Tetrahedron Letters, Vol.30, No.34, pp 4589-4592, 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ORIGINS OF CONFORMATIONAL EQUILIBRIUM ISOTOPE EFFECTS FOR HYDROGEN IN KETONES

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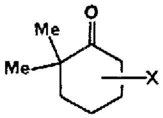
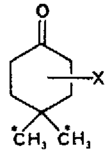
Abstract: Conformational equilibrium isotope effects for hydrogen in cyclohexanones and other ketones are consistent with (i) hyperconjugation, (ii) analogues of hyperconjugation, and (iii) a difference in polarity between C-H and C-D bonds; steric effects are relatively unimportant.

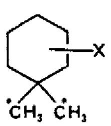
Conformational equilibrium isotope effects (CEIEs)[1,2] for hydrogen in compounds with non-bonding electron pairs[3] result from a combination of steric[4] and anomeric effects,[5] long range analogues of the latter,[3] and electrostatic interactions[3] that are sensitive to the polarity of the solvent. CEIEs for hydrogen in ketones have been measured only by Djerassi and his collaborators[6] using circular dichroism (CD) for **1-4** and several isotopomers of cyclopentanone. We have now measured CEIEs for hydrogen in the cyclohexanones **5-8**, and in the hydrocarbons **9** and **10** for comparison, using ^{13}C NMR chemical shifts for the geminal methyl groups at the fast exchange limit[7] by the methods previously described (Table).[3,8,9]



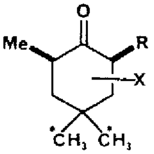
1: X = 3-^{2}H
2: X = 4-^{2}H
3: X = 5-^{2}H
4: X = [$^2H_3$]-*methyl*



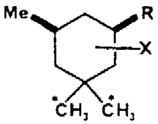
5: X = 2-^{2}H
6: X = 3-^{2}H
7: X = *cis*-2,3-$^2H_2$
8: X = *trans*-2,3-$^2H_2$



9: X = 2-^{2}H
10: X = 4-^{2}H



11: R = H
12: R = Me



13: R = H
14: R = Me

•Sites of ^{13}C (natural abundance) used for chemical shifts and IIEs (equation 1)

The CEIEs were determined from the equation:

$$K = (D + d_{obs} - I_{tE} + I_{cE})/(D - d_{obs} + I_{tA} - I_{cA}) \quad (1)$$

where d_{obs} is the observed difference in chemical shifts for methyl groups *cis* and *trans* to the *nearest* ^{2}H. Chemical shift differences (D) for the geminal methyl groups in the chair conformers of **5-10** were estimated by the dual model method[7] using the anancomeric model compounds **11**(X = ^{1}H) and **12**(X = ^{1}H) for **5-8** and **13**(X = ^{1}H) and **14**(X = ^{1}H) for **9** and **10**. Intrinsic isotope effects (IIEs: I_{tE}, etc, equation 1 ,where subscript c or t refers to ^{13}C in a methyl group *cis* or *trans* to ^{2}H in the E or A conformer) on these chemical shift differences were similarly estimated from **11-14**(X = ^{2}H at one or two of the positions 2-, 3-, 5-, or 6-). The *magnitude* of the difference, d_{obs}, in ^{13}C chemical shifts for the *gem*-methyl groups in each of **5-10** is readily measured with ^{1}H and ^{2}H decoupling. When ^{2}H is substituted in methylene groups immediately adjacent to a *gem*-dimethyl group, as in **6-9**, the larger (*trans*)[11] three bond ^{13}C-^{2}H couplings ($^3J_{CD}$: eg, 0.64±0.02Hz in **6-8**) may be measured in ^{1}H decoupled ^{13}C spectra and used to determine which ^{13}C resonance corresponds to a methyl group *trans* to ^{2}H and therefore to determine the *sign* of d_{obs}; the smaller, *cis*, couplings ($^3J_{CD}$: eg, 0.40±0.04Hz in

6-8) are not always resolvable (see Figure 1). The value of d_{obs}, together with the shift difference D and the intrinsic isotope effects (IIEs)[3] of ^{2}H on ^{13}C chemical shifts (equation 1),[3] gives the equilibrium constant and thence the CEIE.[3] Figure 1 shows the methyl group region of the ^{1}H decoupled ^{13}C NMR spectrum of a mixture of **6**-**8**,[12] without and with ^{2}H decoupling, from which one may conclude that the CEIEs for **7** and **8** are opposite in sign to the CEIE for **6**.

