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INTRINSIC ASYMMETRY

ITS EFFECT ON THE CHEMICAL SHIFT OF GROUPS WHICH ARE NOT DIASTEREOTOPIC

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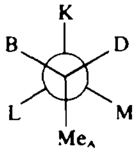
Abstract—The effect of intrinsic asymmetry on chemical shifts in a more generalized situation than that of diastereotopic groups is illustrated using substituted ethanes in which rotation is slow on the NMR timescale. The effect of different substituents on the magnitude of the asymmetry shifts is demonstrated and is tentatively linked to bond polarisability.

Intrinsic asymmetry and its effects on chemical shifts in NMR spectroscopy has been of recurrent interest since Gutowsky's original paper,[1] and the subject has been reviewed recently.[2] The essence of intrinsic asymmetry in this context, although it has never been so stated, is that the chemical shift of a group A shown as a Me group in **1** will change if the groups B and D are interchanged to give **2**.

That this does not disagree with the accepted description of the effects of intrinsic asymmetry on the chemical shifts of diastereotopic groups is easy to demonstrate. The consequence of intrinsic asymmetry for diastereotopic groups is normally stated in a form such as: "If in **3** the populations of the three possible conformations **4**–**6** were the same, the chemical shift of A would still be different from the chemical shift of B". This can be paraphrased; either the shift of A when it is between L and M, **4**, is different from the chemical shift of B when it is between L and M, **6**, (i.e. A – LM ≠ B – LM) or A – KL ≠ B – KL or A – KM ≠ B – KM. That one of these be true is the minimum requirement; it is of course likely that if one of these inequalities hold, then they all hold. Thus stated, the essential similarity to the statement in the first paragraph of this paper is apparent, for comparing A – LM and B – LM is precisley looking at the effect of the reversal of groups B and D in **1** where B = Me, D = X. Thus the essence of intrinsic asymmetry as defined in the first paragraph, insofar as it does not apply to diastereotopic groups of nuclei, but to a single nucleus or group of nuclei, is a more general statement than that commonly used up to now. All of the interest to date has been in examples where two of groups A, B and D in **1** are the same and therefore diastereotopic, but the basic concept as presented above does not require diastereotopic groups. Such groups are, in fact a complicating factors.



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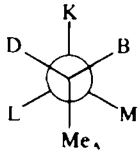

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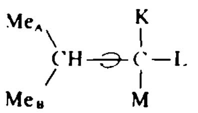

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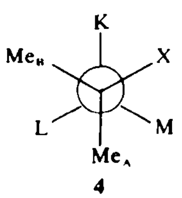
Further, the basic concept does not require that in the second group in **1** K, L and M be different. All that is necessary is that L and M be different. Thus in molecules such as $Me_2CX–CXMe_2$ which have the appearance of high symmetry the effects of intrinsic asymmetry should be seen in the difference in chemical shift between Me groups A in situations **7** and **8**!

If rotation about the central bond in ABDC–CKLM, **1**, takes place rapidly on the NMR timescale, there are introduced two large complications which make the study of intrinsic asymmetry particularly difficult. Three conformations are now populated, and there will be a different intrinsic asymmetry contribution in each case. Further, the populations of the three conformations are unlikely to be equal. Thus any observed difference in chemical shifts is due to a complex weighted combination of intrinsic asymmetry and conformational effects.

The consideration of diastereotopic groups, even in molecules where populations of the three conformations are equal[3] is not wholly satisfactory since the observed chemical shift difference is the mean of the difference produced by the changing intrinsic asymmetry effects in the three conformations.

