Shielding Contributions to ^{1}H and ^{13}C Nuclear Magnetic Resonance Shifts in Cyclohexane, Methylcyclohexane, and n-Butane

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Anisotropy effects (σ_{an}), linear and square electric field contributions (σ_E, σ_{E^2}), and sterically induced polarizations (σ_{st}) are evaluated on the basis of MM2-generated molecular structures using a computer program (SHIFT) which allows the point of action of inducing and polarized bonds to be varied, and the number of interacting atoms or bonds to be selected. The linear electric field effect (σ_E) can be excluded as the source of the equatorial–axial ^{1}H shift difference, and of the methyl substituent effects, similarly σ_{an} for the methyl effect, and very likely for the equatorial–axial difference. Steric forces F (σ_{st}) describe distant shielding effects for ^{13}C with a sensitivity of $k_c \cong 1$ p.p.m. µdyn^{-1}, and for ^{1}H with $k_H \cong 0.05$ p.p.m. µdyn^{-1} with the correct order of magnitude, including the expected ^{13}C shielding in n-butane rotamers. In conclusion, the application of all now available computational options without arbitrary limitations shows that only a few limiting shielding mechanisms can be excluded, and that a parametrization of screening factors on the basis of hydrocarbon n.m.r. data alone is not feasible.

Although the shielding difference between equatorial and axial protons[1] and the effect of alkyl groups on ^{1}H and particularly on ^{13}C n.m.r. screening constants[2] in alkanes is of extreme practical importance, not much progress in the evaluation of the responsible shielding mechanisms has been reported after the pioneering work of ApSimon *et al.*[3] and Zürcher.[4] We believed it to be timely to initiate a new study on these basic screening contributions as new experimental data are becoming available with the advent of high-field n.m.r. spectrometers,[5] and high-speed computers enable us to carry out comprehensive calculations on all possible effects without the limitations forced upon earlier workers.

The problems involved *e.g.* with the susceptibility $\Delta\chi$ selection for C–C and C–H bonds as well as with the computational procedures have been recognized,[1,3,4] and became apparent again from the few more recent studies devoted to shielding effects of carbon–heteroatom single bonds,[6,7] or of amides.[8,9] The discrepancies betweeen some earlier approaches to ^{1}H shielding variations in hydrocarbons are most obvious from their alternative description in the literature as either anisotropy,[3] 'steric',[10] or electrostatic field[11] effects. In the present paper an effort is made to analyse *all* pertinent shielding contributions in cyclohexane, methylcyclohexane, and n-butane on the basis of variable computational procedures and of realistic molecular geometries, and to compare the corresponding ^{1}H and ^{13}C n.m.r. screening factors. We are aware of the possibility that the abolition of arbitrary decisions favouring one or two mechanisms, and the improvement of calculational options, may well lead to largely negative conclusions with respect to the many parameters in the shielding contributions. There is, however, no justification to maintain earlier restrictions, *e.g.*, for the point of action along C–X or C–H bonds.

Methods

(1) *Calculation of Molecular Structures and Shielding Effects.*—During the evaluation of steric effects on ^{13}C n.m.r. shielding constants we observed an error of *e.g. ca.* 500% if non-relaxed idealized molecular geometries are used; this is the result of the steep potentials responsible for non-bonded interactions, and the general relaxation of local distortions within carbon frameworks.[12a] Even for linear electric-field effects, which are less sensitive to geometry variations, an error of *e.g. ca.* 200% was encountered if Dreiding models and manual operations were used instead of suitable computer programs.[12b] Most of the earlier workers had been forced to use idealized or Dreiding models as a basis; that the replacement by *X* ray-derived structures was reported not to affect significantly the calculated anisotropy and field effects for a steroid[3d] may be due to the inherently smaller geometry sensitivity of these contributions and to the observation of only time-averaged methyl protons with possible error cancellations. We obtained the basic conformations for all structures by molecular mechanics calculations (MM2)[13,14] which have been demonstrated to lead to realistic energy-minimized geometries.[14] The force field-generated structures served as input for a program package SHIFT which allows calculation of the linear and square electric field contributions σ_E, σ_{E^2}, as well as the anisotropy and steric effects σ_{an},σ_{st} (see below), while other contributions (through bond, reaction field, *etc.*) are considered to be constant [equation (1)].

