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ISOTOPE EFFECTS—III

HYDROGEN ISOTOPE EFFECTS ON CONFORMATIONAL EQUILIBRIA DERIVATIVES OF CYCLOHEXANE

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Abstract—Conformational equilibrium isotope effects (in J mol^{-1}) have been measured for deuteriation of one methyl or methylene group in the *trans* stereoisomers of 1,3-dimethylcyclohexane (-46 ± 10), 2,6- (-80 ± 28) and 3,5-dimethylcyclohexanone (40 ± 15), and 3-methyl- (48 ± 3) and 3-hydroxymethyl-1-trifluoromethylcyclohexane (45—49 ± 3 in toluene, acetone or methanol). The observed effects are independent of solvent for the hydroxymethyl group. The isotope effects for the methyl group in *trans*-**4** are proportional to the number of deuterium atoms.

Relatively few steric isotope effects have been reported for systems in which the steric strain energy associated with the site of isotopic substitution can be measured or estimated and all have been for the replacement of hydrogen by deuterium; published data has been briefly summarised.[1] Kinetic steric isotope effects have been measured only for *either* conformational rate processes with very large steric strains in the transition states (typically 80–100 KJ mol^{-1}) *or* reactions in which steric strain (or its relief) is only a minor part of the total energy of activation. Conformational equilibria are attractive for the study of steric isotope effects when the strain energy is small but require very high sensitivity (10 J mol^{-1} or better). We have shown[1] that weighted average NMR chemical shifts δ may be used in eqn (1)[2]

$$K = (\delta_E - \delta)/(\delta - \delta_A) \qquad (1)$$

(δ_E and δ_A are the chemical shifts for a specified nucleus in the two chair conformers, Figs. 1 and 2, and must be derived more or less indirectly) with sufficient sensitivity using proton decoupled ^{13}C spectra and that the systematic errors that affect the evaluation of K are largely avoided when a *ratio* of equilibrium constants K^D/K^H is determined for isotopically differentiated species. In our earlier examples of conformational equilibrium isotope effects (CEIEs)[1] $K^H = 1$ (apart from a ^{13}C effect which is expected to be much smaller than deuterium isotope effects and therefore negligible at present sensitivities) and in this paper we report results for equilibria with $K^H = 1$ using ^{13}C spectra and with $K^H \neq 1$ using ^{19}F spectra which allow the following to be demonstrated for the first time:

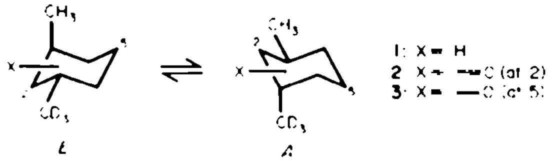


Fig. 1. Conformational equilibria in d$_3$-derivatives of the *trans* isomers of **1–3**: the *E* conformer (eq. CD$_3$) has an *axial* CH$_3$ (the resonance observed in the ^{13}C NMR spectrum) and *vice versa*.

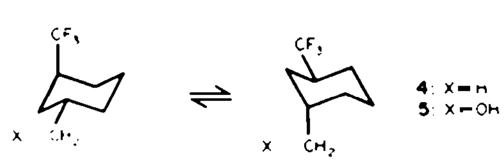


Fig. 2. Conformational equilibria in *trans*-**4** (d$_0$ d$_3$) and *trans*-**5** (d$_0$ and d$_2$): the *E* conformer has an *axial* CF$_3$ and the *A* conformer has an *equatorial* CF$_3$.