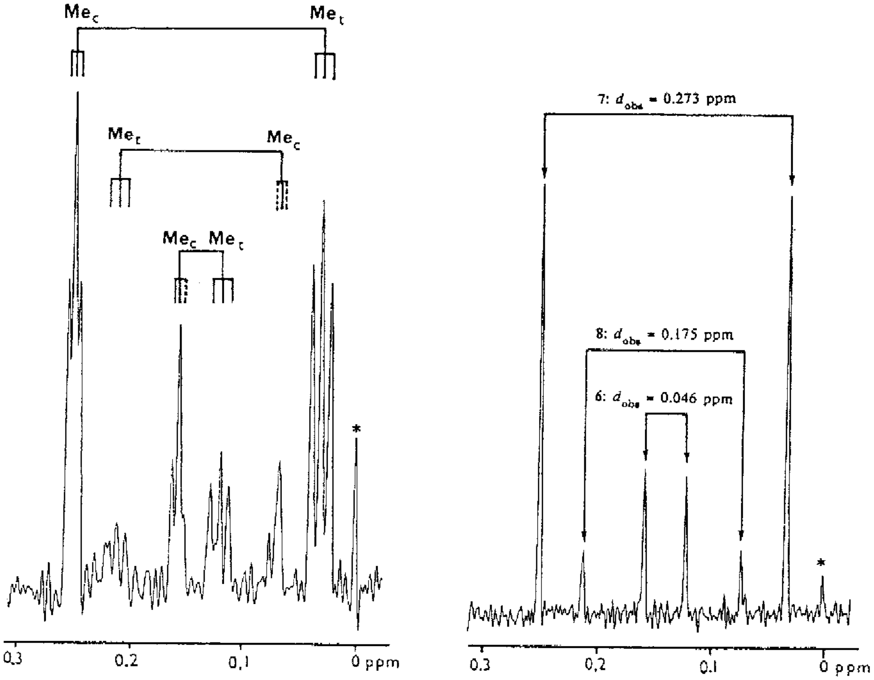


Figure 1. ^{13}C spectra for the geminal methyl groups of a mixture of **6**, **7**, and **8** in CS_2 at 304K: (a) ^{1}H decoupled, showing the difference in $^{3}J_{CD}$ for Me *cis* (splittings not well resolved for **6** and **8**) and *trans* to ^{2}H at C-3; (b) ^{1}H and ^{2}H decoupled. (*C_6H_{12} internal reference)

In **5** and **10** the long range $^{13}C(Me)$-^{2}H couplings, $^{4}J_{CD}$ and $^{5}J_{CD}$,[11] are too small to be resolved. We derive the relative signs of the CEIEs in **5** and **6** on the assumption that the two isotopic substitutions in **7** and **8** have (approximately) additive effects on the CEIE (the CEIEs in **7** and **8** are the difference and sum respectively of the CEIEs in **5** and **6**, see Table). The resonances for the methyl groups in the hydrocarbon **10** were assigned using [4(t)-^{2}H]-1(t)-[^{13}C]-methyl-1(r)-methylcyclohexane.[13]

Table. CEIEs for compounds **1**-**4** (ΔH°, in isopentane-methylcyclohexane), from variable temperature circular dichroism,[6] and **5**-**10** (ΔG°, in C_6D_6 at 304K), from ^{13}C chemical shifts (equation 1).

	ΔH° /(J mol^{-1})		ΔG° /(J mol^{-1})		ΔG° /(J mol^{-1})
1	-40	**5**	153±6	**9**	12±1
2	-18	**6**	-17±2	**10**	8±3
3	-11	**7**	173±3		
4	-14	**8**	130±3		

The large CEIEs for the ketones 5, 7, and 8 with 2-^{2}H, with protium preferring the axial position, are *not* consistent in sign or magnitude with a predominant steric effect.[4] These CEIEs, however, are consistent with (i) hyperconjugation weakening the *axial* C-H(D) by interaction with the π^* orbital of the C=O,[14] (ii) the lower stretching frequency for analogous C-H(D) bonds in simple ketones,[15] and (iii) the lower values of spin spin constants $^1J_{CH}$ (or $^1J_{CD}$) for *axial* C-H compared with *equatorial* C-H,[16] analogous to reductions in $^1J_{CC}$ in 2(ax)-methylcyclohexanones.[17]

The CEIEs in **1-3** and **6** are superficially consistent with a steric effect, assuming that the axial C-H(D) is more hindered than the equatorial, but this is misleading for **1**, **3**, and **6**. The CEIEs in **1**, **3**, and **6** are opposite in sign to those in the corresponding saturated hydrocarbons 9 and 10[18] and in [^{2}H]cyclohexane itself,[19,20] in all of which (relatively weak) *trans* diaxial σ-σ^* orbital interactions weakening *axial* C-H bonds[20] appear to be the dominant origin of the CEIEs. The CEIEs in 1, 3, and 6, therefore, must result from one or more effects that either strengthen the axial, or weaken the equatorial, 3(5)-C-H bonds enough to overcome the *weakening* of axial C-H bonds by *trans* diaxial σ-σ^* interactions that must be considered 'normal' in cyclohexane itself. We suggest that {3(5)eq-C-H)σ-π^* orbital interactions, involving the minor lobe of the equatorial 3-C (sp^3)σ orbital, weaken the *equatorial* 3(5)-C-H bonds in these ketones.[21] At present we have no direct evidence for such weakening in 1, **3**, and **6** but this will be investigated through IR spectra and $^1J_{CH}$ coupling constants. The CEIE observed in **2**,[6] however, may well be dominated by steric interactions between an axial 2-methyl group and axial 4-C-H(D).[18]