$$\sigma = \sigma_E + \sigma_{E^2} + \sigma_{an} + \sigma_{st} + \sigma_{other} \qquad (1)$$

(2) *The Location of Dipoles and Field Gradients along Bonds.*—While it has been demonstrated already for σ_{an} and σ_E that the different dipole locations can lead to quite variable σ_{an}/σ_E ratios,[3] the point of action of sterically induced field gradients as proposed first by Grant and Cheney[15] and later modified by us[16] was always[10,12a,15,16] put on the hydrogen end of the polarized C–H bond. The program SHIFT provides for a choice of the point of action along non-C–C bonds for all effects; the selected results given in Tables 1—3 show that even a change of sign is possible as a result of such variations. It must be borne in mind that the point of action, given in Tables 1—3 in fractional bond length distances from carbon towards X or H, refers to the inducing dipole for σ_{an} and σ_{E^2}, but to the polarized bond for σ_E and σ_{st}; this means that *e.g.* σ_{an} from the '10%' point of action calculation may well be combined with σ_{el} from the '50%' calculation (Table 1).

(3) *The Selection of Interacting Atoms and Bonds.*—In analysing substituent effects it is customary to neglect secondary effects at the observed atoms.[3,4,10,12,15] such as geometry changes brought about by substituent variation. The square electric field and the 'steric' (non-bonded) contributions in Table 1 show considerable variations even on vicinal C–H

Table 1. Screening effects of single C–H bonds in cyclohexane on an equatorial–axial proton[a]

Point of action[b]→		10%				50%				90%			
on	of: H	σ_E[c]	σ_{E^2}[d]	σ_{an}[e]	σ_{st}[f]	σ_E[c]	σ_{E^2}[d]	σ_{an}[e]	σ_{st}[f]	σ_E[c]	σ_{E^2}[d]	σ_{an}[e]	σ_{st}[f]
H_{eq}	βe	−29	0.137	0.055	−1.181	−42	0.714	0.147	−1.854	−46	0.279	0.226	−1.204
	βa	−30	0.145	0.066	−1.290	−43	0.222	0.159	−1.905	−47	0.781	0.231	−1.048
	γe	−11	0.005	−0.031	0.014	−16	0.009	−0.031	0.016	−22	0.015	−0.028	0.012
	γa	4	0.011	0.024	0.020	−5	0.014	0.039	−0.015	−5	0.017	0.052	−0.265
	δe	−8	0.002	−0.037	0.008	−10	0.004	−0.047	0.013	−6	0.007	−0.060	0.018
	δa	−5	0.006	−0.017	0.015	−8	0.007	0.033	0.016	−6	0.008	0.039	0.005
H_{ax}	βe	−30	0.146	−0.120	1.272	−43	0.224	0.157	−1.893	−47	0.285	0.232	−0.961
	βa	−3	0.043	0.064	−0.158	−21	0.094	−0.150	−1.019	−22	0.233	−0.165	−5.307
	γe	−8	0.012	0.139	0.009	−5	0.024	−0.104	0.006	0	0.052	−0.139	0.002
	γa	−36	0.095	−0.078	−0.002	−21	0.088	0.122	0.166	−19	0.069	0.082	0.189
	δe	−4	0.006	−0.017	0.006	−4	0.011	−0.031	0.004	−7	0.019	−0.025	0.002
	δa	0	0.008	−0.032	0.014	1	0.012	−0.008	0.013	6	0.019	0.008	0.002

[a] Procedures and definitions see text. [b] Point of action in fractions of the C–X (or C–H) bonds from C towards X (H). [c] In elementary charge units $e \cdot 10^4$ (17.8 p.p.m./e^{-1}). [d] In units of 10^{12} dyn cm^{-2} ≙ 0.75 p.p.m.[17] [e] In (p.p.m.).[1] [f] In units of 10^5 dyn ≙ 0.5 p.p.m. (see text).