Is thus seems to me worth while to look at the question of intrinsic asymmetry in situations uncomplicated by problems of diastereotopicity and internal rotation and I would now report on several molecules of the type $Me_2CX–CYMe_2$ where X may or may not be the same as Y, and their NMR spectra at low temperatures where



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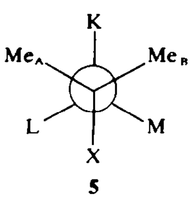

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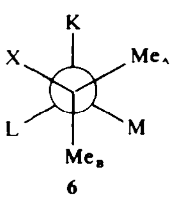

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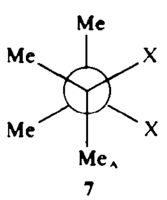

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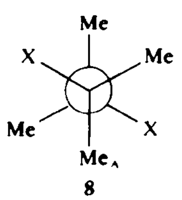

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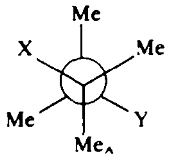
rotation about the central C–C bond is slow on the NMR timescale. The critical fact to be determined is the extent to which the chemical shift of Me_A in **9**, i.e. the chemical shift of the Me group in the *trans*-conformation, is different from the chemical shift of Me_A in **10**, i.e. one of the chemical shifts in the *gauche*-conformation. The magnitude of this difference is a quantitative measure of intrinsic asymmetry.



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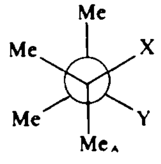

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RESULTS AND DISCUSSION

The NMR spectra of the compounds **11–22** are temperature dependent. As an example, that of **12** at room temperature comprises a singlet due to Me_X, an unsymmetrical doublet due to Me_Y and a multiplet due to Y = H. As the temperature is lowered signals broaden and split and at −120°, the Me_X signal is a 1:4.25:1 triplet, the Me_Y signal is three doublets of relative intensities as for the Me_X signal, and the tertiary hydrogen signal is complex. Rotation about the central bond has become slow on the NMR timescale and the observed spectrum is a composite of that of the *gauche* and that of the *trans*-isomer, there being different amounts of the two isomers present. It is the chemical shifts of the various Me signals at low temperature that are of significance to this paper, and these are shown in Table 1. Further details of spectra are in the Experimental.

$(Me_X)_2CX{-}\circlearrowleft{-}CY(Me_Y)_2$

	11	**12**	**13**	**14**	**15**	**16**	**17**
X	Cl	Br	I	Cl	Br	I	C≡N
Y	H	H	H	Cl	Br	I	C≡N

	18	**19**	**20**	**21**	**22**
X	I	Ph	m-Cl–Ph	Et	CH_2tBu
Y	pMeO–Ph	Ph	m-Cl–Ph	Et	CH_2tBu

In all cases separate signals are seen for *gauche* and *trans* isomers; for each geminal $Me_2C\langle$ group there is a singlet from the *trans* isomer and a doublet from the *gauche* isomer (complicated when X or Y is hydrogen by further coupling). In certain cases, only one part of the doublet for the *gauche* isomer is observed and it is reasonably concluded that the other part overlaps the signal for the *trans*-isomer.

It is necessary to decide which of the two signals arising from a *gauche* conformation should be compared with the corresponding signal of the *trans* conformation, i.e. which is due to Me-*trans*-to-Me in the *gauche* conformation. I have assigned the signal nearer to the *trans*-signal to this Me thereby if anything underestimating the magnitude of the intrinsic asymmetry shift. In certain cases, discussed in the Experimental, there is specific evidence that this assignment is correct.

There are three significant facts to emerge from the results in Table 1. The least surprising is that when X and Y are alkyl groups, i.e. little different from the Me groups whose shifts are being measured (entries **21** and **22** in the Table), the intrinsic asymmetry shifts are small or unmeasurable. Rather more surprising is the fact that when *X* and Y are diamagnetically anisotropic phenyl groups (entries **19** and **20** in Table 1), the intrinsic asymmetry shifts are immeasurably small. The third fact is that only when at least one of X and Y is a halogen atom are substantial intrinsic asymmetry shifts (up to 15.0 Hz at 100 MHz) obtained, and that these are larger for iodine than for bromine, which in turn produces larger shifts than chlorine. Further if X is a halogen atom, and Y is a H atom, the intrinsic asymmetry produced in Me_Y is greater than that in Me_X (compare entries **11a** and **11b** or **12a** and **12b**). It seems likely that the shifts in the examples **11–16** are a consequence of the C–hal bonds rather than the C–H ones.