(a) The equality of CEIEs for deuteriation of the same group (unhindered methyl on a cyclohexane ring) studied in two different compounds (**1** and **4**) using nuclei (^{13}C and ^{19}F) involving different possibilities for systematic and random errors;

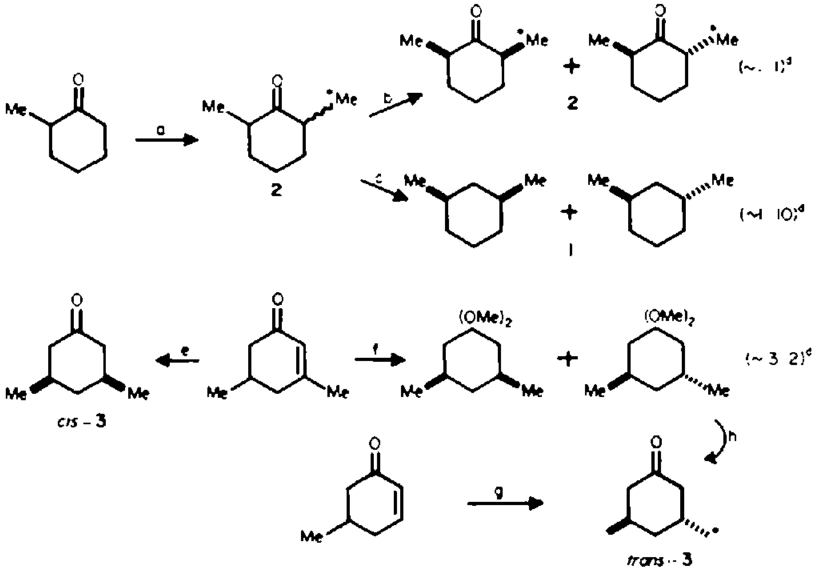
(b) The CEIE for deuteriation of a Me group (in **4**) is proportionate to the number of deuterium atoms;

(c) The absence of a solvent effect on a CEIE (in *trans*-**5**).

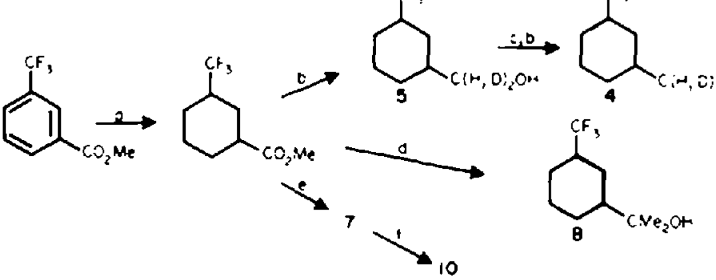
The compounds used in this work were prepared by known methods, or simple adaptations of them, as shown in Schemes 1 and 2 require few comments. The enrichment in *trans* compounds resulting in steps b and c (Scheme 1) are examples of the effect of A-strain[3] (in the protonated form of the ketone in step b[4] and in the intermediate hydrazone in step c). The use of ketals to separate *trans*-**3** from its *cis* isomer greatly improves the efficiency of the preparative gas liquid chromatography (PGLC).

An extensive series of derivatives of trifluoromethylcyclohexane have been prepared by Della,[5] who characterised the *cis* isomers as well as *cis*/*trans* (~4 : 1) mixtures. The liquids **4–8** agree in properties very closely with the compounds described by Della except for the refractive index for **5**, the structure of which was confirmed by elemental analysis for **5**-d$_0$ as well as by spectra (^{1}H and ^{19}F, in agreement with Della; mass). Similarly the structure of the salt **10** was confirmed by analysis and NMR spectra although, as expected, its m.p. was lower than that of the pure *cis* isomer.

The mixtures of *cis* and *trans* isomers of the trifluoromethylcyclohexane derivatives **4–10** were *not* separated because (a) the anancomeric *cis* isomers served as useful internal references for ^{19}F spectra, (b) in several instances mixtures of isotopically differentiated species gave clearly separated ^{19}F resonances so that very reliable

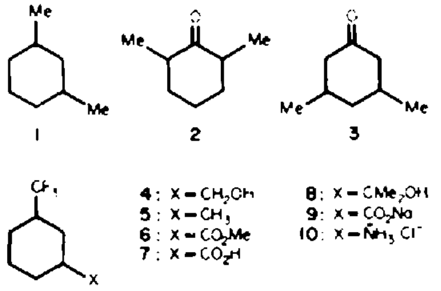


Scheme 1. a: Me_2CO_3 + NaH; MeI *or* CD_3I; HCl/AcOH/H_2O. b: 98% H_2SO_4. c: N_2H_4 + KOH/O(CH_2CH_2OH)$_2$. d: PGLC. e: H_2 + Pd/C[7]. f: H_2 + Rh/Al_2O_3.[8] g: CD_3MgI + CuCl.[9] h: 2M HCl. (*Site of isotopic substitution)