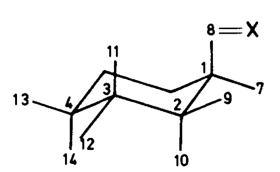
Table 2. Summarized effects on equatorial and axial protons in cyclohexane[a]

Point of action→		10%			50%			90%		
Observed atom	Selection mode→	A	B	C	A	B	C	A	B	C
H_{eq}	E	−0.0145			−0.023			−0.026		
	E^2	0.604	1.880	0.260	0.929	2.643	0.209	1.199	3.276	0.260
	an	0.174	−0.062	0.227	0.320	0.726	0.174	0.881	1.390	0.227
	st	−4.851	−5.074	−1.023	−7.487	−8.928	−0.053	−4.987	−12.142	−1.023
H_{ax}	E	−0.0127			−0.0187			−0.0177	−0.0177	
	E^2	0.204	2.669	0.908	0.883	3.335	0.832	1.316	1.316	0.909
	an	−0.039	0.563	−0.012	0.011	0.664	0.244	0.003	0.003	−0.012
	st	−2.826	−4.667	0.182	−5.463	−7.639	0.188	−12.150	−12.150	0.182
H_e–H_a[b]	E	−0.002			−0.004			−0.009		
	E^2	0.400	−0.789	−0.648	0.046	−0.692	−0.623	−0.117	−1.068	−0.649
	an	0.213	−0.625	0.239	0.309	0.062	−0.07	0.878	0.741	0.239
	st	−2.025	−0.407	−1.205	−2.024	−1.289	−0.24	7.163	1.233	−1.205

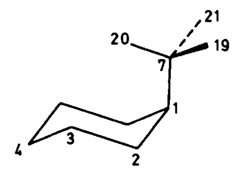
[a] Selection mode A–C (of interacting atoms or bonds) see text. Footnotes and units see Table 1, with these exceptions: σ_E in e units, σ_{E2} in 10^{12} dyn cm^{-2}.

bonds as a consequence of small equatorial–axial geometry differences. Opposite to these high-order effects, σ_{an} and σ_e remain fairly constant with alternatively equatorial and axial C–H bonds. We also note that possible hybridization differences between stereoisomeric C–H bonds (see ref. 16 and papers cited therein) and non-classical contributions, such as hyperconjugation effects, are not taken into account. Aware of these limitations, and the largely only operational justification for the usual treatment of localized substituents effects, we used the following selection modes.

(A) Only interacting *C–H* bonds and/or *H* atoms are considered, but geminal bonded atoms are omitted [*e.g.* in (**1**) for the evaluation of the substituent effects on X all C–H/XH are taken into account except H-7]. (B) All interacting C–H and C–C bonds or H and C atoms are considered, except direct and geminal bonds [*e.g.* in (**1**) all atoms except H-7, C-1, C-2]. (C) As (B), with the omission of direct geminal *and* vicinal bonds [*e.g.* in (**1**) all atoms except C-1, H-7, C-2, H-9, H-10, C-3].



(**1**)



(**2**)

In evaluating substituent effects (Table 3) we always substracted the effects of the replaced C–H bond from the substituent contributions; although some results suggested *e.g.* C–H anisotropy contributions to be negligibly small,[3b] the size of C–H interactions, depending very much on the calculation modes (compare Tables 1 and 3), supports the conclusion of earlier workers to include these effects explicitly.[1,3,4]

In the calculations of the methyl substituent effects only the interactions originating from the substituent alone were considered, *e.g.* C-7, C-1, H-19, H-20, H-21 in (**2**).

