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Substituent chemical shifts (in NMR spectroscopy

Part 11†. Does C—C bond anisotropy contribute to proton chemical shifts?‡

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ABSTRACT: A previous model for the calculation of proton chemical shifts in substituted alkanes based upon partial atomic charges and steric interactions has been modified by the replacement of the C—C bond anisotropy term with an orientation-dependent γ effect (i.e. $C\cdot C\cdot C\cdot H$). The new scheme (CHARGE5) predicts the proton chemical shifts of a variety of acyclic, cyclic and polycyclic hydrocarbons over 188 data points spanning 2 ppm to within <0.1 ppm, an improvement over the previous model with three fewer variable parameters. Systems considered include cyclobutanes, cyclopentanes, cyclohexanes, norbornanes, *cis*- and *trans*-decalin, perhydrophenalene, anthracene, adamantane, androstane, methylbutanes and *tert*-butylmethanes. The significance of these results is discussed with respect to the development of a comprehensive theory of proton chemical shifts and it is concluded that C—C bond anisotropy does not in general contribute significantly to proton chemical shifts, although a possible specific shielding effect in planar eclipsed $C\cdot C\cdot C\cdot C$ fragments is noted. © 1998 John Wiley & Sons, Ltd.

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INTRODUCTION

One of the most striking features concerning the theoretical foundation of magnetic resonance is that, although proton spectra were the first to be used by the general chemist and constitute the beginner's introduction to NMR in every college, there is still no generally accepted quantitative explanation of proton chemical shifts. The recent quantum mechanical calculations of nuclear chemical shifts[2] have not proved successful for protons and proton databases[3a] have not achieved the same success as the comparable C-13 databases. The most useful methods for predicting proton chemical shifts remain the simple linear models[3b] for olefinic, aromatic and alkane protons in which there are no stereochemical effects.

Some time ago, Gasteiger and Marsili[4] and Abraham and Grant[5] in the CHARGE2 scheme noted a remarkably good correlation between the proton chemical shifts of substituted alkanes and the charge densities on the protons as calculated by their semi-empirical modelling schemes. This was all the more striking as the charge densities were calculated by electronegativity equalization[4] and by reference to the experimental dipole moments,[5] i.e. both schemes were completely independent of NMR.

Encouraged by this good agreement, we began a study to extend this correlation to construct a simple computational model based on the CHARGE2 program capable of predicting proton chemical shifts to an experimentally useful degree of accuracy, say 0.1 ppm. The parameterization in CHARGE2 was first modified to produce more accurate chemical shifts for substituted methanes and ethanes. The long-range effects of substituents on proton chemical shifts were then considered.[6] Theoretical analysis based on FPT/INDO theory showed that H–H steric effects are shielding at the protons in contrast to X–H steric interactions which are deshielding. In addition, there was experimental evidence for a large orientational effect of the methyl group in a $CH_3\cdot C\cdot C\cdot H$ fragment in that the γ proton is shielded in the *gauche* orientation but deshielded in the *trans* (*anti*) orientation. These interactions were included in the program using both a non-orientational dependent γ effect (CHARGE3A) and an explicit orientational γ effect (CHARGE3B). Both schemes gave similar agreement with the data for the available proton chemical shifts at that time.

Other possible mechanisms influencing proton chemical shifts were then considered. A detailed analysis of the proton chemical shifts of fluoro-substituted alkanes based on electric field theory gave complete agreement with the observed substituent chemical shift (SCS), thus fully confirming the theoretical basis of the electrical field model.[7] This was then incorporated into the CHARGE program.

A similar analysis of the proton chemical shifts of some chloro-, bromo- and iodo-substituted alkanes in terms of the above electric field model plus steric effects

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also gave calculated shifts in good agreement with the observed shifts, although in the case of the bromo and iodo substituents additional electronic effects were identified.[8]

The SCSs induced by the polar and magnetically anisotropic carbonyl group have also been collated and analysed and shown to be quantitatively explained in terms of a non-axially symmetric anisotropy together with the electric field effect.[9] Hence the major interactions invoked in explaining proton chemical shifts have been identified and quantified, with one exception.

One other possible contribution to proton chemical shifts is the C—C bond anisotropy. This was suggested by Moritz and Sheppard[10] in the early days of NMR as a possible explanation of the difference between the axial and equatorial proton shifts in cyclohexane. However, explanations based on this interpretation usually required a value of the C—C anisotropy in excess of that theoretically allowed in order that the magnetic susceptibility in any direction be diamagnetic (see Ref. 11 for a full discussion). The introduction of the C—C anisotropy term into the CHARGE program was therefore considered in detail using the standard McConnell equation:[12]

$$\delta_{\text{anisot}} = \Delta\chi^{\text{C-C}}(1 - 3\cos^2\phi)/3r^3 \qquad (1)$$

where $\Delta\chi^{\text{C-C}}$ is the anisotropy of the C—C bond and r and ϕ the distance and angle, respectively, of the proton from the C—C bond considered. It was found that the addition of the C—C anisotropy term to the CHARGE3A program in which there was no orientation dependent γ effect greatly improved the quality of the results and this new scheme (CHARGE4) is the best available calculation at present.[13] The value of the C—C bond anisotropic susceptibility found was also well below the theoretical limit supporting this procedure. However, when the C—C anisotropy term was included in CHARGE3B, in which there was already an explicit orientation-dependent γ effect, there was no better agreement with the observed data.