A final interesting point is that the effect of two C–hal bonds compared with that of one C–hal bond, and one C–H bond is not consistent. Two C–Cl bonds produce no intrinsic asymmetry shift (entry **14**); two C–Br bonds, entry **15**, produce a reduced intrinsic asymmetry shift, *cf* entries **12a** and **12b**; two C–I bonds, entry **16**, produce a slightly enhanced shift, *cf* entries **13a** and **13b**. This last comparison may be complicated by an unavoidable change of solvent, but the effect of solvent changes is small as illustrated below.

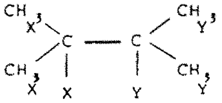
That there should be intrinsic asymmetry shifts is not unexpected. The chemical shift in a group such as Me_A of **1** or **2** reflects a local magnetic field which is a modification of the applied magnetic field resulting from the interactions of all atoms or groups of atoms close to Me_A. In changing from **1** to **2** there is an alteration in the geometry of some of these interactions (notably those of B and D with L and M) so the local magnetic field and therefore the chemical shift of Me_A should change. What is interesting and perhaps unexpected is the variation in the magnitude of the intrinsic asymmetry shift in the examples shown, where much is kept constant, viz. the four Me groups, and X and Y are varied in a systematic way.

The most striking feature of the results in Table 1 is that large shifts are associated with molecular fragments with high diamagnetic susceptibilities and vice versa. Typical values[4] ($-10^6\chi$) are C≡N, −0.8; H, 2.9; C, 6.0; Cl, 17.2; Br, 26.5; I, 40.5. It is surprising that the phenyl groups have little effect, because there is expected to be conjugative exaltation of the diamagnetic susceptibility.

If, on the other hand, one thinks in terms of electrical polarisability, the electrical equivalent of diamagnetic susceptibility, the phenyl group is less susceptible to exaltation.[5] The effect of changing the configuration can then be considered to be electrical, for in changing the configuration of the molecule (i.e. going from structure **1** to structure **2**), interactions along the ethane bond change, and thus there are small changes in the polarisation of the various bonds. The intrinsic asymmetry shifts of this paper might then be considered as the consequences of these electrical changes, observed when subsequently the substance is put in a magnetic field.

I should like to call attention to two further examples of intrinsic asymmetry of the same type as I define here, which are already in the literature. Newmark and

Table 1. Chemical shift of the methyl groups in *gauche*- and *trans*-conformations of compounds **11–22** when rotation is slow on the NMR timescale[f]



	Compound	% trans conformation	Methyl Signal Chemical Shift[a]				Intrinsic Asymmetry Shift[b]		Reference
			Which hydrogen	in trans Isomer	two different shifts in gauche isomer				
11 a	X = Cl	59	X	1.579	1.629	1.414	5.0	(16.5)	i,iii,iv
11 b	Y = H		Y	1.050	1.126	0.967	7.6	(8.3)	
12 a	X = Br	68	X	1.787	1.874	1.625	8.7	(16.2)	i,iv
12 b	Y = H		Y	0.041	1.186	0.925	11.6	(14.3)	
13 a	X = I	88	X	1.915	2.060	1.696	14.5	(36.4)	i,iv
13 b	Y = H		Y	(e)	(e)	(e)	(e)		
14	X = Y = Cl	79	X	1.726	(d)	1.590	0	(13.6)	i
15	X = Y = Br	75	X	1.994	2.032	1.800	3.8	(19.4)	i
16	X = Y = I	94	X	1.932	2.082	1.716	15.0	(21.6)	i
17	X = Y = C ≡ N	92	X	1.492	(d)	1.250	0	(24.2)	
18 a	X = I, Y = pMeOPh	67	X	1.858	1.922	2.121	6.4	(26.3)	i
18 b			Y	1.642		1.342	0	(30.0)	i
19	X = Y = phenyl	64	X	1.167	(d)	1.450	0	(28.3)	ii
20	X = Y = *m*-chlorophenyl	54	X	1.146	(d)	1.428	0	(28.2)	i
21	X = Y = ethyl	33	X	0.683	(d)	0.733	0	(5.0)	i,ii
22	X = Y = neopentyl[c]	36	X	0.920	0.927	0.914	0.6	(0.7)	v

[a] δ-values.

