Calculated and Experimental Equilibrium Steric Isotope Effects for Carbon in *cis*-1-[^{13}C]Methyl-4-methylcyclohexane

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A conformational steric isotope effect for carbon in a methyl group in *cis*-1,4-dimethylcyclohexane has been measured as +1.24 ± 0.25 J mol^{-1} in acetone and +1.25 ± 0.20 J mol^{-1} in benzene (both at 300 K), *i.e.*, inverse, with ^{12}C preferring to be axial, and smaller in magnitude than estimates from force field calculations.

Conformational equilibrium isotope effects (c.e.i.e.s) for hydrogen in derivatives of cyclohexane have been measured in several different systems.[1—4] In the few instances studied such isotope effects are insensitive to solvent polarity[1,2] and are therefore reasonably considered to be essentially steric in nature.[5] Equilibrium carbon isotope effects have been observed for degenerate equilibria in carbocations[6] but attempts to measure c.e.i.e.s for carbon have failed to achieve adequate sensitivity[7] (see Table 1). We have calculated carbon isotope effects for methyl groups in several derivatives of cyclohexane using two force fields, markedly different so far as hydrogen non-bonded interactions are concerned, as a guide to designing experiments to measure such c.e.i.e.s.[8] The estimates (to about 0.5 J mol^{-1}) in Table 1 showed that a sensitivity better than 1 J mol^{-1} was probably necessary and that 0.1 J mol^{-1} was desirable. The only method currently available for measuring c.e.i.e.s in saturated hydrocarbons uses n.m.r. chemical shifts at the fast exchange limit. A precision of about 4 J mol^{-1} was achieved by Booth and Everett[7] using a high-field spectrometer with isotopically normal compounds.

We have used the difference (d) in chemical shifts between *cis*-(**1A**) ($K \neq 1$) and *cis*-(**1B**) ($K = 1$) (all compounds were isotopically enriched to 90 atom % ^{13}C at the sites indicated) to determine the carbon-13 c.e.i.e. R [$= K(\mathbf{1B})/K(\mathbf{1A}) = 1/K(\mathbf{1A})$] for *cis*-1,4-dimethylcyclohexane (**1**) using equation (1), where D (= 5.96 p.p.m. for acetone as solvent

$$K(\mathbf{1A}) = [D - 2(d - d_a)]/[D + 2(d - d_e)] \qquad (1)$$

and 5.98 p.p.m. for benzene as solvent) is the difference between the carbon chemical shifts (derived from low-temperature measurements and solvent effects for model compounds) for the methyl groups in *cis*-(**1Ae**) and *cis*-(**1Aa**), d is the difference in chemical shifts between (**1A**) and (**1B**), and d_a and d_e are intrinsic isotope effects on ^{13}C chemical shifts in the individual chair conformers. Because $\nu_0 d$ (ν_0 = 62.85 MHz, the operating frequency of the spectrometer) is far smaller than the line widths attainable ($w_{1/2} \nless 0.15$ Hz) it is not possible to measure d in a single solution. *cis*-(**1A**) and *cis*-(**1B**) were compared using *trans*-(**2**) as a common reference allowing the use of very small sweep widths (50—100 Hz) and dilute solutions (total concentration of solutes 0.10 M). The absence of significant intrinsic isotope effects d_a and d_e in *cis*-(**1**) was inferred from the negligible difference d in ^{13}C chemical shifts for the methyl carbons in the anancomeric compounds *trans*-(**1A**) and *trans*-(**1B**) using *cis*-(**2**) as a common reference.

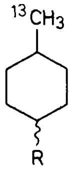
Table 1. Positions of resonances (in Hz) for ^{13}CH$_3$ in *trans*-(**1**) and *cis*-(**1**), and the derived conformational equilibrium isotope effects, ΔG° (in J mol^{-1}), at 306 K.

Compound	Solvent $(CD_3)_2CO$	 C_6D_6
trans-(**1A**)	−14.099±0.001[a]	−12.128±0.005[a]
trans-(**1B**)	−14.096±0.001[a]	−12.128±0.001[a]
$\nu_0 d$ (no c.e.i.e.)	+0.003±0.001	0.000±0.005
cis-(**1A**)	−28.317±0.006[b]	−28.347±0.004[b]
cis-(**1B**)	−28.356±0.005[b]	−28,386±0.004[b]
$\nu_0 d$	−0.038±0.008	−0.039±0.006
K(**1A**) (=1/R)	1.00049_0	1.00049_2
ΔG° (obs.)	+1.24±0.25	+1.25±0.20
ΔG° (calc.) for methylcyclohexane[c]	−1.7 and −2.5 (two force fields)[d]	

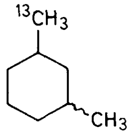
[a] Relative to ^{13}CH$_3$- in *cis*-(**2**). [b] Relative to ^{13}CH$_3$- in *trans*-(**2**). [c] Ref. 8. [d] Gas phase.

The measured isotope effects (Table 1), assuming d_a and d_e may be neglected, are independent of the polarity of the solvent, within the errors of the two sets of measurements. The experimentally observed effect corresponds to ^{12}C preferring the *axial* orientation, contrary to expectations based on amplitudes of vibrations and to the sign of the calculated effects.[8] There is a qualitatively similar difference between observed[9] and calculated[8] conformational equilibria in [^{2}H$_1$]cyclohexane. These discrepancies suggest that current molecular mechanics programs cannot reproduce vibration frequencies adequately for c.e.i.e.s.

The measurements were made with a Bruker AM250 spectrometer with efficient hydrogen decoupling[10] using solutions containing (**2**) and *either* (**1A**) *or* (**1B**), at 306 K (the best temperature for stability and reproducibility). Two pairs of lines [from *cis*-(**2**) and *trans*-(**1A**) or *trans*-(**1B**); *trans*-(**2**) and *cis*-(**1A**) or *cis*-(**1B**)] were sufficiently well separated for one pair to be observed in narrow-sweep spectra (50—100 Hz) without appreciable interference from aliased signals of the other pair. The transformed spectra (*e.g.*, 2K real points: digital resolution 0.024—0.048 Hz) were phased by eye, transferred to another computer and fitted (least squares criterion) to Lorentzian absorption line functions, with automatic phase refinement and baseline correction. The errors in the line positions (Table 1) were typically about

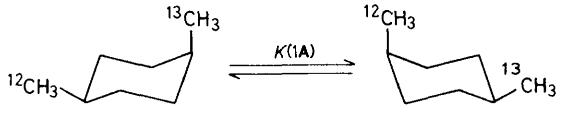


(**1**)



(**2**)

A : R = CH$_3$
B : R = ^{13}CH$_3$



cis-(**1Aa**) *cis*-(**1Ae**)

0.001 Hz for the narrow lines of the anancomeric compounds *trans*-(**1**) and *cis*-(**2**) and 0.004—0.006 Hz for the broader lines for *cis*-(**1**) and *trans*-(**2**).

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