The Nuclear Magnetic Resonance Method for Determining Conformational Preferences in Substituted Cyclohexanes. Allowance for Ring Deformation

By G. E. HAWKES and J. H. P. UTLEY*

(*Department of Chemistry, Queen Mary College, Mile End Road, London, E.*1)

Summary The effect of remote alkyl substituents on the chemical shifts of methine protons in cyclohexyl compounds probably arises from changes in the polarisability of the ring due to deformation (and hence the inductive effect of the C-1 substituent), and not only from the accompanying changes in anisotropic shielding.

THERE is currently much discussion about the validity of the n.m.r. method for determining group conformational preferences in substituted cyclohexanes.[1] A common method involves the use in the Eliel equation of methine proton chemical shifts for conformations with the substituent axial or equatorial and the time-average shift of the rapidly inverting system. It has recently been shown that chemical shifts for the axial and equatorial methine protons are effected by the 4-t-butyl group, much used for conformation holdings. The substituent effects are particularly large in *cis*- and *trans*-4-t-butylcyclohexanecarbonitrile.[1a]

We have attempted to discover the origin of the substituent effect. Our values for methine proton chemical shifts of substituted cyclohexanecarbonitriles in CS_2 are given in Table 1. Of particular interest are the values for 4,4-dimethylcyclohexanecarbonitrile. At −90° the substituent effect is very similar to that of the 4-t-butyl group and at probe temperature the time-average signal is about 11 Hz. upfield of the cyclohexanecarbonitrile signal.

Substituent effects on complex formation between cyclohexanecarbonitriles and iodine monochloride have been explained on the basis of the cyclohexane ring being

TABLE 1. *Methine proton shifts*† *of substituted cyclohexanecarbonitriles*

Substituent	H equatorial +30°	H equatorial −90°	H averaged +30°	H axial +30°	H axial −90°
4-t-Butyl	280·0	284·1	—	220·5	225·2
H	—	294·4	257·5	—	242·3
4,4-Me$_2$	—	287·6	246·7	—	227·7

† Measured to ±0·2 Hz. at 100MHz and expressed as Hz. downfield from Me$_4$Si using approximately 1M-solutions in CS$_2$.

TABLE 2. *Contributions to the shielding parameter*† *σ (p.p.m.) for the* C-1 *proton of substituted cyclohexanecarbonitriles as a function of internal ring angle*

Component	C-1 proton / Angle	103·5°	105·5°	107·5°	109·5°	111·5°	113·5°	115·5°	117·5°	119·5°
Σ Ring C–C + Σ C-2,3,5,6 × C–H bonds	ax.	−0·1867	−0·4092	−0·5887	−0·7448	−0·8881	−1·0110	−1·1482	−1·1959	−1·2468
	eq.	−1·1445	−1·2085	−1·2304	−1·2526	−1·2644	−1·2646	−1·2595	−1·2504	−1·2461
Σ C-4 hydrogens (×2)	ax.	−0·0527	−0·0573	−0·0602	−0·0623	−0·0629	−0·0627	−0·0610	−0·0593	−0·0529
	eq.	−0·0022	−0·0061	−0·0101	−0·0139	−0·0179	−0·0221	−0·0271	−0·0326	−0·0414
Σ C-4 methyls (×2)	ax.	+0·0142	+0·0039	−0·0046	−0·0104	−0·0152	−0·0185	−0·0199	−0·0203	−0·0172
	eq.	+0·0158	+0·0154	+0·0146	+0·0128	+0·0103	+0·0077	+0·0036	−0·0013	−0·0072
ΣC-4 Bu^t eq. H ax.	ax.	−0·0204	−0·0260	−0·0304	−0·0334	−0·0344	−0·0345	−0·0329	−0·0308	−0·0244
	eq.	+0·0104	+0·0064	+0·0025	−0·0012	−0·0048	−0·0089	−0·0135	−0·0183	−0·0239
ΣC-1–CN eq. or ax.	ax. or eq.	−0·9707	−0·9070	−0·8426	−0·7784	−0·7145	−0·6513	−0·5887	−0·5287	−0·4696
Σ C-1 C≡N eq. or ax.	ax. or eq.	+0·7634	+0·7788	+0·7934	+0·8070	+0·8200	+0·8321	+0·8436	+0·8543	+0·8645