It is clear, therefore, that an orientation-dependent $\text{C}\cdot\text{C}\cdot\text{C}\cdot\text{H}$ effect is necessary to reproduce the observed proton chemical shifts in hydrocarbons but the central question is whether this is due to the C—C bond anisotropy or is simply an electronic effect. This becomes even more relevant when it is realized that the experimental and theoretical basis for the C—C anisotropy term as it is currently presented is open to question. Equation (1) assumes axial symmetry along the C—C bond and the measured anisotropy in ethane which, of course, has a threefold axis of symmetry agrees with this.[11] However, C—C bonds in organic compounds do not in general possess axial symmetry (e.g. the diamond structure cannot be magnetically anisotropic by symmetry). Hence there is no good reason to assume this symmetry in the calculations. Apsimon *et al.*[14] using a more complex equation involving two axes of anisotropy, did not achieve any better results and in addition it has been stated that for these dipolar equations to be valid the distances involved must be several times the bond lengths.[11] This would invalidate all explanations involving the C_β—C_γ bonds.

It therefore seemed of interest to determine whether the proton chemical shifts in the large hydrocarbon data set now available could be reproduced without involving C—C anisotropy and whether this would give better agreement than previously. We examine this question in detail here and we shall show that the use of a simple orientation-dependent carbon γ effect, when parameterized, gives in general better agreement than the CHARGE4 scheme over this wide range of hydrocarbons. The significance of this result will be discussed in the context of present theories of proton chemical shifts.

THEORY

As the theory has been detailed previously,[1] only a brief summary of the latest version (CHARGE4) is given here. The CHARGE scheme 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 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 K and a γ effect from atom L.

The charge (q_I) on atom I resulting from atom J is given by the equation

$$q_\text{I}(\alpha) = (E_\text{J} - E_\text{I})/A(\text{I, J}) \qquad (2)$$

where E_J and E_I are the electronegativities of atoms I and J and $A(\text{I, J})$ is a constant dependent on the exchange and overlap integrals for the I—J bond. In CHARGE there is a set of parameters $A(\text{I, J})$ for all the bonding pairs under consideration.

The β effect is the influence of atom K on atom I and is proportional to both the electronegativity of atom K and the polarizability of atom I. Taking the electronegativity of hydrogen as a base, the β effect is defined by

$$q_\text{I}(\beta) = (E_\text{K} - E_\text{H})P_\text{I}/c \qquad (3)$$

where c is a constant.

In order to account for the variation of polarizability with charge, the β effect calculation is carried out iteratively, according to Eqn (4), where P_I is the polarizability of atom I with charge q_I and $P_\text{I}{}^0$ and $q_\text{I}{}^0$ are the corresponding initial values:

$$P_\text{I} = P_\text{I}{}^0[1.0 + 3.0(q_\text{I}{}^0 - q_\text{I})]$$

for $q_\text{I} > q_\text{I}{}^0$

$$P_\text{I} = P_\text{I}{}^0 \exp[-b(q_\text{I}{}^0 - q_\text{I})] \qquad (4)$$

The γ effect of any substituent is given by Eqn (5), which is the product of the probabilities of the atoms involved:

$$q_\text{I}\gamma(\gamma) = 0.0050 P_\text{I} P_\text{I}{}^0 \qquad (5)$$

However the important carbon γ effect (i.e. $\text{C}\cdot\text{C}\cdot\text{C}\cdot\text{H}$) is parameterized separately and is constant for any

$C \cdot C \cdot CH$, $C \cdot C \cdot CH_2$ or $C \cdot C \cdot CH_3$ interaction. The substituent effect of the methyl group was considered separately. For the molecular fragments $CH_3 \cdot CH(C) \cdot CH(C)$ or $CH_3 \cdot CH(C) \cdot CH_2(C)$ the experimental data were fitted with a carbon γ effect which is a function of both the $CH_3 \cdot C \cdot C \cdot H$ dihedral angle (θ) and the $C \cdot C \cdot C \cdot H$ dihedral angle (ϕ). The approximation chosen was a simple $\cos\theta \sin\phi$ function:

$$q_H = A_1 \cos\theta \sin\phi + k \qquad 0 < \theta < 90^\circ$$
$$q_H = A_2 \cos\theta \sin\phi + k \qquad 90 < \theta < 180^\circ \qquad (6)$$

For the $CH_3 \cdot C_q \cdot CH$ or $CH_3 \cdot C_q \cdot CH_2$ fragments, where C_q is a quaternary carbon and no longer possesses two different substituent atoms, a simpler function of θ only was used and this was taken as $B \cos\theta$ ($\theta < 90^\circ$) and $C \cos\theta$ ($\theta > 90^\circ$).