[b] In Hz at 100 MHz operating frequency. For solvents, see Experimental.

[c] Results are measured and transcribed from the 220 MHz spectrum.

[d] Not observed and presumably underneath the signal of the *trans* isomer.

[e] The spectrum was too complex to analyse.

[f] At various low temperatures, see Experimental or *loc. cit.*

(i) This work; (ii) C. H. Bushweller and W. G. Anderson, *Tetrahedron Letters*, 1811 (1972); (iii) Ref. 10; (iv) Ref. 11; (v) J. E. Anderson and H. Pearson, *J. Am. Chem. Soc.* **97**, 764 (1975).

Sederholm[6] have reported the ^{19}F spectra of the compounds **23** and **24** when rotation is slow on the NMR timescale. **23** shows a singlet S for the *trans*-conformation

$CF_2Br–CCl_2Br$ **23** $CF_2Br–CFBr_2$ **24**

and an AB quartet for the *gauche*-conformation, the relative chemical shifts of S, A and B being 0, 113.5 and 298.3 Hz (at 56.4 MHz operating frequency), the intrinsic asymmetry shift being therefore at least 113.5 Hz. **24** shows similar spectra to **23**, complicated by further coupling to the additional fluorine atom. The relative chemical shifts of S, A and B are respectively 0.0, 316.3 and 487.0 Hz (at 56.4 MHz operating frequency) where the intrinsic asymmetry shift is at least 316.3 Hz.

It would be foolish to attribute the magnitude of the intrinsic asymmetry in these latter cases to specific bonds, but these results do nothing to contradict the suggestion that the magnitude of the asymmetry is related to the polarisability of the bonds involved.

Another factor whose importance in determining the magnitude of the intrinsic asymmetry shift ought to be discussed, is steric interactions. If these differ in the two isomers, they may produce different distortions so that the groups whose shifts are being compared are not in precisely the same position. Another quite simple way of saying this is that the dihedral angles will not be precisley those of 60° and 180° implied by the diagrams drawn, and will vary from configuration to configuration. I think that there is no doubt that these differences in position obtain, but it is not clear how they should affect the shifts observed, and most particularly, how they alone could explain the differences in intrinsic asymmetry shifts reported in Table 1. That no shifts are observed with entries **19** to **21** where X's are large substituents phenyl or ethyl, suggests that this steric effect is not large. It cannot be excluded that in these two cases the steric shift is in the opposite sense to the shift due to differing polarisability. It is however, my opinion that nothing in this present work indicates that this steric factor is important.

Several other demonstrations of intrinsic asymmetry chemical shifts in molecules less symmetrical than the ones I discuss have been given.[2,3,7-9] Only those which involve low temperature NMR spectroscopy avoid the problem of conformational averaging. Thus, the otherwise elegant demonstration by McKenna *et al.*[3] that the hydrogens A and B in **25** have different chemical shifts, even though the populations of the three likely conformations about the bond shown are equal, is of little use in deciding the factors affecting the magnitude of intrinsic asymmetry shifts. This arises because the observed shift of δ_{AB} is the *average* of the shift produced in these three separate conformations.

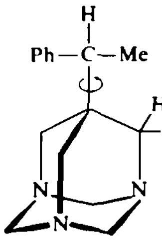


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Table 2 shows the effect of changing the solvent on the Intrinsic Asymmetry shift in $(CH_3)_2CCl$–$CH(CH_3)_2$. The methyls on the carbon bearing the chlorine are little affected by the change in solvent, the shift varying between 5.0 and 5.3 Hz. For the other methyl the shift varies from 7.6 to 9.5 Hz. The latter variation is probably significantly greater than experimental error. However the effect is small, and we would comment no further than to say that the results in Table 1 for different compounds run in different solvents can probably be compared quite safely. This topic has been discussed by Binsch.[8]

EXPERIMENTAL

NMR spectra were measured and calibrated as described previously.[10] Relative amounts of isomers were measured from NMR spectra using a planimeter. The NMR spectra of the compounds **11**–**13** have been reported completely elsewhere,[11] but have not been discussed in terms of intrinsic asymmetry.