Scheme 2. H_2 + PtO_2/AcOH. b: $LiAlH_4$ *or* $LiAlD_4$. c: TosCl + pyridine. d: MeMgI. e: OH^-; H^+. f: NaN_3 + H_2SO_4.

measurements of isotope effects could be made by internal comparison, which eliminates uncertainties that result from preparing separate solutions (as is necessary for the ^{13}C spectra used for **1**–**3**), and the possible slight variation in the *cis/trans* ratio do not matter, and (c) allowed the preparations to be carried out on a considerably larger scale which facilitates purification.



4: X = CH_2OH
5: X = CH_3
6: X = CO_2Me
7: X = CO_2H
8: X = CMe_2OH
9: X = CO_2Na
10: X = $NH_3^+Cl^-$

EXPERIMENTAL

NMR spectra. Routine ^1H and ^{19}F spectra and ^{19}F variable temperature spectra (CF_3CCl_3 as lock, with a frequency counter to calibrate spectra) were measured with a Perkin–Elmer R32 spectrometer (^1H at 90 MHz, ^{19}F at 86.676 MHz). Spectra for isotope effects were measured with proton decoupling on Brüker WH90 (^{13}C at 22.63 MHz, using a sweep width of 1000 Hz and accumulating FIDs into 8 K memory addresses to give a digital resolution of 0.0108 ppm; ^{19}F at 84.676 MHz, sweep width 250 Hz, FID 8 K addresses, digital resolution 0.00072 ppm) and Varian CFT 20 (^{13}C at 20 MHz, sweep width 1000 Hz, 8 K addresses, digital resolution 0.012 ppm) FT spectrometers using deuterium internal locks. Temperatures were controlled to ±1 K and were checked with methanol samples.[4]

Mass spectra. Mass spectra were measured with A.E.I. MS 9 and Varian CH7 spectrometers and confirmed the abundance of the required isotopic species was always >95%.

GLC. Analytical GLC was carried out on Pye 104 or Hewlett–Packard 5700A chromatographs using flame ionisation detectors and packed columns (10% Carbowax 1540 at 70°). Preparative GLC was carried out on a Pye 105 chromatograph using 5 or 10 m × 1 cm packed columns with 10% OV1 at 100–130°.

2,6-*Dimethylcyclohexanone* (d_0 *and* d_3). 2-Methylcyclohexanone (56 g) was condensed with dimethyl carbonate (65 ml) using sodium hydride (60% dispersion in oil, 44 g) in benzene (600 ml) at 80° (6 hr) to give 2-methoxycarbonyl-6-methylcyclohexanone (55 g), b.p. 100–106°/10 mm, n_D^{18} = 1.4703. The latter (4.25 g) was methylated with *either* methyl *or* methyl-d_3 iodide (3.8 g) and sodium hydride (free from oil, from 1 g of the suspension) in ether (25 ml) at 20° (8 d), the product (4 g) was hydrolysed with AcOH (30 ml), water (3 ml) and c HCl (15 ml) (4 d at b.p.), and the resulting 2,6-dimethyl- or 2-methyl-6-methyl-d_3-cyclohexanone (1.95 g) was distilled, b.p. 174–176°/760 mm. The mixtures (*cis* : *trans* 9:1) were isomerised as described by D'Silva and Ringold[4] giving ~1:1 mixtures, separated by PGLC.

1,3-Dimethylcyclohexane. 2,6-Dimethylcyclohexanone (d_0 *or* d_3) mainly *cis*, 2.5 g) was reduced with N_2H_4 (hydrate, 100%, 2 ml), KOH (2.8 g), and diethylene glycol (20 ml) at 200° and the crude product (**1**, d_0 or d_3; *cis* : *trans* = 1 : 9) was separated by PGLC.