The total charge is given by Eqn (7) and the partial atomic charges (q) converted to shift values using Eqn (8):

$$q_I = q_I(\alpha) + q_I(\beta) + q_I(\gamma) \qquad (7)$$

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

The effects of more distant atoms on the proton chemical shifts were considered to be due to steric, anisotropic and electric field contributions. $H \cdots H$ steric interactions were found to be shielding and $X \cdots H$ ($X = C$, F, Cl, Br, I) interactions deshielding according to the equation

$$\delta_{\text{steric}} = a_S(1/r^6 - 1/r^6_{\text{min}})$$
$$\delta_{\text{steric}} = 0 \quad \text{for } r \geqslant r_{\text{min}} \qquad (9)$$

where r_{min} is the sum of the van der Waal's radii of the interacting atoms. Equation (9) has a cut-off at $r = r_{\text{min}}$, thus preventing a large number of very small contributions being calculated. Further, any $X \cdots H$ steric contributions on a methylene or methyl proton resulted in a push–pull effect (shielding) on the other proton(s) on the attached carbon.

The C—C anisotropy was included using Eqn (1) 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. $H—C_\alpha—C_\beta$).

Finally, the effects of the electric field of the C—H bonds, although small, are significant and were calculated from the equation

$$\delta_{\text{el}} = A_Z E_Z \qquad (10)$$

where A_Z is a constant and E_Z the component of the electric field along the C—H bond given by the procedure in Ref. 7. In CHARGE4 these contributions were cutoff at the same value of r_{min} as the steric term. These contributions were then added to the shifts of Eqn (8) to give the calculated shift:

$$\delta_{\text{total}} = \delta_{\text{charge}} + \delta_{\text{steric}} + \delta_{\text{anisotropy}} + \delta_{\text{el}} \qquad (11)$$

The modifications to the above scheme to be evaluated here are as follows. The C—C anisotropy contribution is now replaced by an orientation-dependent $C_\beta—C_\gamma$ term. It was found that a simple $\cos\theta$ term gave answers identical with those from the $\cos^2\theta$ function used previously[6] and therefore the carbon γ effect (GSEF) for any $C \cdot C \cdot CH$ proton is given by

$$\text{GSEF} = A - B\cos\theta \qquad (12)$$

The cut-off at r_{min} of the steric term [Eqn (9)] was initially introduced as a consequence of using the Morse equation[15] to derive the steric repulsions. Now that the simpler r^{-6} steric function has been shown to have a sound theoretical basis, the cut-off at r_{min} is no longer meaningful. This was therefore removed, but a global cut-off at 6 Å was introduced for computational reasons. At this distance all the steric terms are negligible. Hence, Eqn (9) is replaced by

$$\delta_{\text{steric}} = a_s/r^6$$
$$\delta_{\text{steric}} = 0 \quad \text{for } r > 6\ \text{Å} \qquad (13)$$

As a consequence of this change, the push–pull term needed to be amended as now the situation could arise of a carbon atom with a symmetric steric effect on a CH_2 group as in $C \cdots CH_2$ (e.g. the C_ε carbon atom in adamantane). It is clearly unreasonable to assume a push–pull effect for both the hydrogens in the methylene group in such a case and the push–pull term was amended so that in such situations the normal steric term applied, i.e. the CH_2 protons were treated exactly the same as two separate CH protons. (In the previous version these protons were outside the cut-off limit.) For completeness the cut-off for the electric field contribution was also removed, though for the very small C—H electric field contribution again for computational reasons a global cut-off of 6 Å was retained.

These simple amendments were introduced into the CHARGE scheme which was then parameterized and tested on the observed proton chemical shifts of all the hydrocarbon data.[13] Full experimental details of all the assignments plus spectra are given elsewhere.[13,16] All the geometries of the compounds investigated were obtained by geometry optimizations using the GAUSSIAN94 program at the RHF/6–31G* level.[17] Again full details of these optimizations and geometries are given in Ref. 16. The GAUSSIAN94 calculations were performed on the University of Liverpool Central Computing facility. All other computations were performed on a PC. The CHARGE5 calculations for the alkane set of compounds considered here (40 molecules) runs in 45 seconds on a Viglen 130 MHz Pentium PC. The iterations were performed with the use of two computer programs available to us, CHOLESKY,[18a] a least mean square analysis of m linear equations in n unknowns, and CHAP,[18b] a nonlinear least mean square analysis of m equations in n unknowns.

