3$ | 0.86 | 0.90 | 0.99 |
| | 2,4,6a | 0.47 | 1.02 | 0.60 |
| | 2,4,6e | 1.61 | 1.49 | 1.48 |
| Trans-cis-1,3,5-trimethylcyclohexane | | | | |
| | 1-$CH_3$ | 0.97 | 0.90 | 0.88 |
| | 1e (CH) | 2.02 | 1.97 | 2.02 |
| | 2,6a | 1.02 | 1.14 | 1.10 |
| | 2,6e | 1.43 | 1.45 | 1.45 |
| | 3,5a (CH) | 1.61 | 1.62 | 1.52 |
| | 3,5-$CH_3$ | 0.83 | 0.90 | 0.98 |
| | 4a | 0.48 | 0.86 | 0.51 |
| | 4e | 1.60 | 1.64 | 1.45 |

[A] Data from Ref. 1 except where stated. [B] This work. [C] Ref. 35. [D] Ref. 22.

The importance of the methyl function can be seen in the much improved agreement in the methyl-cyclohexanes. E.g. $H_{2a}$ in cis-1,3-dimethylcyclohexane (obs. 0.54, calc. 0.53 cf. CHARGE3A of 0.93ppm), $H_{2,4,6a}$ in cis,cis-1,3,5-trimethylcyclohexane, and $H_{4a}$ proton in trans,cis-1,3,5-trimethylcyclohexane (obs. 0.48 ppm, calc. 0.51ppm) in contrast to the CHARGE3A value of 0.86ppm. The improvement in the scheme is also apparent in the methyl SCS values for substituted cyclohexanes (table 3) in which the CHARGE4 scheme fits the 2a and 2e protons SCS in methylcyclohexane with an rms of only 0.06ppm versus 0.14ppm for the CHARGE3A scheme. Further the SCS of the 3-endo and 3-exo protons in endo-methyl and exo-methyl norbornane (table 4) are in much better agreement with the observed values.

In principle a more complex methyl function could be applied, although it is unclear whether any such function reflects an intrinsic through bond charge effect or merely accounts for possible deficiencies in the chosen scheme.

**Table 3.** Observed[A] vs. calculated methyl SCS in cyclohexanes.




| Proton | Equatorial Methyl | | | Axial Methyl | | |
|---|---|---|---|---|---|---|
| | Expt. | CHARGE3A | CHARGE4 | Expt. | CHARGE3A | CHARGE4 |
| 1a | 0.15 | 0.26 | 0.23 | - | - | - |
| 1e | - | - | - | 0.30 | 0.29 | 0.29 |
| 2a | -0.31 | -0.07 | -0.29 | 0.21 | 0.14 | 0.27 |
| 2e | -0.03 | -0.09 | -0.12 | -0.20 | -0.11 | -0.15 |
| 3a | 0.02 | 0.00 | 0.03 | 0.13 | 0.25 | 0.19 |
| 3e | 0.00 | 0.06 | 0.02 | -0.15 | -0.16 | -0.15 |
| 4a | -0.08 | 0.00 | 0.03 | 0.00 | -0.03 | 0.01 |
| 4e | 0.01 | 0.00 | 0.03 | 0.00 | 0.00 | -0.01 |
| Me[B] | 0.86 | 0.90 | 0.98 | 0.93 | 0.90 | 0.82 |

[A] Data from Ref. 36. [B] Methyl shift.

**Table 4.** Observed[A] vs. calculated methyl SCS in norbornanes**.**

| Proton | 2-Exo-methyl | | | 2-Endo-methyl | | |
|---|---|---|---|---|---|---|
| | Expt. | CHARGE3A | CHARGE4 | Expt. | CHARGE3A | CHARGE4 |
| 1 | -0.37 | -0.07 | -0.23 | -0.21 | 0.03 | -0.02 |
| 2n | 0.33 | 0.11 | 0.12 | - | - | - |
| 2x | - | - | - | 0.42 | 0.05 | 0.08 |
| 3n | 0.26 | 0.18 | 0.18 | -0.63 | -0.21 | -0.52 |
| 3x | -0.54 | -0.27 | -0.56 | 0.27 | 0.19 | 0.18 |
| 4 | -0.03 | 0.01 | 0.01 | -0.08 | 0.00 | 0.03 |
| 5n | -0.06 | 0.06 | 0.07 | -0.08 | -0.08 | -0.08 |
| 5x | -0.03 | 0.00 | 0.03 | 0.01 | -0.01 | 0.01 |
| 6n | -0.02 | 0.03 | -0.04 | 0.39 | 0.55 | 0.43 |
| 6x | 0.01 | -0.03 | 0.01 | -0.20 | -0.36 | -0.31 |
| 7a | -0.15 | -0.17 | -0.14 | 0.07 | -0.04 | 0.01 |
| 7s | 0.15 | 0.14 | 0.13 | 0.15 | -0.02 | 0.00 |
| Me[B] | 0.86 | 0.90 | 0.93 | 0.93 | 0.90 | 0.89 |

[A] Data from Ref. 1. [B] Methyl shift.