3,5-Dimethylcyclohexanone. 3,5-Dimethylcyclohex-2-enone was hydrogenated over (a) Pd/C[7] and (b) Rh/Al_2O_3[7,8] to give (a) *cis*- and (b) *cis*- and *trans*- (~3 : 2) 3,5-dimethylcyclohexanone. The latter mixture (20 g) was converted by methyl orthoformate (43 g), MeOH (10 ml) and c HCl (0.25 ml) into the dimethyl ketals (14 g), b.p. 85°/15 mm, which were separated by PGLC and hydrolysed by 2M HCl. *trans*-3-Methyl-5-(methyl-d_3)-cyclohexanone (**3**) was prepared from 5-methylcyclohexen-2-enone (2.8 g) using CD_3MgI (from CD_3I, 4.0 g, and Mg, 0.6 g) and CuCl (0.1 g)[9] and purified as the semicarbazone, which was hydrolysed by 2M HCl.

Derivatives of trifluoromethylcyclohexane. *m*-Trifluoromethylbenzoic acid (40 g) was esterified with MeOH (16 g), c H_2SO_4 (4 ml) and benzene (100 ml) and the methyl ester (32 g), b.p. 92°/25 mm (lit.[5] 103–104°/25 mm) was hydrogenated over PtO_2 giving **6** (*cis* : *trans* = 4 : 1). The ester **6** was hydrolysed[5] to **7**, n_D^{23} = 1.4185 (lit.[5] n_D^{21} = 1.4170, *cis*), and reacted with MeMgI in ether to give **8**, b.p. 45°/0.15 mm, n_D^{28} = 1.4296 (Found: C, 57.23; H, 809; F, 27.48. $C_{10}H_{17}OF_3$ requires: C, 57.13; H, 8.15; F, 27.11%). Reduction of **6** (5 g) by $LiAlH_4$ or $LiAlD_4$ (1 g) in ether gave **5** (d_0 and d_2), n_D^{18} = 1.4224 (d_0), n_D^{18} = 1.4216 (d_2) (lit. n_D^{28} = 1.4126, *cis*). (Found: C, 52.64; H, 6.94; F, 31.58. Calc. for $C_8H_{13}OF_3$: C, 52.74; H, 7.19; F, 31.28%). The alcohols **9**-d_0 and **9**-d_2 were separately converted into tosylates, each of which (1.65 g) was reduced with $LiAlH_4$ and with $LiAlD_4$ (0.5 g in boiling ether, 1 d) to give 50–70% yields of **4** (d_0 – d_3), b.p. 123–124°/760 mm (lit.[5] b.p. 123–124° for 9-d_0). The acid 7 was converted by the Schmidt reaction[5,10] into **10**, m.p. 192–193° (lit.[5] m.p. 217–218°, *cis*). (Found: C, 41.42; H, 6.34; N, 6.81; F, 27.79; Cl, 17.56. Calc. for $C_7H_{13}NF_3Cl$: C, 41.29; H, 6.43; N, 6.88; F, 27.98; Cl, 71.42%).

RESULTS AND DISCUSSION

The ^{13}C and ^{19}F NMR chemical shifts are collected in Tables 1–4 (the ^1H chemical shifts measured routinely for all the compounds studied have no special interest). Because the methods used to derive chemical shifts for use in Eqns (1) and (2) are markedly different for the two types of spectra they will be discussed separately.

The ^{13}C chemical shifts in Table 1 show that deuterium isotope effects fall off rapidly witm distance in the compounds **1–3**, as in many examples in the literature and are as small as 0.01 ppm when transmitted through three bonds.[11] It seems safe to assume that such direct isotope effects transmitted through five bonds for spatially well separated groups will be between 0 –0.005 ppm at *most*, so that the chemical shifts δ of the CH_3 groups in **1–3**(d_3) may be used together with values of δ_E and δ_A estimated for the isotopically normal compounds **1–3**. When the difference of chemical shifts $\delta^D - \delta^H = \Delta\delta$ is small in relation to $\delta_E - \delta_A$ and direct isotope effects are neglected equation 1 may be used to derive