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. The

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

Molecule	Group	Experimental[a]	CHARGE5	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	0.86	0.86
Isobutane	CH	1.74	1.77	1.77
	CH_3	0.89	0.91	0.90
n-Butane	CH_2	1.29	1.11(*t*), 1.30(*g*)	1.25(*t*), 1.39(*g*)
	CH_3	0.89	0.83(*t*), 0.86(*g*)	0.91(*t*), 0.83(*g*)
2-Methylbutane	CH	1.45	1.82(*t*), 1.41(*g*)	1.91(*t*), 1.62(*g*)
	CH_2	1.20	1.28(*t*), 1.06(*g*)	1.47(*t*), 1.30(*g*)
	CH_3 (Et)	0.86	0.91(*t*), 0.87(*g*)	0.79(*t*), 0.87(*g*)
	CH_3 (*i*Pr)	0.87	0.90(*t*), 0.88(*g*)	0.87(*t*), 0.90(*g*)
2,2-Dimethylbutane	CH_2	1.20	1.28	1.33
	CH_3	0.82	0.92	0.83
	*t*Bu	0.85	0.92	0.91
2,3-Dimethylbutane	CH	1.41	1.09(*t*), 1.35(*g*)	1.49(*t*), 1.67(*g*)
	CH_3	0.83	0.91(*t*), 0.93(*g*)	0.89(*t*), 0.87(*g*)
2,2,3-Trimethylbutane	CH	1.38	1.47	1.48
	CH_3	0.83	0.96	0.85
	*t*Bu	0.83	0.95	0.89
2,2,3,3-Tetramethylbutane	*t*Bu	0.87	1.00	0.87
Neopentane	CH_3	0.93	0.95	0.92
Di-*tert*-butylmethane	CH_2	1.23	1.15	1.26
	*t*Bu	0.97	0.92	0.89
1,1-Di-*tert*-butylethane	CH	1.18	1.18	1.20
	CH_3	0.86	1.03	0.77
	*t*Bu	0.98	0.97	0.87
2,2-Di-*tert*-butylpropane	CH_3	0.83	1.08	0.79
	*t*Bu	0.99	0.99	0.83
Tri-*tert*-butylmethane	CH	1.38	0.88	0.94
	*t*Bu	1.22	0.94	0.83

[a] Data from Ref. 13.

iteration proceeded smoothly to give an rms error of 0.10 ppm, slightly better than the previous scheme. This was achieved also with a reduction in the number of variable parameters from thirteen to ten as it was found that in CHARGE5 only one carbon steric coefficient was required instead of the four used in CHARGE4 for the different types of carbon atom (quaternary, CH, CH_2, CH_3), see later. The values of the carbon γ term were generally similar to those of CHARGE4 demonstrating that the iteration was behaving in an analogous manner. The values of the parameters obtained will be considered later. Here we wish to consider first the agreement between the calculated and observed shifts given in Tables 1–5.

In general both schemes give very good agreement with the observed shifts thus providing the first definitive quantitative explanation of the proton chemical shifts in these molecules. In detail both sets of results for the acyclic alkanes (Table 1) are very similar, the only significant discrepancy in the data set being the values for tri-*tert*-butylmethane for which both the methine and *tert*-butyl protons are significantly in error. This is probably due to the fact that this is a very sterically hindered molecule and in addition the methine proton is very sensitive to the carbon γ effect, having nine γ carbons. The sensitivity of this result to the molecular geometry is clearly shown by the calculated shifts using an alternative molecular mechanics (PCMODEL)[19] geometry of 1.13 (CH) and 0.90 (Me). For these reasons, it was considered prudent not to weight these values in the iteration. The effects of the *tert*-butyl groups in both the acyclic and cyclic molecules (t-Bu·CH and t-Bu·CH_2 fragments) were treated in a similar manner to CHARGE4 in that the methyl γ effect was not used for the *tert*-butyl group but the *tert*-butyl group has a separate small deshielding γ effect. This produced consistent and reasonable results.

The extensive data set for the cyclic compounds (Tables 2–5) also includes some very strained and sterically hindered molecules and with the proton chemical shifts ranging from 0.3 to 2.2 ppm this provides a stringent test of any theoretical calculation. Both schemes again reproduce the observed data fairly well but there are some interesting differences. Cyclobutane is now well reproduced in CHARGE5 as compared with CHARGE4, thus indicating that the large steric strain in the cyclobutane ring does not appear to influence the proton chemical shifts.