The compounds with X = Y = Cl, Br, CN, **14**, **15**, and **17** are well known.[12,13] The compound with X = I, Y = *p*-MeOPh, **18**, was an adventitious product of an attempted synthesis of 2,2 - dimethyl - 3 - iodo - 3 - p - anisylbutane,[14] and was not sufficiently stable for analysis. It melts at 68–72° and its structure was assigned on the basis of its NMR spectrum.

The compound X = Y = *m*-chlorophenyl, **20**, was an adventitious product of an attempted synthesis of 2,3,3 - trimethyl - 2 - *m* - chlorophenylbutane,[14] m.p. 134–5°. (Found: C, 70.80; H, 6.67. $C_{18}H_{20}Cl_2$ requires: C, 70.36; H, 6.56%).

The compound X = Y = I, **16**, was prepared in an NMR tube by adding a small crystal of iodine to a soln of 2,3 - dimethyl - 2 - butene. After several hr at ambient temp. a new signal develops with a chemical shift close to that expected for the di-iodide. The intensity of the olefin signal is diminished in intensity by this time. No attempt was made to isolate and characterise this diiodide. That the signal split to a doublet and a singlet at low temp. in a manner quite analogous to that of the other dihalides was taken as a final proof of structure.

The solvent used in the results reported in Table 1 was dichlorodifluoromethane except that for **14**, **15**, **18** and **20**, solubility in this solvent at low temperatures was insufficient. The results for these compounds are for vinyl chloride soln. **11** was studied in several solvents as is reported in Table 2, and the absence of a shift in **14** was confirmed by additional measurements in dimethylether soln.

Tables 1 and 2 describe the NMR spectra of compounds studied at low temp., which in all cases is about −125°. The free-energy differences between the *trans* and one *gauche* conformation at this temp., calculated from the expression $\Delta G_0 = 2.3R.148.2 \log k$ where $k = 2p_{trans}/(1 - p_{trans})$ are as follows (entry number in Table 1, free energy difference (cal mol^{-1})) **11**, 304; **12**, 426; **13**, 791; **14**, 794; **15**, 527; **16**, 1014; **17**; 923; **18**, 412; **19**; 373; **20**, 251; **21**, 0; **22**, 35.

The two signals due to the t-butyl group of 2 - chloro - 2,3,3 - trimethylbutanes when rotation is slow on the NMR timescale[11] appear at δ 1.12 and δ 0.98. The former downfield signal being more intense is due to the two Me's of the t-Bu group *trans-to-a*-Me group along the central bond. This suggests that the downfield of two signals due to the isopropyl group in the *gauche* isomer **11b**, at δ = 1.126 should be assigned to the Me-*trans*-to-Me. This applies also to **12b**.

Examination of molecular models and a comparison of the various chemical shifts of t-Bu-Me signals of 2 chloro - 2,3,3 - trimethylbutane and 2 chloro - 2,3 - dimethyl - 2 - phenyl - butane[15] when rotation is slow on the NMR timescale, suggest that Me-*trans*-to-Ph should be particularly far downfield. It is thus reasonable to postulate for compounds **19** and **20**, that it is the signal presumed to overlap the signal from the *trans*-isomer that should be compared with the signal from the *trans*-isomer that is, that the intrinsic asymmetry shift is 0.

Table 2. Effect of solvent on intrinsic asymmetry shifts in $(CH_{3A})_2CCl$–$CH(CH_{3B})_2$

Solvent		Methyl Hydrogen Chemical Shifts[a]			Intrinsic Asymmetry Shift[b]
		trans	gauche		
CF_2Cl_2	A	1.579	1.629	1.414	5.0 (or 21.5)
	B	1.050	1.126	0.967	7.6 (or 15.9)
Vinyl chloride	A	1.607	1.554	1.392	5.3 (or 16.2)
	B	1.082	0.997	0.884	8.5 (or 11.3)
Dimethyl ether	A	1.611	1.558	1.407	5.3 (or 15.1)
	B	1.117	1.022	0.936	9.5 (or 8.6)

[a] δ-value.
[b] In Hz at 100 MHz operating frequency.

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