**Figure 6.** Nomenclature used for 5α-androstane

5α-Androstane has been included as a test of the general applicability of the scheme to the important class of compounds of steroids, and to determine the importance of long range effects, e.g. whether the C ring effects the proton chemical shifts in the A ring.

The geometry of the flexible 5-membered D ring was obtained using ab initio calculations at the RHF/6-31G* level of theory. However, the exact conformation in solution of the unsubstituted ring has not been analysed and may be different to the calculated 13-envelope (C14, C15, C16 and C17 are more or less in a plane with only a 9.5° twist). This may effect the calculated shifts of these protons which have thus been excluded from paramaterisation in the data set.

It can be seen in Table 5 that the improvement from the CHARGE3A to CHARGE4 scheme is appreciable. In particular the calculated values, marked in italics, of the 5, 9 and 14 β-CH protons (which all contain the $CH_3.C_q.CH$ fragment) are greatly improved. The rest of the calculated shifts are also in good agreement with the experimental data.

The effect of the geometry on the calculated shifts was considered by comparing the results using the ab initio geometry with an adapted crystal structure. We were unable to find crystal data for the unsubstituted 5α-androstane, so the data for 5α-androstane-3β,17β-diol monohydrate[37] was used removing the water molecule and replacing the hydroxyl groups with a proton. The rms variation in the calculated values using the two geometries was 0.09 ppm, the greatest deviation being seen for the 11β and 17α protons of -0.18 and 0.30 ppm respectively.

**Table 5.** Observed vs. calculated proton chemical shifts for 5α-androstane**.**

| Proton | Experimental | | Calculated | |
|---|---|---|---|---|
| | Ref. 29 | This work | CHARGE3A | CHARGE4 |
| 1α | 0.89 | 0.87 | 0.52 | 0.91 |
| 1β | 1.66 | 1.67 | 0.91 | 1.53 |
| 2α | 1.50 | 1.48 | 1.39 | 1.54 |
| 2β | 1.41 | 1.41 | 1.39 | 1.49 |
| 3α | 1.23 | 1.21 | 1.12 | 1.17 |
| 3β | 1.67 | 1.67 | 1.64 | 1.75 |
| 4α | 1.22* | 1.22* | 1.13 | 1.37 |
| 4β | 1.22±0.04* | 1.22* | 1.03 | 1.39 |
| 5 (CH) | 1.06 | 1.02 | *0.47* | *1.00* |
| 6α | 1.22* | 1.22* | 0.98 | 1.38 |
| 6β | 1.22±0.04* | 1.22* | 1.42 | 1.52 |
| 7α | 0.93 | 0.91 | 0.67 | 0.75 |
| 7β | 1.69 | 1.68 | 1.76 | 2.00 |
| 8 (CH) | 1.29 | 1.28 | 1.24 | 1.34 |
| 9 (CH) | 0.69 | 0.68 | *0.00* | *0.72* |
| 11α | 1.55 | 1.53 | 0.60 | 1.42 |
| 11β | 1.26 | 1.26 | 1.11 | 1.43 |
| 12α | 1.10 | 1.09 | 0.78 | 1.25 |
| 12β | 1.71 | 1.70 | 1.60 | 1.60 |
| 14 (CH) | 0.90 | 0.89 | *0.38* | *0.82* |
| 15α | 1.65 | 1.63 | 1.42 | 1.64 |
| 15β | 1.15 | 1.14 | 1.33 | 1.42 |
| 16α | 1.56* | 1.58* | 1.56 | 1.58 |
| 16β | 1.56±0.16* | 1.61* | 1.49 | 1.57 |
| 17α | 1.13 | 1.12 | 1.02 | 1.42 |
| 17β | 1.42 | 1.39 | 1.56 | 1.52 |
| 18-Me | 0.69 | 0.69 | 0.95 | 0.73 |
| 19-Me | 0.79 | 0.78 | 0.95 | 0.70 |

* Unresolved.

## Discussion.

Over the 188 parameterised data points, including some of those in androstane an rms of only 0.11ppm is obtained, significantly improved from the CHARGE3A scheme ( 0.19ppm).