The proton shifts in *cis*-decalin are now in general better reproduced in CHARGE5. The numbering is

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

Molecule	Group[a]	Experimental[b]	CHARGE5	CHARGE4
Cyclobutane	CH_2	1.96	2.02	1.49
Cyclopentane	CH_2	1.51	1.46	1.49
Cyclohexane	a	1.19	1.19	1.11
	e	1.68	1.68	1.69
Norbornane	1,4 (CH)	2.19	1.95	1.92
	endo	1.16	1.16	1.30
	exo	1.47	1.52	1.50
	7a,s	1.18	1.17	1.30
Bicyclo[2.2.2]octane]	CH	1.50	2.01	2.02
	CH_2	1.50	1.44	1.44
trans-Decalin	1,4,5,8a	0.93	1.02	1.02
	1,4,5,8e	1.54	1.53	1.63
	2,3,6,7a	1.25	1.22	1.17
	2,3,6,7e	1.67	1.72	1.75
	9,10 (CH)	0.88	0.86	0.87
cis-Decalin	1,5a	1.59	1.48	1.13
	1,5e	1.18	1.19	1.24
	2,6a	1.19	1.24	1.13
	2,6e	1.70	1.74	1.69
	3,7a	1.32	1.38	1.20
	3,7e	1.38	1.57	1.60
	4,8a	1.45	1.38	1.36
	4,8e	1.45	1.49	1.58
	9,10 (CH)	1.64	1.44	1.52
Perhydrophenalene	1,3,4,6,7,9a	0.95	1.06	1.03
	1,3,4,6,7,9e	1.57	1.56	1.66
	2,5,8a	1.29	1.22	1.20
	2,5,8e	1.65	1.76	1.78
	10–12 (CH)	0.96	0.87	0.90
	13 (CH)	0.32	0.38	0.39
Perhydroanthracene	1,4,5,8a	0.95	1.04	1.05
	1,4,5,8e	1.56	1.55	1.65
	2,3,6,7a	1.23	1.21	1.19
	2,3,6,7e	1.67	1.72	1.77
	9,10a	0.72	0.87	0.93
	9,10e	1.43	1.39	1.56
	11–14 (CH)	0.91	0.89	0.92
Adamantane	CH	1.87	2.08	1.98
	CH_2	1.75	1.49	1.35
Bornane	2*n*	1.23	1.20	0.97
	2*x*	1.49	1.55	1.53
	3*n*	1.13	1.19	1.09
	3*x*	1.71	1.70	1.80
	4 (CH)	1.60	1.56	1.75
	7,8-CH_3	0.83	0.87	0.82
	10-CH_3	0.83	0.95	0.99
tert-Butylcyclohexane	1a (CH)	0.94	0.97	1.00
	1-*t*Bu	0.83	0.88	0.93
	2,6a	0.91	0.99	0.90
	2,6e	1.75	1.61	1.85
	3,5a	1.19	1.17	1.09
	3,5e	1.75	1.72	1.70
	4a	1.08	1.19	1.13
	4e	1.64	1.70	1.72

Table 2. Continued

Molecule	Group[a]	Experimental[b]	CHARGE5	CHARGE4
cis-4-*tert*-Butylmethylcyclohexane	1a-CH_3	0.86	0.84	0.83
	1e (CH)	1.90	1.94	2.00
	2,6a	1.45	1.36	1.37
	2,6e	1.49	1.47	1.55
	3,5a	1.17	1.15	1.09
	3,5e	1.49	1.63	1.70
	4a (CH)	0.93	0.96	1.00
	4e-*t*Bu	0.84	0.88	0.93
trans-4-*tert*-Butylmethylcyclohexane	1a (CH)	1.24	1.37	1.36
	1e-CH_3	0.86	0.83	0.99
	2,6a	0.93	0.82	0.79
	2,6e	1.73	1.66	1.59
	3,5a	0.93	0.98	0.94
	3,5e	1.73	1.63	1.87
	4a (CH)	0.95	1.00	1.01
	4e-*t*Bu	0.84	0.88	0.94

[a] a = Axial; e = equatorial; *x* = exo; *n* = *endo*.
[b] Data from Ref. 13.

given in Fig. 1 from Ref. 20 and corresponding assignment in Table 2. There is still some ambiguity concerning the assignment of these shifts. In Ref. 13 the proton shifts below the coalescence temperature were measured and the assignment obtained from an HMQC correlation from the C-13 shifts together with consideration of the axial and equatorial splitting patterns. This is unambiguous but the assignment of the carbon shifts for the molecule below the coalescence temperature, although reasonable, is not unequivocal. Carbons 1,5 and 4,8 may be interchanged and also carbons 2,6 and 3,7 and this would have consequences for the proton assignments given. Further experimental evidence would be required for a definitive assignment.

Other molecules for which the present scheme fits better than CHARGE4 include adamantane and bornane, although the methylene protons of the former are still not particularly well reproduced. In CHARGE4 and particularly CHARGE5 the calculated shifts of both the bridge and *endo* protons of norbornane (but not bornane) were not in good agreement with the observed shifts. A possible explanation of this comes from the work of Marshall *et al.*[21] in their explanation of the anomalous values of the vicinal proton couplings in the $CH_2 \cdot CH_2$ group in this molecule, in which the *exo–exo* coupling of *ca.* 12 Hz is significantly greater than the *endo–endo* coupling (*ca.* 9 Hz), although both the dihedral angles are 0°. They found from FPT/INDO calculations that there was a significant interaction between the orbitals of the methylene bridge and the $CH_2 \cdot CH_2$ group and this interaction only affected the *endo–endo* coupling. It is therefore possible that this interaction could affect the corresponding proton chemical shifts and in CHARGE5 this was modelled simply by an r^{-6} shielding function from the eclipsed $C \cdot C \cdot C \cdot C$ fragment and also an additional shielding to the *endo* proton chemical shifts at these close distances (<2.7 Å). With this small addition, the data for both norbornane and the methyl-substituted norbornanes (Table 4) is reasonably well reproduced, although there are still some discrepancies, e.g. the C-2 methine protons are not well reproduced by either scheme.