$$K^D/K^H = 1 - (2 + K^H + 1/K^H)\Delta\delta/(\delta_E - \delta_A) \qquad (2)$$

[with neglect to higher powers of $\Delta\delta/(\delta_E - \delta_A)$]. We use the anancomeric compounds *cis*- and *trans*-**11** to derive the difference (+0.30 ppm) in values of δ(e) *cis*-**1** (one conformer only contributes significantly to the conformational equilibrium so that δ(e) equals the observed δ and δ(e)-*trans*-**1** (= δ_A for *trans*-**1**-d_3, neglecting the direct isotope effect), which is thereby estimated to be 23.27 ppm. Since K^H = 1 for *trans*-**1**, δ(a) = 2δ – δ(e) = 18.17 ppm (= δ_E for *trans*-**1**-d_3) (Scheme 3). Similarly the values of δ_E and δ_A for **2**-d_3 were estimated from **2** and **12**.[12] In the absence of anancomeric derivatives of **3** we use **11** to provide the necessary correction. The excellent additivity observed for ^{13}C chemical shifts in six-membered ring compounds generally suggests that the values of δ_E and δ_A derived in this way will be very good for *trans*-1 and *trans*-2 (errors <0.1 ppm) but are less certain for *trans*-3. The values of K^D, $\Delta\Delta G°$ and the relative steric isotope effects, the CEIE as a percentage of the strain energy, are given in Table 2.

The large differences of chemical shifts for axial and equatorial CF_3 groups on a cyclohexane ring are insensitive to substituents in the 3- and 4-positions (see

Table 1. ^{13}C NMR chemical shifts[a] (Me_4Si, 0.5M as internal reference) of derivatives of 1,3-dimethylcyclohexane (1M in $CDCl_3$) at 300K. Deuteriation is assumed to be at the higher numbered methyl groups

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-Me
cis-1	32.83	44.55	32.83	35.08	26.49	35.08	22.97
trans-1	27.24	41.25	27.24	33.79	20.84	33.79	20.72
(trans-1-d_3	0	-0.06	-0.24	-0.06	-0.01	0.02	0.04)[b]
cis-11	33.08	44.55	33.08	44.56	33.08	44.56	23.27
trans-11[c]	29.02	41.24	27.05	45.45	27.03	41.24	19.36[d] 23.57[e]
cis-2	-[f]	45.44	37.37	25.69	37.37	45.44	14.64
(cis-2-d_3	-[f]	0	0	0	0	-0.22	0)[b]
trans-2	-[f]	42.76	34.84	20.29	34.48	42.76	16.04
(trans-2-d_3	-[f]	0.02	0	0	0	-0.17	-0.02)[b]
cis-12[g]							14.74
trans-12[g]							17.56[d] 15.19[e]
cis-3	-[f]	49.37	33.26	42.74	33.26	49.37	22.41
trans-3	-[f]	48.33	29.70	39.59	29.70	48.83	20.89
(trans-3-d_3	-[f]	0	-0.02	-0.07	-0.26	0	0.02)[b]

[a] Digital resolution 0.02 p.p.m. [b] Shifts relative to signals in d_0 species; precise shifts for methyl groups are given in Table 2. [c] Axial Me at C-1 [d] Axial [e] Equatorial [f] Not recorded. [g] Mixture of stereoisomers: resonances not assigned apart from 2- and 6-methyl groups.

Table 2. Hydrogen isotope effects on conformational equilibria in *trans*-(1–3) (1M in $CDCl_3$) at 300K based on ^{13}C NMR chemical shifts (relative to 0.5M Me_4Si)

Comound	Chemical shifts (p.p.m.) $\Delta\delta$[a]	δ_E[b]	δ_A[b]	K^D/K^H[c]	$\Delta\Delta G^0$ /J mol^{-1}	$\Delta\Delta G^0$ /E_s[d]
trans-1-d_3	+0.026	18.17	23.27	1.018	−46±10[e]	−0.65±0.14%
trans-2-d_3	−0.018	16.99	15.09	1.032	−80±28[e]	−1.1±0.4%
trans-3-d_3	+0.012	19.07	22.71	1.016	−40±15[e]	−0.7±0.3%