† +ve value denotes shielding.

flattened by the 4-t-butyl group.[2] This would be expected to alter the anisotropic shielding of the ring protons. Using the McConnell equation as modified by ApSimon and his co-workers[3] we have calculated as a function of ring angle the shielding parameters for the C-1 protons of the two chair conformations of cyclohexanecarbonitrile, *cis*- and *trans*-4-t-butylcyclohexanecarbonitrile, and the two chair conformations of 4,4-dimethylcyclohexanecarbonitrile. The calculation requires a knowledge of the H–C(ring)–H angles as a function of the internal ring angle and this is derived from expressions quoted by Mislow.[4] The distances and angles between points on a particular bond and the methine proton were calculated trigonometrically *via* projection on to a vertical plane through C-1 and C-4. The values for the C–H and C–C bond anisotropies were those of ApSimon and his co-workers[3] and for the C≡N group Reddy and Goldstein's value was used.[5] The correction term introduced by ApSimon into the modified McConnell equation required a value for the diamagnetic susceptibility of C≡N which was taken from the literature.[6]

The results are given in Table 2. Values calculated for an internal ring angle of 111·5° may be taken as those for an unstrained chair conformation.[7] Smaller ring angles correspond to puckering and larger ones to flattening. Considering separately the conformers with the methine protons axial and equatorial, and summing the contributions accordingly, it seems that the calculated anisotropic effects of the 4-t-butyl and *gem*-dimethyl groups on chemical shift are small, corresponding at 100 MHz. to less than 4Hz. The calculated differences in shielding parameters are of the right order, ($\sigma_{eq} - \sigma_{ax}$) for cyclohexanecarbonitrile being 0·35 p.p.m. which corresponds with the measured values of 0·23—0·48 p.p.m. for cyclohexane[8] depending on temperature (the effect of the nitrile group on the methine proton is independent of conformation). The calculated effects of ring flattening and puckering in *cis*- and *trans*-4-t-butylcyclohexanecarbonitrile are shown in the Figure. This indicates that the chemical shifts of the methine protons are sensitive to ring flattening, the equatorial proton becoming shielded and the axial proton becoming deshielded

The results of the calculation (Table 2; Figure 1) differ from reality (Table 1) on at least two points. (i) the observed difference ($\sigma_{eq} - \sigma_{ax}$) is 0·52 p.p.m. not 0·35 p.p.m. (ii) Relative to the values for the presumably unstrained cyclohexanecarbonitrile conformers the equatorial proton of *cis*-4-t-butylcyclohexanecarbonitrile is shielded by 0·10 p.p.m. (qualitatively correct) but the axial proton of *trans*-4-t-butylcyclohexanecarbonitrile is shielded by 0·17 p.p.m. (qualitatively wrong).

We suggest that the discrepancies are a result of assuming that the powerful inductive effect of nitrile groups is the same in both conformations. It is known that the dipole moments of the two conformers of cyclohexyl fluoride differ significantly[9a] the value for the equatorial fluoride being the greater by 16%. The dipole moment of n-propyl fluoride is similarly conformation-dependent.[9b] Vectorial addition of bond moments does not account for the difference and the results therefore indicate that polarisabilities along the planar W conformations present in the equatorial cyclohexyl fluoride and the staggered, *trans*,conformation of n-propyl fluoride are greater than in the alternative conformations.

The nitrile group, like fluorine, is powerfully electron-withdrawing, and it is likely that the induced charge is more dispersed in the equatorial conformer than the axial conformer. The nitrile group would exert an inductive deshielding influence on both methine protons. However, from the above considerations the induced charge at C-1 is less with CN equatorial and in that conformer the axial