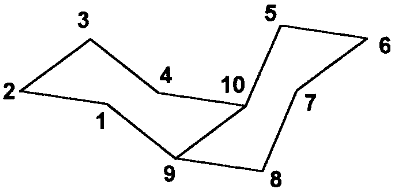


Figure 1. Numbering used for *cis*-decalin.

In contrast, the extensive data set for the methylcyclohexanes (Table 3) shows excellent agreement between the observed and calculated shifts for both schemes. The treatment of the methyl group γ effect given in Ref. 13 is unchanged in the present scheme (although the parameters are slightly changed; see later) and the good agreement shown here reinforces the general validity of this treatment of the methyl group effect.

5α-Androstane (Fig. 2) was originally 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.

It can be seen from Table 5 that the calculated shifts for both CHARGE4 and CHARGE5 are in general in very good agreement with the experimental data, with the CHARGE5 results in slightly better agreement with

Table 3. Observed vs calculated proton chemical shifts (δ) of methylcyclohexanes

Molecule	Group[a]	Experimental[b]	CHARGE5	CHARGE4
eq-Methylcyclohexane	1a	1.32	1.33	1.34
	1e-CH_3	0.86	0.83	0.98
	2,6a	0.88	0.85	0.82
	2,6e	1.68	1.70	1.57
	3,5a	1.20	1.18	1.14
	3,5e	1.68	1.69	1.71
	4a	1.11	1.21	1.14
	4e	1.68	1.69	1.72
ax-Methylcyclohexane	1a-CH_3	0.93	0.82	0.82
	1e	1.98	1.92	1.98
	2,6a	1.40	1.38	1.38
	2,6e	1.48	1.59	1.54
	3,5a	1.32	1.34	1.29
	3,5e	1.53	1.54	1.55
	4a	1.19	1.18	1.12
	4e	1.68	1.69	1.68
1,1-Dimethylcyclohexane	1a-CH_3	0.87	0.84	0.82
	1e-CH_3	0.87	0.85	0.99
	2,6a	1.09	1.04	1.17
	2,6e	1.32	1.25	1.29
	3,5a	1.36	1.37	1.37
	3,5e	1.48	1.56	1.54
	4a	1.04	1.21	1.13
	4e	1.65	1.71	1.71
trans-1,2-Dimethylcyclohexane	1,2a (CH)	0.94	1.03	1.09
	1,2e-CH_3	0.88	0.87	0.93
	3,6a	0.88	0.84	0.84
	3,6e	1.63	1.59	1.55
	4,5a	1.21	1.20	1.17
	4,5e	1.66	1.71	1.74
cis-1,3-Dimethylcyclohexane	1,3a (CH)	1.34	1.34	1.38
	1,3e-CH_3	0.86	0.84	0.98
	2a	0.54	0.51	0.53
	2e	1.63	1.58	1.45
	4,6a	0.76	0.87	0.84
	4,6e	1.63	1.65	1.61
	5a	1.25	1.17	1.17
	5e	1.69	1.71	1.74
trans-1,4-Dimethylcyclohexane	1,4a (CH)	1.26	1.23	1.24
	1,4e-CH_3	0.86	0.85	1.00
	2,3,5,6a	0.90	0.82	0.80
	2,3,5,6e	1.65	1.63	1.57
cis,cis-1,3,5-Trimethylcyclohexane	1,3,5a (CH)	1.39	1.27	1.37
	1,3,5e-CH_3	0.86	0.84	0.99
	2,4,6a	0.47	0.57	0.60
	2,4,6e	1.61	1.59	1.48
trans,cis-1,3,5-Trimethylcyclohexane	1-CH_3	0.97	0.83	0.88
	1e (CH)	2.02	1.97	2.02
	2,6a	1.02	1.04	1.10
	2,6e	1.43	1.55	1.45
	3,5a (CH)	1.61	1.52	1.52
	3,5-CH_3	0.83	0.84	0.98
	4a	0.48	0.47	0.51
	4e	1.60	1.60	1.45

[a] a = Axial; e = equatorial.

[b] Data from Ref. 13.