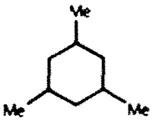
[a] Measured in spectra expanded to 3 or 6 mm/memory address, ±0.003 p.p.m. [b] Calculated from model compounds neglecting possible direct isotope effects (see text). [c] Calculated from equation 2 with K^H = 1. [d] Steric strain energies E_s are taken as equal to the conformational free energies for axial methyl groups in methylcyclohexane (7.1 kJ mol^{-1}) and in 2-methyl- (7.5 kJ mol^{-1}) and 3-methyl-cyclohexanone (5.6 kJ mol^{-1}) respectively.[16] [e] Error limits come from adding the probable extreme range of direct isotope effects (0 to −0.005 p.p.m.) to $\Delta\delta$ in addition to the experiemntal errors and are thought to be conservative.

Table 3. ^{19}F NMR chemical shifts of derivatives of trifluoromethylcyclohexane in CCl_4 (10% w/v; CCl_3F as internal standard: Φ scale) at 308K and of E and A conformers (Fig. 2) of *trans*-4, -5, and -8 (ppm from *cis* isomer) at 163K

Compound	Φ (cis) (p.p.m.)	Φ (trans) (p.p.m.)	Conformers of trans isomer E	A
4	74.9 (74.88)[a]	72.3	7.840	−0.035
5	74.8 (74.84)[a]	72.0	7.844	−0.144
5-d_2			7.844	−0.144
6	74.8 (74.80)[a]	74.3		
7	75.1 (74.87)[a]	74.5		
8	74.9	67.8	7.921	–[b]
9[c]	74.5	73.5		
10[d]	74.6 (74.65)[a]	72.9		

[a] In MeOH[5] [b] Not observed. [c] In MeOH. [d] In $CDCl_3$

Ref. 5,13 and Table 3) and to changes of solvent, e.g. 7.37 + 0.06 ppm for 13 in five solvents ranging from cyclohexane to methanol.[5] In proton decoupled ^{19}F spectra of 4 and 5 line widths are ~1 Hz at 300K and several pairs of isotopically differentiated derivatives of the trans isomers of 4 and 5 give well separated lines in the mixtures (Fig. 3). That these differences in chemical shifts result indirectly from CEIEs and not to any significant



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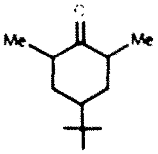

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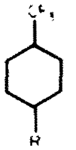
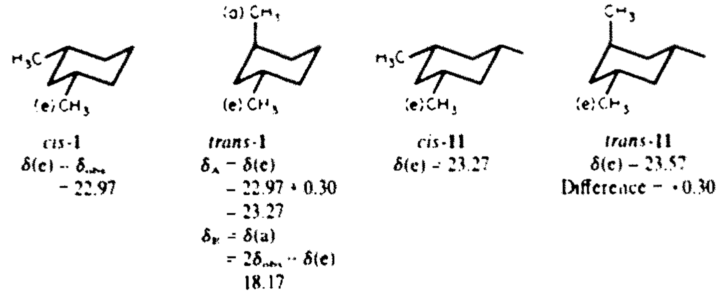


13: R = t-Bu
14: R = Me



Scheme 3. Derivation of δ_E and δ_A (ppm) for $-CH_3$ groups in the *E* and *A* conformers of *trans*-1-d_3 neglecting direct isotope effects.

Table 4. Hydrogen isotope effects on conformational equilibria in *trans*-4 and *trans*-5 (0.1M) based on ^{19}F NMR chemical shifts

Compound	Solvent (T/K)	$\Delta\delta^a$ p.p.m.	$\delta_E - \delta_A{}^b$ p.p.m.	$K^{H\,c}$	$K^D/K^{H\,d}$	$\Delta\Delta G^{o\,e}$ (J mol^{-1})	$\Delta\Delta G^o/E_s{}^f$ (%)
trans-4-d_3	Me_2CO(298)	0.029_4	−7.20	2.73	1.021	48±3	−0.68%
-d_3		$0.008_6{}^g$			1.006_3	$15._6{}^h$	
-d_2		$0.008_8{}^g$			1.006_1	$15._1{}^h$	
-d_1		$0.009_3{}^g$			1.006_7	$16._5{}^h$	
-d_0							
trans-5-d_2	Me_2CO(298)	0.028_2	−7.31	2.67	1.020	49±3	−0.66
	MePh (273)	0.030_2	−7.44	2.70	1.021	47±3	−0.64
	" (308)	0.028_9	−7.26	2.35	1.019	49±3	−0.66
	MeOH (273)	0.029_6	−7.44	2.66	1.020	45±3	−0.61
	" (308)	0.028_9	−7.26	2.25	1.019	48±3	−0.65