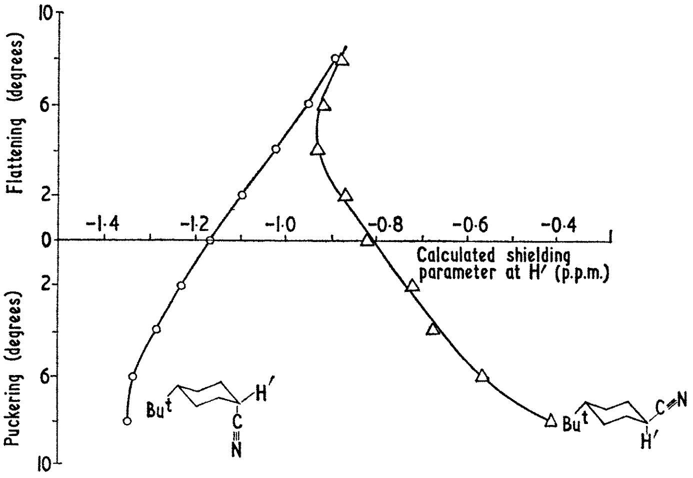
Table 3. *Conformational preferences in the 4,4-dimethylcyclohexyl system*

Group X	Solvent	Chemical shift† 4-Bu^t compound *ax*.H	Chemical shift† 4-Bu^t compound *eq*.H	4,4-Me$_2$	K_{30}*	$-\Delta G^0_X$
CN	CCl_4	228·3	287.4	251·1	1·59	0·28
	$CDCl_3$	232·8	293·0	255·1	1·70	0·31
	$(CD_3)_2CO$	242·7	297.9	264·7	1·51	0·24
	CS_2	220·5	280·0	246·7	1·27	0·14
OH	CCl_4	339·7	393·0	349·6	4·39	0·88
	$CDCl_3$	348·9	400·8	357·9	2·54	0·55
	$(CD_3)_2CO$	342·3	394·8	351·6	4·65	0·91
Br	CCl_4	(384·7)‡	(457·0)‡	409·8	1·88	0·38
	$CDCl_3$	(394·0)	(465·8)	416·0	2·26	0·48
	CS_2	(381·8)	(453·8)	405·8	2·00	0·41
CO_2H	$CDCl_3$	223·6	268·7	225·2	22·2	1·85
	$(CD_3)_2CO$	219·5	262·3	220·8	31·9	2·05

* Calculated using Eliel's equation.
† Measured at 30° at 100 MHz. and expressed as Hz. downfield from Me_4Si.
‡ Converted into values at 100 MHz. from values in ref. 1b.

methine proton is less deshielded than the equatorial proton of the alternative conformer. Consequently ($\sigma_{eq} - \sigma_{ax}$) is greater than indicated by bond anisotropy calculations. The explanation of the second discrepancy follows from this. We assume that the inductively deshielding effect of the axial nitrile group is not likely to be a function of the geometry of the cyclohexyl group and will not vary greatly with ring flattening. The difference between chemical shifts for the equatorial methine protons of cyclohexanecarbonitrile and *cis*-4-t-butylcyclohexanecarbonitrile at −90° (0·10 p.p.m.) is therefore probably due to changes in anisotropic shielding with ring geometry. From Figure 1 we judge the ring flattening to be 2—3°. The effect of similar ring flattening on the conformer with an equatorial nitrile would be not only to leave the W coplanar conformation undisturbed but to bring more bonds towards its plane. To explain the observed increase in shielding of axial methine protons as a result of ring flattening it is therefore necessary further to assume that the polarisability of the cyclohexyl group along the equatorial vector increases as the ring flattens. The consequent lessening of the inductive deshielding of the axial methine proton must more than offset the accompanying increased deshielding due to changes in the anisotropic component.

The effect of 4,4-dimethyl substitution is very similar to that of the 4-t-butyl group and supports the view that the strain imposed by the equatorial t-butyl group is approximately equivalent to that of an axial methyl group. A crude estimate using a standard function[10] suggests that ten C–C–C bond angle deformations each of 3° would require 1·8 kcal.mole^{-1}, of the same order as the conformational preference of the methyl group.



Figure

The similarity of the 4-t-butyl and 4,4-dimethyl substituent effects offers the hope that chemical shifts from 4-t-butyl "locked" compounds may be combined with values from the conformationally mobile 4,4-dimethyl series to give directly conformational preferences at probe temperature. The substituent effects on chemical shift would be mutually compensating in the Eliel equation. This method gives reasonable values[11] for the conformational preferences of CN,OH,Br, and a rather high value for CO_2H (Table 3).

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