Table 4. Observed[a] vs calculated proton chemical shifts (δ) of methylnorbornanes

	2-*exo*-Methyl			2-*endo*-Methyl		
Proton[b]	Expt.	CHARGE5	CHARGE4	Expt.	CHARGE5	CHARGE4
1	1.82	1.74	1.69	1.98	1.98	1.90
2*n*	1.49	1.12	1.42	0.93[b]	0.84	0.89
2*x*	0.86[c]	0.87	0.93	1.90	1.51	1.59
3*n*	1.43	1.35	1.48	0.53	0.49	0.79
3*x*	0.93	0.81	0.94	1.74	1.71	1.68
4	2.16	1.98	1.93	2.11	1.97	1.95
5*n*	1.11	1.18	1.37	1.08	1.17	1.23
5*x*	1.44	1.54	1.53	1.47	1.50	1.52
6*n*	1.14	1.08	1.27	1.55	1.44	1.73
6*x*	1.46	1.52	1.51	1.27	1.28	1.20
7a	1.04	1.03	1.16	1.25	1.10	1.31
7s	1.33	1.32	1.43	1.33	1.16	1.30

[a] Data from Ref. 13.
[b] *n* = *endo*; *x* = *exo*; a = anti; s = syn
[c] Methyl shift.

the observed shifts. Indeed, out of the 28 recorded shifts, only three are more than 0.15 ppm in error in CHARGE5, an impressive achievement when it is considered that two possible geometries of the 5α-androstane, the *ab initio* one considered here and a derived crystal geometry were shown to give differences in the calculated shifts of the 11β and 17α protons of −0.18 and 0.30 ppm respectively.[13] The *ab initio* calculations gave the geometry of the flexible 5-membered D ring as a 13-envelope (C14, C15, C16 and C17 are more

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

	Experimental		Calculated	
Proton	Ref. 22	Ref. 13	CHARGE5	CHARGE4
1α	0.89	0.87	1.00	0.91
1β	1.66	1.67	1.53	1.53
2α	1.50	1.48	1.57	1.54
2β	1.41	1.41	1.44	1.49
3α	1.23	1.21	1.19	1.17
3β	1.67	1.67	1.74	1.75
4α	1.22[a]	1.22[a]	1.34	1.37
4β	1.22 ± 0.04[a]	1.22[a]	1.22	1.39
5 (CH)	1.06	1.02	1.15	1.00
6α	1.22[a]	1.22[a]	1.35	1.38
6β	1.22 ± 0.04[a]	1.22[a]	1.40	1.52
7α	0.93	0.91	0.97	0.75
7β	1.69	1.68	1.94	2.00
8 (CH)	1.29	1.28	1.12	1.34
9 (CH)	0.69	0.68	0.75	0.72
11α	1.55	1.53	1.51	1.42
11β	1.26	1.26	1.34	1.43
12α	1.10	1.09	1.05	1.25
12β	1.71	1.70	1.60	1.60
14 (CH)	0.90	0.89	0.83	0.82
15α	1.65	1.63	1.68	1.64
15β	1.15	1.14	1.49	1.42
16α	1.56[a]	1.58[a]	1.58	1.58
16β	1.56 ± 0.16*	1.61[a]	1.65	1.57
17α	1.13	1.12	1.16	1.42
17β	1.42	1.39	1.56	1.52
18-Me	0.69	0.69	0.80	0.73
19-Me	0.79	0.78	0.80	0.70

[a] Unresolved.

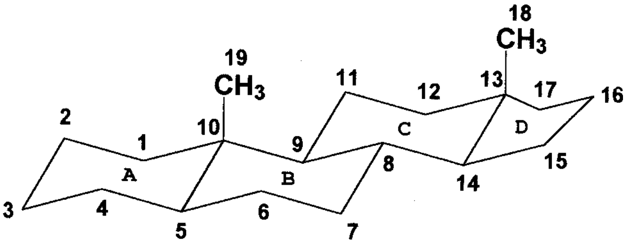


Figure 2. Numbering used for 5α-androstane.

or less in a plane with only a 9.5° twist). However, the exact conformation in solution of the unsubstituted ring has not been determined and may be different to the calculated and this may effect the calculated shifts of these protons (Table 5).

DISCUSSION

The above results demonstrate unequivocally that the introduction of an orientation-dependent carbon γ effect produces agreement with the observed shifts of hydrocarbons as good, as if not better than the scheme including the C—C anisotropy term. It was noted previously[13] that the anisotropy term was mainly due to the contributions from the C_β—C_γ bond with only minor contributions from the more distant C—C bonds, and this result confirms and extends this conclusion. Indeed, iteration of the parameterized scheme including only the more distant C—C bond anisotropic term gave an almost zero value for the anisotropic coefficient. Hence we may safely conclude that there is no evidence for a general long-range (further than C_β—C_γ) C—C anisotropic contribution to proton chemical shifts in hydrocarbons.