This improvement from the CHARGE3A to CHARGE4 scheme of ca. 40% is remarkable considering the latter effectively contains only two more variables. The four additional methyl variables $A_1$, $A_2$, C and k are balanced by a reduction of the H..H steric parameters. The effect for a CH proton shielding a CH proton ($CH \rightarrow CH$) or a CH proton shielding a $CH_2$ proton ($CH \rightarrow CH_2$) has been equalised. Similarly, the H..H steric interactions from $CH_2$ and $CH_3$ protons on CH or $CH_2$ protons are the same i.e. $CH_2 \rightarrow CH = CH_2 \rightarrow CH_2$ and $CH_3 \rightarrow CH = CH_3 \rightarrow CH_2$. Indeed, the reduction in the steric parameters in the CHARGE4 scheme resulted in a worsening of the rms by less than 0.01 ppm. Further such fine distinctions may have been questionable when applied to H..H shielding effects in heterocyclic systems.

$$\delta_{steric} = a_s\,(1/r^6 - 1/r_{min}^6) \qquad (9)$$

The paramaterised values of the steric coefficients ($a_s$) of eqn. 9 for H..H shielding interactions are: $r_{min}$ (H..H) = 3.190Å, $a_s$ (CH→CH/CH2) = -55.0, $a_s$ (CH2→CH/CH2) = -49.0, $a_s$ (CH3→CH/CH2) = -29.0 (all the H..H steric effects on methyl protons are zero); and for the C..H deshielding interactions are: $r_{min}$ (C..H) = 3.345Å, $a_s$ (C→CH) = 270.0, $a_s$ (C→CH2) = 345.0, $a_s$ (C→CH3) = 165.0 .

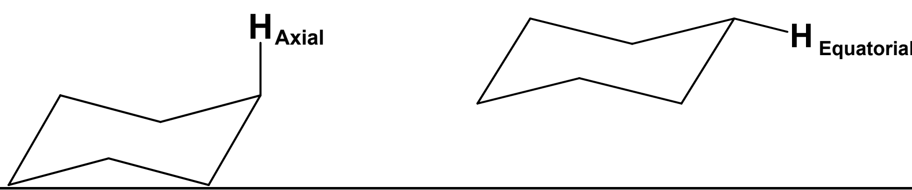
The new variable $\Delta\chi^{C\text{-}C}$ optimises to a reasonable value of $3.0 \times 10^{-6}$ $cm^3$ $mol^{-1}$. The C-H linear electric field follows Zurcher[19] treatment but is based upon partial atomic charges calculated within the CHARGE4 scheme. This term has no bearing on the fit of the scheme per se, but reduces the H..H steric contribution.

It is of some interest to consider the underlying rationale of the $\gamma$ methyl effect (eqn. 8). We suggest the asymmetry of the equation is related to the chiral nature of the attached carbon atom (i.e. Me.<u>C</u>.C.H). This explains why the equation does not hold for isopropyl groups where the relevant carbon is no longer chiral. Similarly, the simpler $\cos\theta$ equation for Me.$C_q$.CH/$CH_2$ fragments does not operate for t-butyl groups where now the $\beta$ carbon substituents are identical (i.e. all methyls).

This asymmetry may be due to the unusual magnetic anisotropy of the $C_\beta$–$C_{Me}$ bond or more probably to the asymmetry in the electron distribution around the $\beta$ carbon atom influencing the adjacent hydrogen. Further theoretical studies which are outside the scope of this manuscript are required to substantiate these suggestions.

The contributions to the chemical shifts of the protons in cyclohexane from the CHARGE4 scheme are given in Figure 7. The difference between the axial and equatorial protons is multi-functional, with contributions caused by H..H steric, C-C anisotropy and C-H electric field effects. The axial proton is shielded by two protons at the 3,5 axial positions by approximately the same amount as the sum of the magnetic anisotropy from the $C_\beta$-$C_\gamma$ and $C_\gamma$-$C_\delta$ bonds, with a smaller electric field component. Meanwhile, the equatorial proton has no steric or electric field interactions but is deshielded by the C-C anisotropy effects.

**Figure 7.** Contributions to the calculated shifts of the protons in cyclohexane.




| | CHARGE4 | CHARGE4 |
|---|---|---|
| CHARGE | 1.550 | 1.550 |
| H..H STERIC | -0.188 | 0.000 |
| C..H STERIC | 0.000 | 0.000 |
| ANISOTROPY | -0.168 | 0.141 |
| C-H LINEAR ELECTRIC FIELD | -0.086 | 0.000 |
| TOTAL | 1.107 | 1.691 |
| EXPERIMENTAL | 1.19 | 1.68 |

Experimental data from Table 2.

Despite the success of the scheme at predicting the proton chemical shifts of a wide variety of hydrocarbons, certain anomalies remain e.g. cyclopropane and cyclobutane are anomalous, but in the opposite direction. Both ring currents[38] and additional bond anisotropies in these systems have been suggested in an attempt to account for these anomalies.

In summary, the CHARGE4 scheme predicts the proton chemical shifts of alkanes to within 0.11ppm in such diverse systems as androstanes and methyl-norbornanes, and this programme should be applicable to a wide range of substituted alkanes.

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