RE-EXAMINATION OF A CONFORMATIONAL EQUILIBRIUM ISOTOPE EFFECT FOR HYDROGEN
IN 1,1,3,3-TETRAMETHYLCYCLOHEXANE – THE IMPORTANCE OF INTRINSIC ISOTOPE EFFECTS

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Abstract: Neglect of intrinsic isotope effects on ^{13}C chemical shifts is a major
             source of error in the conformational equilibrium isotope effect for
             deuteriation of one methyl group in 1,1,3,3-tetramethylcyclohexane; there
             is no significant solvent effect.

The chair⇌chair conformational equilibrium in 1,1,3,3-tetramethylcyclohexane (1) is

degenerate in isotopically 'normal' molecules, i.e. in molecules with ^{1}H and ^{12}C atoms only.

The change in conformational equilibrium caused by isotopic substitution of hydrogen in one

substituent (H or CH_3 in 1) is a conformational equilibrium isotope effect (CEIE)[1] for

hydrogen. The CEIE may be measured using proton decoupled ^{13}C NMR spectra at natural
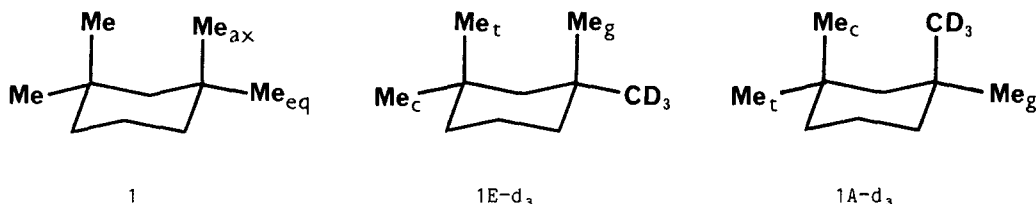
abundance[2] to compare the equilibria in $1(^{13}C_1)$ and in $1(^{13}C_1,\ ^2H_3\text{-}1\text{-methyl}) = 1\text{-}d_3$, where the

relevant ^{13}C is in one of the methyl groups Me_c, Me_t, and Me_g (respectively cis, trans, and

geminal to the $1\text{-}CD_3$ group) or is in the CD_3 itself.[3] Deuteriation of a substituent affects

the chemical shifts of the methyl carbons in two distinct ways, directly through intrinsic

isotope effects (IIEs) in the individual conformers $1E\text{-}d_3$ and $1A\text{-}d_3$ and indirectly through the

CEIE. Anet, Sauders, et alia[5] have estimated $\Delta G^{\ominus}(290K) = -101\pm4$ J mol^{-1} for $1E \rightarrow 1A$ in CS_2.

The sign was derived from the chemical shift of Me_g assuming that the IIE for this group is

shielding (negative).[6] The magnitude was derived from the chemical shift difference between

the Me_t and Me_c, assuming negligible IIEs for these carbons. The latter assumption was

justified by analogy with $2\text{-}d_0$ and $2\text{-}d_6$, in which there is no observable isotope effect on the

^{13}C chemical shift for C-4(6) at the fast exchange limit.[7] The analogy between 1 and 2 so far

as IIEs are concerned is far from good and even if it could be justified the conclusion is not

valid: a difference for $2\text{-}d_0$ and $2\text{-}d_6$ would prove the existence of IIEs in 2 because K = 1 in

both but the converse is not true (see below). We considered it desirable to determine

whether IIEs are significant for Me_c and Me_t in $1\text{-}d_3$ and also to seek possible solvent effects

on the CEIE.

Carbon-13 chemical shifts may be used to determine K for 1-d₃ using equations 1 and 2:

$$K = (\delta_E - \delta)/(\delta - \delta_A) \tag{1}$$

$$K = (D_e - D)/(D - D_A) \tag{2}$$

In equation 1 δ is the measured chemical shift relative to, eg, SiMe₄ for a single methyl group at the <u>fast exchange limit</u> (FEL), eg, near 300K, and δ_E and δ_A are the chemical shifts, which can not be measured directly at the FEL, for the individual conformers 1E-d₃ and 1A-d₃. Use of equation 1 allows a clear distinction to be made between K < 1 and K > 1 if δs for Me_g or for CD_3 are used but the accuracy is not high. In equation 2, D ($=\delta(Me_t)-\delta(Me_c)$) is the measured chemical shift difference at the FEL and D_E and D_A are the corresponding differences for the individual conformers 1E-d₃ and 1A-d₃. The small difference D may be measured accurately and therefore the use of equation 2 can lead to accurate estimates of K and ΔG^O for 1-d₃. Estimates of chemical shifts and shift differences (D_{FEL}) for equatorial (δ_{eq}) and axial (δ_{ax}) methyl groups in conformers of 1-d₀ at the FEL may be obtained from equations 3-5:

$$D_{FEL} = D_{SEL} + D_T + D_S \tag{3}$$

$$\delta_{eq} = (1-d_0) + {}^1/{}_2 D_{FEL} \tag{4}$$

$$\delta_{ax} = (1-d_0) - {}^1/{}_2 D_{FEL} \tag{5}$$

where $D_{SEL} = \delta_{eq} - \delta_{ax}$ for 1-d₀ is measured at the <u>slow exchange limit</u> (SEL), eg, at 173K. D_T is a correction for the difference in temperature between the SEL and FEL for solutions in CS_2. D_S is a solvent correction at the FEL, i.e., $D_S = 0$ for CS_2, the solvent used at the SEL.[5]

Values of δ_E, δ_A, D_E, and D_A, for a given solvent, may be obtained from the pairs of equations 6-8:

For CD_3 in 1-d₃: $\qquad \delta_E = \delta_{eq} + \Delta_{Ed} \qquad \delta_A = \delta_{ax} + \Delta_{Ad} \qquad$ (6)

For Me_g in 1-d₃: $\qquad \delta_E = \delta_{ax} + \Delta_{Eg} \qquad \delta_A = \delta_{eq} + \Delta_{Ag} \qquad$ (7)

For Me_t/Me_c in 1-d₃: $\quad -D_E = D_{FEL} + \Delta_{Et} - \Delta_{Ec} \qquad D_A = D_{FEL} + \Delta_{At} - \Delta_{Ac} \quad$ (8)

where the Δs are estimates of IIEs on chemical shifts in individual conformers, eg, Δ_{Eg} is the effect of deuteriation in an equatorial CH_3 (as in 1E-d₃) on the chemical shift of the geminal axial methyl group.

2-d₀: R=CH₃

2-d₆: R=CD₃

3-d₀: R₁=R₂=CH₃

3E-d₃: R₁=CH₃; R₂=CD₃

3A-d₃: R₁=CD₃; R₂=CH₃

3-d₆: R₁=R₂=CD₃
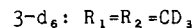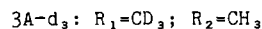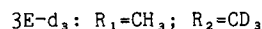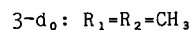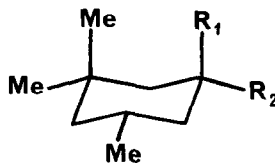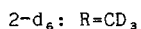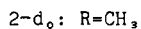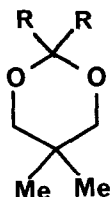
The proton decoupled natural abundance ¹³C spectrum of 1-d₃ shows four resonances near 31 ppm attributed to Me_t, Me_g, Me_c, and CD_3 (from low to high field: the multiplet for CD_3 has not been detected previously[5]). Carbon-12 isotopic substitution in the Me_g group makes it possible to study mixtures of 1-d₃ and either 1-d₀ or 1-d₆. The spectra of such mixtures unambiguously show that IIEs are significant for Me_t and Me_c in 1-d₃, contrary to the earlier assumption,[5] because the <u>average</u> δ for Me_c and Me_t in 1-d₃ is not equal to δ for 1-d₀ nor for 1-d₆.[8]

TABLE Chemical shifts (δ relative to $1\text{-}d_0$), chemical shift differences (D), and estimates of IIEs (Δ), all in ppm, and derived CEIEs, $\Delta G^{\ominus}$ (J mol^{-1})

Chemical shifts, differences, and IIEs	Species	Temp/K	Solvent		
			CS_2[a]	CD_2Cl_2	$(CD_3)_2CO$
D_{SEL}	$1\text{-}d_0$	173	+9.03	–	–
D_T	$3\text{-}d_0$	173–302	−0.06		
D_S	$3\text{-}d_0$	302	0	−0.07	−0.07
D	$1\text{-}d_3$	"	+0.1781	+0.1715	+0.1747
Δ_{Et}	$3\text{-}d_0$, $d\text{-}d_6$	"	+0.0065	+0.0073	+0.0080
Δ_{Ec}	$3A\text{-}d_3$	"	−0.0005	−0.0004	−0.0003
Δ_{At}	$3\text{-}d_0$, $3A\text{-}d_3$	−0.0043	−0.0043	−0.0042	−0.0033
Δ_{Ac}	"	"	−0.0201	−0.0202	−0.0206
$\Delta G^{\ominus}$ (equation 2)	$1\text{-}d_3$	"	−91.3±1	−89.5±1	−90.8±1
δ	$1\text{-}d_6$	"	−0.0088	−0.0089	−b
δ_g	$1\text{-}d_3$	"	−0.0164	−0.0105	–
Δ_{Eg}	$3\text{-}d_0$, $3E\text{-}d_3$	"	−0.068	−0.071	–
Δ_{Ag}	$3\text{-}d_0$, $3A\text{-}d_3$	"	−0.105	−0.107	–
$\Delta G^{\ominus}$ (equation 1)	$1\text{-}d_3$	"	−85±10	−89±10	–
δ_d	$1\text{-}d_3$	"	−1.044	−1.034	−b
Δ_{Ed}	$3\text{-}d_0$, $3E\text{-}d_3$	"	−0.980	−0.968	–
Δ_{Ad}	$3\text{-}d_0$, $3A\text{-}d_3$	"	−0.957	−0.944	–
$\Delta G^{\ominus}$ (equation 1)	$1\text{-}d_3$	"	−75±10	−88±10	–