[a] $\delta^D - \delta^H$; digital resolution 0.00072 p.p.m./memory address. [b] See text. [c] Derived using equation 1; for errors see text. [d] Derived using equation 2. [e] Errors based on ~10% errors for K^H, $\not> \pm 3\%$ for $\delta_E - \delta_A$. [f] Steric strain, E_s, taken as equal to ΔG^o for conformational equilibria in methyl-(7.1 kJ mol^{-1}) and hydroxymethyl-cyclohexane (~7.4 kJ mol^{-1}). [g] Calculated from data for mixtures of d_0 and d_2, d_0 and d_3, d_1 and d_3 isotopic species. [h] Experimental errors ~10% (systematic errors arising from K^H and $\delta_E - \delta_A$ are constant; see text).

extent from direct isotope effects on chemical shifts was demonstrated at 163K for *trans*-5 (d_0 and d_2), for which the values of $\delta_E - \delta_A$ are equal (±0.001 ppm) (Table 3), as well as from the invariance (to < ± 0.002 ppm) of the chemical shifts (relative to CF_3CCl_3) of *cis*-5 and both conformers of *trans*-5 to deuteriation. These very small effects through six bonds are consistent with the observed attenuation of the shielding effects through two and three bonds[14] and the general insensitivity of the chemical shifts of CF_3 groups to distant substituents.

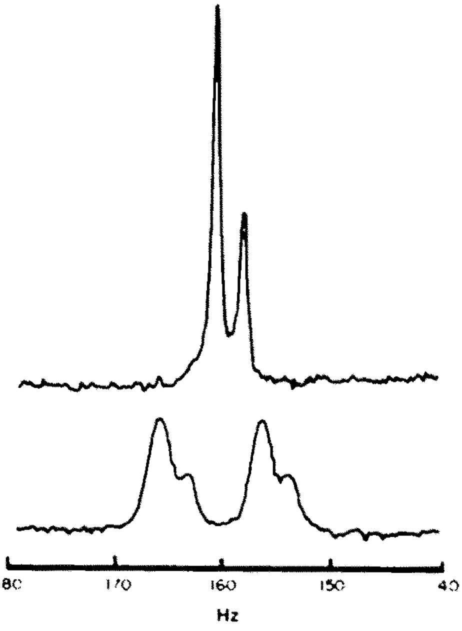


Fig. 3. Proton coupled (a) and decoupled (b) ^{19}F NMR spectra of a mixture of *trans*-5-d_0 and -d_2 (0.1M total concentration in acetone).

For convenience in measurement we used *cis*-4 and *cis*-5 as internal references and assume that there is no temperature effect on the very small differences in chemical shifts of the equatorial CF_3 groups in the anancomeric *cis* isomers and in the A conformers (Fig. 1) of the trans isomers. The values of δ_E and δ_A for **4**, **5** and **8** were directly measured for supercooled solutions in acetone at 163K (it has not been possible to completely freeze out equilibria in the other solvents) and δ_A was corrected to the temperatures at which the isotope effects were measured using Della's variable temperature data for *cis*- and *trans*-**13**.[11] The resulting values of $\delta_E - \delta_A$ for *trans*-4 agree well with the differences of chemical shifts for *cis*- and *trans*-**13** in acetone[11] and have been used for all the isotope effects based on ^{19}F spectra.