Electric-field Effects.—The longitudinal polarization of a bond with polarizability *P* by a charge *q* at distance *r* and an angle θ between field gradient and bond was calculated on the basis of the Buckingham[17] approach[1,3,4] using a point pole model[3,4,7–9] and $P_{C-C} = 0.97$, $P_{C-H} = 0.65$ (in 10^{24} cm^3

Table 3. Methyl substituent effects on protons in cyclohexane[a]

of	on P→[b]	$10^3\sigma_{E^2}$			$10^5\sigma_{st}$			σ_{an}			$10^5\sigma_E$			$\sigma_{Exp.}$[5] (p.p.m.)
		10%	50%	90%	10%	50%	90%	10%	50%	90%	10%	50%	90%	
Me_{eq}	βe	332	278	242	0.282	1.053	1.073	0.15	0.04	−0.08	11	178	329	−0.04
	βa	311	277	249	0.352	1.035	−1.051	0.15	0.04	−0.08	−53	195	347	−0.30
	γa	26	18	−7	0.011	0.010	0.009	−0.01	−0.05	0.07	32	12	−19	0.06
	γe	12	10	6	0.015	0.018	0.022	0.01	0.01	0.01	34	59	101	−0.04
	γe	3	3	−6	0.009	0.013	0.022	0.00	0.01	0.03	21	28	29	−0.01
	γa	15	13	18	−0.008	−0.008	−0.001	0.00	−0.09	0.01	38	44	43	−0.05
Me_{ax}	βe	357	304	278	0.493	1.400	−1.287	−0.05	0.17	−0.07	6	193	342	−0.23
	βa	88	48	−73	0.099	0.380	1.976	0.10	0.05	0.07	44	−29	−271	0.27
	δa	289	232	232	—1.653	0.771	0.202	−0.03	0.10	0.00	−27	70	127	0.25
	δe	24	23	22	0.034	0.027	−0.030	0.10	0.04	−0.02	−45	−67	−100	−0.26
	δe	15	14	13	0.019	0.020	0.020	0.05	0.00	−0.02	−19	−15	0	−0.03
	δa	15	12	9	0.021	0.027	0.027	−0.01	−0.01	−0.02	−31	−49	−68	−0.06

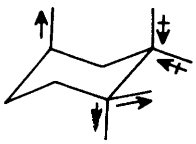
[a,b] See footnotes to Table 1. Selection mode D: only effects of the CH_3 atoms and C-1 are considered, see text. The values given are the differences between R = Me and R = H.

units); $q_H = -0.0581, q_C = +0.0581$ (per C–H bond, in e units) [(equation (2)].

$$\sigma_E = k_1 \Sigma q_x \cdot \cos\theta\, P_{C-X} l_{C-X} r^{-2} \qquad (2)$$

The problems in the parameter and procedure selection have been discussed earlier[1,3,4,7] and recently in detail by Piccini-Leopardi and Reisse.[8] We have used parameters close to those recommended in these papers and to those successfully used in some ^{13}C shielding calculations;[12b,18–20] attempts to optimize the parametrization by comparison to the experimental results were deemed to fail.

The shielding difference, $\Delta_{e/a} = 0.5$ p.p.m., between equatorial and axial protons in cyclohexane[1] had been used by ApSimon *et al.* as a basis for deriving anisotropy effects of C–C and C–H bonds.[3a] It is not clear why these workers dismissed all interactions except σ_{an}; in particular, an equatorial C–H bond will feel the polarization by four vicinal gauche C–H bonds; an axial C–H, however, will feel the effect of only two vicinal gauche bonds, but *e.g.* additionally of the two parallel axial γ-C–H bonds. The deshielding of axial protons observed in several compounds has in fact led Boaz[11] to assume the latter effect to dominate.



All calculations (Table 2), however, show that linear field effects should not contribute significantly to $\Delta_{e/a}$; if a dielectric constant of $\varepsilon > 1$ were considered for equation (2), the σ_E difference would become <0.1 p.p.m. This result is supported by a negligible solvent effect on $\Delta_{e/a}$, as measured for 1,3-*cis*-dimethylcyclohexane in $CDCl_3$–CCl_4 (solvent effect <0.01 p.p.m.).