[a] Containing C_6D_6, 5% by volume, to provide a lock.

[b] Measurements using Me_g and Me_d are at present difficult or impossible using $(CD_3)_2CO$ as solvent.

Measurements of IIEs for the 5-methyl carbons in $3A\text{-}d_3$ and $3\text{-}d_6$ gave values for $3E\text{-}d_3$ by difference (Table). These IIEs are both shielding, notably Δ_{Ac}, and deshielding, notably Δ_{Et}. These relatively large effects oppose one another so that in an equilibrating system such as $1\text{-}d_3$ the observable effect is relatively small and in other instances could be negligible. Clearly it is not reliable to assume that IIEs on ^{13}C chemical shifts are negligible when the carbon nucleus is separated from the perturbing deuterons by four or more bonds. [5,7] The IIEs for Me_g and CD_3 in $1\text{-}d_3$ were estimated from $3A\text{-}d_3$ and $3E\text{-}d_3$ (1:1 mixture). All are negative (Table), justifying the earlier assumption,[5] and show that K is > 1.

The CEIE in $1\text{-}d_3$ was measured in three solvents differing greatly in polarity (Table). The model compound 3 was used (i) to estimate the temperature effect on D_{SEL} from 173K to

302K: the observed value of D_T = -0.06 ppm (CS_2) justifies the limits (D_T ≯ 0.1 ppm) previously assumed,[5] (ii) to determine solvent effects D_S on D_{SEL} + D_T at 302K, and (iii) to estimate IIEs in 1E and 1A from values for 3E-d_3 and 3A-d_3:[9] these estimates were also used to calculate the IIE in 1-d_6 relative to 1-d_0, with good agreement between observed (-0.0088 ppm in CS_2, -0.0089 in CD_2Cl_2) and calculated (0.0088 and 0.0084 ppm) values. The values of $\Delta G^\ominus$ measured using equation (2) (Table) show that neglect of IIEs[5] leads to errors of about 10%, comparable with estimates for 1,1,3,3-tetramethylpiperidinium ion[1b] and contrary to their neglect by Anet, Saunders, et alia.[5] Our results also show that this CEIE is essentially independent of solvent. It is therefore probably a true steric isotope effect in the sense of arising from contributions by Van der Waals nonbonded repulsions to the vibrational force constants of C-H(D) bonds in the overcrowded axial methyl groups in 1.[10] It must be noted, however, that such changes in vibration frequences have not been observed in compounds for which CEIEs have been measured

NOTES AND REFERENCES

1. (a) K. W. Baldry and M. J. T. Robinson, Tetrahedron, 1977, 33, 1663; (b) Idem, J.Chem. Res. (S), 1977, 86, and J.Chem.Res. (M), 1977, 1001.

2. In principle such a CEIE could be measured by ^{1}H NMR but the spectra are complex and the chemical shifts relatively small, in comparison with line widths, so that low precision would result.

3. It may readily be shown that when RT≫ΔG^O(1-d_3)≫ΔG^O(1-$^{13}C_1$), D for 1-d_3 will be essentially the same as D for 1($^2H_3$-1-methyl) and the effect on K of neglecting the ^{13}C CEIE will be negligible. The only CEIE yet measured for $^{13}C/^{12}C$ is indeed small relative to the CEIE in 1-d_3.[4]

4. S. L. R. Ellison, M. S. Fellows, M. J. T. Robinson, and M. J. Widgery, J.Chem.Soc.Chem. Comm., 1984, 1069.

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6. Deshielding by deuterium as little as two bonds from ^{13}C has now been observed: see P. E. Hansen, Ann.Rep.NMR Spec., 1983, 15, 106.

7. F. A. L. Anet and A. Dekmezian, J.Am.Chem.Soc., 1979, 101, 5449.

8. C. G. Andrews, G. N. Chmurny, and E. B. Whipple, Org.Magn.Reson., 1981, 15, 324.

9. Isotope effects for all the C atoms in 3, together with the syntheses of the isotopomers, will be published elsewhere.

10. R. E. Carter and L. Melander, Adv.Phys.Org.Chem., 1973, 10, 1.