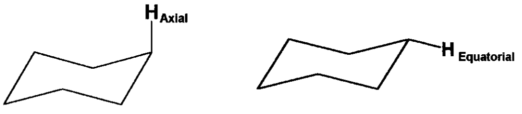
This is further supported by comparison of the anisotropic contribution of the C_β—C_γ bonds with the simple cos θ dependence obtained here. The value of B in Eqn (12) was determined in the present iteration to be 0.11 ppm. This gives a functional dependence of the proton chemical shift in an H · C · C · C fragment almost identical with the anisotropic term in Ref. 13, in which the contribution varied from -0.12 ppm at 0° to $+0.09$ ppm at 180°. There are, however, some differences in the two approaches in that the anisotropic contribution depends also on the bond lengths and angles in the H · C · C · C fragment, which is not the case for Eqn (12). These differences appear relatively minor even for the variety of compounds considered here.

There are, however, certain situations in which the more distant anisotropic contribution to the proton chemical shifts may be significant. One of these is the bridging protons in norbornane, and it is possible that there may be a shielding or anisotropic contribution from the eclipsed CH_2—CH_2 bonds in the norbornane molecule. Certainly the planar C · CH_2—CH_2 · C fragment will have greater directional anisotropy than an equivalent staggered fragment. Hence an extra shielding term proportional to r^{-6} was introduced for this fragment. However, a more detailed theoretical study of the shielding and anisotropy of an eclipsed C—C fragment would be necessary before this treatment could be taken further.

The values of the remaining parameters obtained in the CHARGE5 scheme are generally similar to those found in CHARGE4, again confirming the general similarity of the two schemes. The carbon γ effect is a function of the type of hydrogen involved, i.e. the value of A in Eqn (12) varies from 0.01 ppm (C · C · CH) to 0.17 ppm (C · C · CH_2 and C · C · CH_3) and these follow a similar trend to the corresponding values in CHARGE4 (0.06, 0.27 and 0.18 ppm, respectively). The parameterized values of the steric coefficients (a_s) of Eqn (13) for H · · · H shielding interactions with the CHARGE4 values [Eqn (9)] in parentheses are ($CH \rightarrow CH/CH_2$) = -63.0 (-55.0), ($CH_2 \rightarrow CH/CH_2$) = -48.5 (-49.0), ($CH_3 \rightarrow CH/CH_2$) = -48.2 (-29.0), ($CH_3 \rightarrow CH/CH_2$) = -34.0 (0..0); and for the C · · · H deshielding interaction $a_s = 229.0$ for all C → H interactions compared with the CHARGE4 values of (C → CH) 270.0, (C → CH_2) 345.0 and (C → CH_3) 165.0.

The H · · · H and C · · · H steric coefficients are similar for CHARGE5 than CHARGE4, as expected.

The parameters for the γ methyl effect [Eqn (6)] are -0.67, 0.04 and 0.30 ppm for A_1, A_2 and k, respectively, which are also similar to those of CHARGE4 (-0.38, 0.13 and 0.09 ppm, respectively), hence the effect of this term is unchanged in CHARGE5.



	CHARGE5	CHARGE4	CHARGE5	CHARGE4
CHARGE	1.538	1.550	1.828	1.550
C—C ANISOTROPY	0.000	−0.168	0.000	0.141
H · · · H STERIC	−0.331	−0.188	−0.060	0.000
C · · · H STERIC	0.137	0.000	0.017	0.000
C—H ELECTRIC FIELD	−0.159	−0.086	−0.109	0.000
TOTAL	1.185	1.107	1.676	1.691
EXPERIMENTAL	1.19		1.68	

Figure 3. Contributions to the calculated shifts of the protons in cyclohexane.

The contributions to the chemical shifts of the protons in cyclohexane from the CHARGE5 scheme are now different from those from CHARGE4 (Fig. 3). The difference between the axial and equatorial protons is still multi-functional, with contributions due to the different charges as well as the H···H and C—H steric terms and the C—H electric field effects. Both the axial and equatorial protons are shielded by the two protons at the 3,5-axial positions, but the steric effect at the aaxial protons is much greater. The C_δ carbon atom provides the only deshielding steric term and again the effect is greater at the axial proton. The electric field component is shielding and similar at the equatorial and axial protons.

CONCLUSION

The CHARGE5 scheme in which there is no C—C bond anisotropy term predicts the proton chemical shifts of alkanes as well as if not better than the analogous scheme (CHARGE4) including C—C anisotropy. Thus there is no reason to invoke C—C anisotropy in describing proton chemical shifts. There may be a possible contribution from eclipsed C·C fragments but this could also be due to electronic effects. The present scheme gives a quantitative description of proton chemical shifts for a diverse range of hydrocarbons and should thus be applicable to a wide range of substituted alkanes. There are, however, still some significant anomalies in certain molecules. A more sophisticated carbon γ orientation dependence could be considered as there is no theoretical reason to use only a cos θ type dependence. Also, the carbon steric effect including the push–pull term could well be developed further to produce better results. These developments are, however, dependent upon further theoretical advances in this area.

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