Similarly, the ^1H n.m.r. substituent effects in methylcyclohexane[5] cannot be ascribed to E_Z, if one compares the values in Table 3 on the basis of ~20 p.p.m./e,[1] which with all calculation modes leads to σ_E effects smaller by at least a factor of ten.

Square electric-field effects were again calculated according to Buckingham[17] using polarizabilities P as above and ionization

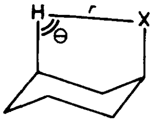
$$\sigma_{E^2} = k_2 \cdot 3P_{C-X} \cdot I_Y \cdot r^{-6} \qquad (3)$$

potentials of $I_H = 21.78 \times 10^{-12}$ erg, $I_C = 16.62 \times 10^{-12}$ erg.[21] Other than expected earlier[1,3] they appear not to be negligible (Tables 1—3), but they reflect neither $\Delta_{e/a}$ nor the methyl substituent effects in cyclohexane correctly. It should be borne in mind that the r^{-6} dependence makes this high-order effect extremely sensitive to geometry choice and calculational procedure (see Table 2).

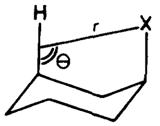
Anisotropy Effects.—These were calculated on the basis of the McConnell equation[1] (4) using susceptibility parameters

$$\sigma_{an} = k_3\, \Sigma\, \Delta\chi(1 - 3\cos^2\theta)/r^3 \qquad (4)$$

$\Delta\chi_{CC} = 9.0$, $\Delta\chi_{CH} = 7.54$ (10^{-30} cm^3 $molecule^{-1}$ units).[3b] The



(3a)



(3b)

$\Delta\chi$ values used are in agreement with those used in other studies.[3b,7] and in particular with independent magneto-optic measurements.* Some of the confusing different $\Delta\chi$ parameters in the literature[1,3,4,7] must be ascribed to the attempted derivatization from n.m.r. shifts by neglecting other shielding contributions (see above), and *e.g.* to the use of experimental data from compounds in which the substituent variation also leads to conformational changes in the vicinity of the observed proton.† ApSimon *et al.* have pointed out that equation (4) should be complemented by correction terms for distances $r < 3$ Å.[3a] In view of the uncertainties already involved in the parametrization and of the relatively small influence of such a correction in other cases we have so far only included equation (4) in our program.

The results for cyclohexane (Table 2) indicate that $\Delta_{e/a}$ is predicted correctly only if we place the dipole centre of the C–H bond close to the hydrogen (90%), but not as usual at the centre of the C–H bond. The calculated anisotropy contributions of the methyl substituent (Table 3) are generally too small to account for the few larger experimental effects.

Sterically Induced Polarizations.—'Steric' effects on proton shielding have usually been disregarded,[3,4] or, in the case of highly crowded environments, ascribed to high-order van der Waals', or square electric field effects.[1] Only Cheney[10] has presented a shift correlation of protons in some strained C–H bonds with the sterically induced charge polarizations described earlier by Grant and Cheney[15] for ^{13}C n.m.r. shielding effects; in view of the possibly varying ring-current effects in the investigated compounds,[10] and of the calculational simplifications,[16] including the omission of other effects, the correlation was not only surprisingly good, but also yielded a sensitivity which was well in the range of *ca.* 20 p.p.m./e for ^1H as compared with *ca.* 200 p.p.m./e for ^{13}C.[10] Since in most cases (for possible exemptions, see ref. 16) the steric forces on C–H bonds will push the electrons towards the carbon atom, and since the non-bonded repulsion responsible here is always at least exponential in the distance r between the C–H bond and the interacting atom, this effect is in fact difficult to differentiate from the constantly deshielding van der Waals' or square electric field effect with the distance dependence r^{-6} (see above).