The large uncertainties in the CEIEs for *trans*-**1**, -**2** and -**3** arise from errors in measurements of chemical shifts and from the neglect of direct isotope effects on chemical shifts (see estimates above), which make the errors in estimating $\delta_E - \delta_A$ unimportant, while $K^H \approx 1$. In contrast the errors for *trans*-4 and -5 are mainly due to uncertainties in K^H and in $\delta_E - \delta_A$ because direct isotope effects and experimental errors are very small. The estimates of K^H required in equation 2 were derived using eqn (1). The resulting value of ΔG^0_{AE} (trans-5) - 2.4 kJ mol^{-1} agrees well with the ratio (A:E ~ 5:1, corresponding to ΔG^0_{AE} 2.2 ± 0.2 kJ mol^{-1}) of peak areas at low temperatures. Similarly satisfactory agreement between results from equation 1 at 220–320K and low temperature measurements of peak areas for *cis*-**14** was found by Della.[13] An error of 10% in $K^H = 2.73$ leads to an error of 5% in $\Delta\Delta G^\circ$. The very small range of values of Φ for *cis*-(**4**–**10**) (and other examples given by Della[5]) and the even smaller solvent effects for **13** (±1% of the difference of chemical shifts for axial and equatorial CF_3 groups) suggest that our values of $\delta_E - \delta_A$ are very unlikely to be in error by as much as 3%, which leads to a similar error in K^H. Since these errors are constant for various isotopic species of a given compound the isotope effects for successive deuteriations in *trans*-**5** ($d_0 - d_3$) are more comparable than the effects for different compounds or different solvents and show that the effect per deuterium is constant to within the experimental error ($\not>$10%) in the measurements of chemical shifts.

There are no significant differences in the CEIEs for Me groups in *trans*-(**1**–**3**), which have comparable steric strain energies for methyl groups but very different environments electronically, but the large uncertainties may obscure effects due to, e.g. an isotope effect on the porarity of a C–H bond. The CEIEs for *trans*-**4** and -**5** are much more precise and show a striking regularity. The values of $\Delta\Delta G^\circ$ are equal for $CH_3(d_0 \rightarrow d_3)$ and $CH_2OH(d_0 \rightarrow d_2)$ and are proportionate to the number of hydrogen atoms replaced in Me_3. The first result is consistent with the common interpretation of conformational equilibria in cyclohexane, that is that the strain associated with an axial group –CHXY is largely attributable to repulsions between the hydrogen in –CHXY (with the X and Y groups or atoms pointing away from the centre of the ring when larger than H) and the syn-1,3-diaxial ring H atoms. It is far from obvious how Allinger's concept of the dominant importance of gauche repulsions between equatorial H atoms[16] can explain these isotope effects but a comparison of CEIEs for deuteriation of ring hydrogens and of side chain hydrogens with higher accuracy than is at present possible might be decisive.

The absence of a solvent effect on the CEIE in *trans*-**5** is consistent with the small solvent effect on the equilibrium in *trans*-**5** and does not exclude the possibility that deuteriation changes the polarity of the C–H bond so that a solvent effect on a CEIE for Me may occur in other systems, including **2** and **3**. The equality of the CEIEs for *trans*-**1** and -**4** (Tables 2 and 4) and the simple proportionality between the magnitudes of the CEIEs and number of D atoms for *trans*-**4** are welcome confirmation that steric isotope effects result primarily from 'simple' changes in zero point energies for localised C–H vibrations, as has been explicit in many discussions of such isotope effects[15] and in corrections for incomplete deuteriation,[12] and are not sensitive to structural changes that do not significantly change the steric strains.

The relative steric isotope effects (Tables 2 and 4) are all close to −0.6% (the negative sign implies that deuterium is "smaller" than protium, as expected for steric isotope effects), within experimental error and are similar to values for NMe (−0.6 ± 0.1% in **15**, 0.47 ± 0.04% in **16**)[18] but larger rather in magnitude than the effect (−0.36 ± 0.07%) observed for the severely overcrowded CMe groups in the transition state for the racemisation of 4,5-dimethyl-9,10-dihydrophenanthrene.[17] This emphasises that severely strained systems may not be a reliable guide to the possible importance of steric factors in transition states with modest steric strains. We hope soon to develop the more sensitive methods needed to measure CEIEs in compounds with small steric strains.

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