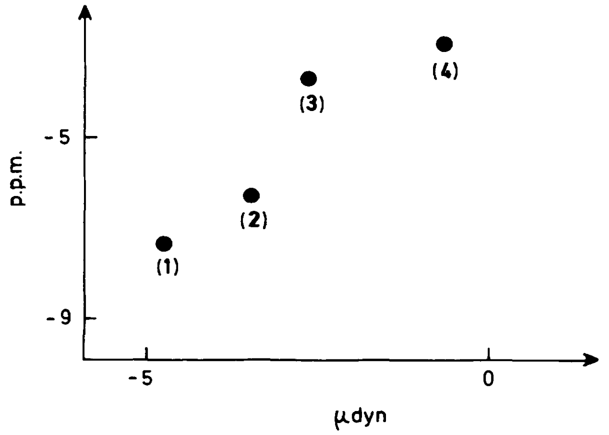


Figure 1. Syn-γ ^{13}C N.m.r. shifts as a function of steric forces F in (**1**) 2-*endo*-methylnorbornane; (**2**) axial methylcyclohexane; (**3**) 2-*exo*-methylnorbornane; (**4**) 7-methylnorbornane. Calculated with equation (5) using all C and H interactions except geminal positions (Mode B). Sensitivity (slope) $m_c = (1.1 \pm 0.3)$ (p.p.m. μdyn^{-1}); correlation coefficient r 0.93

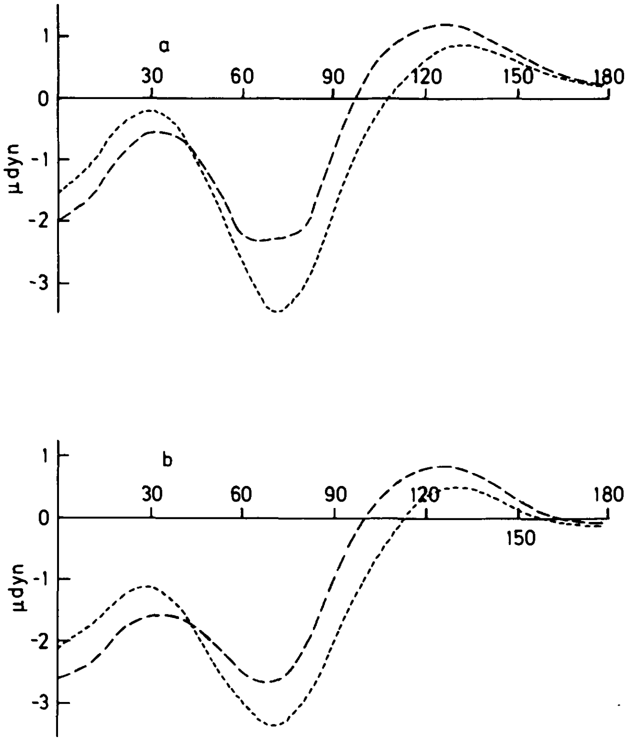


Figure 2. Steric forces F on C-1 in n-butane as a function of the torsional angle ψ, calculated with equation (5) with selection mode B (· · · ·) or C (– – – –). a, Point of F action at the hydrogen atom; b, at 80% from the carbon atom towards hydrogen

Using conformationally relaxed molecular structures and the force field-derived function (5) for the steric forces we obtained a

$$F = k_4 \frac{18\varepsilon}{r^*}\left[\left(\frac{r^*}{r}\right)^{10} - \left(\frac{r^*}{r}\right)^{7}\right]\cos\theta \qquad (5)$$

sensitivity of (2 ± 0.2) p.p.m. μdyn^{-1} for ^{13}C shift in alicyclic frameworks.[12a,16] The earlier calculations[10,12a,15,16] were based on a possibly unrealistic model by placing the point of action of the force gradient arbitrarily at one end of the polarized C–H bond [model (**3a**)]. We now varied the point of action [model (**3b**)] and could show that the calculated F values are indeed very sensitive against this for single protons, particular in the vicinity of the substituent (Table 3), but that the typical 'syn-γ'-effect of an axial methyl group on ^1H (Table 3) and in particular on ^{13}C shifts (see below, and Figure 1) are not affected so much by the calculational procedure. If we subsequently used only those interactions (selection mode B), and substituent effects which are less dependent on the calculational

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* See last footnote in ref. 3*b*, p. 2374, in which based on new magnetic birefringence data from Buckingham the $\Delta\chi$ values derived before[3a,b] were changed.

† Thus, most of the cycloalkanols used in ref. 3*a* contain methyl groups close to the hydroxy-group attached to the observed X-proton; this gives rise to changes in the rotamer distribution (although not really to hindered rotation[3a]). MM2 calculations[12a,16] predict *e.g.* for *exo*-2-norborneol a C-2–OH rotamer population change of *ca.* 70% upon introduction of a 3-*exo*-methyl substituent.

ambiguities we obtain a satisfactory correlation with a sensitivity (slope) of $m_c \cong 1$ p.p.m. μdyn^{-1};* this is not too far away from the earlier value of $m_c \cong 2$ p.p.m. μdyn^{-1} which was obtained with the substituent interactions alone (= selection mode D, as for Table 3). If we apply the different response scale of *ca.* 20 p.p.m./e for ^{1}H and *ca.* 200—400 p.p.m./e for ^{13}C, a sensitivity against steric forces of m_H 0.05—0.025 (p.p.m. μdyn^{-1}) for protons is expected. Inspection of the calculated F differences in Table 2 with the aid of the scaling factor in (5) $k_4 \triangleq m_H$ shows that $\Delta_{e/a}$ in cyclohexane can in fact be due to F variations, yet the ambiguity involved in the calculation does not allow a firm conclusion. In contrast, the long-range effect of an axial methyl group on the *syn*-γ-proton (Table 3) is in the predicted range, if we use a similar calculation ('10%' option: close to the hydrogen) and $m_H = 0.05$ (0.1 p.p.m. *de*shielding, experimental *de*shielding by 0.25 p.p.m.); all other long-range F effects are calculated to be smaller by a factor of ten, again in general agreement with experiment (Table 3).

Finally, we calculated the steric forces F on the methyl C-1 in n-butane for different torsional arrangements. The calculated shielding variation (Figure 2) is well in the range of expected values,[2] which for n-butane of course are only indirectly accessible.[22] These calculations were performed using different points of action along the polarized C–H bonds, and show a little deviation between an '80%' and '100%' mode (Figure 2a, b). Furthermore, the F values obtained are not much affected by different selection modes (B or C) in the calculation.

Conclusions.—As a result of the many calculational options provided by an extended computer program, and from the consideration of many possible shielding contributions, we are faced with a situation where only few mechanisms can be excluded, and where only certain long-range effects can be rationalized with some confidence. In principle it would be desirable to parametrize the shielding contributions by comparison with experimental data, as has been done by ApSimon *et al.* for carbonyl effects.[3d] While the distinct anisotropy and linear electric field effects of the polar oxo group justify such a procedure,† multilinear regression analysis of the present hydrocarbon shielding data based on equations (2)—(5) with the corresponding sensitivities k as variable failed as expected, yielding correlation coefficients $R < 0.85$ and completely unrealistic k parameters. If more than two shielding mechanisms and, in particular, all the calculational options described above are taken into account, the parametrizations become rapidly underdetermined. Significant progress can be expected from the use of better and more shift data in solution, which become accessible by high-field and two-dimensional n.m.r. techniques, from n.m.r. measurements of the anisotropic properties in liquid crystals and in solid single crystals, as accessible by CP-MAS techniques, and from independent physical measurements, *e.g.* of magneto-optic properties.

Acknowledgements

This work was financially supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

References

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Received 1*st October* 1984; *Paper* 4/1688

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* For the sake of comparison with the earlier calculations[12a,16] the same compounds[16] and hydrogen as the point of action were used here.

† Recently a multilinear regression analysis on oxo effects including not only time-averaged and distant methyl protons in steroids[3d] but more data derived from the androstane skeleton protons was successfully completed.[19b]