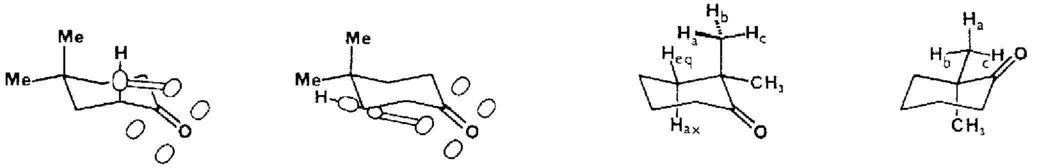


Figure 2. Possible origins of CEIEs in (a) [2-^{2}H]- and (b) [3-^{2}H]-4,4-dimethylcyclohexanone, and (c) and (d) in 2-[^{2}H$_3$]methyl-2-methylcyclohexanone.

Djerassi suggested that the CEIE in **4** could be explained by steric repulsions between the carbonyl oxygen and the *equatorial* 2-methyl group but this does not agree with conformational equilibria in 2-methylcyclohexanone and related compounds.[22] We suggest an alternative analysis, analogous to that made for the CEIE in 2,2-dimethyl-1,3-dioxan,[3] that treats the three hydrogens of a methyl group separately. In an axial 2-methyl group in (Figure 2) **4** there is (i) a hindered hydrogen (H$_a$), which should give rise to a 'normal' steric CEIE, such as is found in 1-[^{2}H$_3$]methyl-1-methylcyclohexane[10] and similar hydrocarbons[1] (ii) a hydrogen (H$_b$) analogous[23] to an *equatorial* 3(5)C-H, as in **1** and **6**, and (iii) a hydrogen (H$_c$) analogous to an *axial* 3(5)-C-H in **1** and **6**. The hydrogens H$_b$ and H$_c$, if the analogies are valid, should give rise to a contribution to the CEIE in **4** favouring *axial* 2-C^{1}H$_3$, ie, an *inverse* effect. At present we have no information about any special effects that may be present in the equatorial 2-methyl group in **4**, except that solvent effects in an analogous ketone[10] are consistent with a polar isotope effect favouring equatorial 2-C^{2}H$_3$.

Djerassi *et alia* observed no significant solvent effects on CEIEs studied by CD.[6] We have found[10] that CEIEs in the ketones **5-8**, as in 1,3-dioxans,[3] show a significant solvent dependence, qualitatively consistent with ^{1}H being more negative than ^{2}H, which will be included in a full paper.

We thank the S.E.R.C. for a Research Studentship (to C.A.C.) and a grant to the Laboratory towards the cost of the Bruker AM250 spectrometer used in this work.

NOTES AND REFERENCES

1. K.W. Baldry and M.J.T. Robinson, *Tetrahedron*, 1977, **33**, 1663.
2. In assigning signs to CEIEs we will follow earlier precedents[1,3] by considering *axial* groups to be more hindered than *equatorial*, so that a CEIE favouring an axial deuteriated (or other heavy isotopically substituted) group is a 'normal' steric isotope effect.
3. C.A. Carr, S.L.R. Ellison, and M.J.T. Robinson, preceding paper.
4. R.E. Carter and L.A. Melander, *Adv. Phys. Org. Chem.*, 1973, **10**, 1.
5. A.J. Kirby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, Berlin and Heidelberg, 1983
6. Summarised by G. Barth and C. Djerassi, *Tetrahedron*, 1981, **37**, 4123.
7. The slow exchange limit for the conformational equilibria in the ketones **5-8** cannot be reached at accessible temperatures and the chemical shifts d_E and d_A must be estimated from two series of model compounds with 2- and/or 6-methyl groups: see C.A. Carr, M.J.T. Robinson, and C.D.A. Tchen, *Tetrahedron Lett.*, 1987, 897.
8. S.L.R. Ellison, M.J.T. Robinson, and J.G. Wright, *Tetrahedron Lett.*, 1985, 2585
9. The results given here for **5**, **7**, and **8** are in qualitative agreement with similar but less accurate data on 3,3-dimethylcyclohexanone with ^2H in the 2-, 4-, and 6-positions,[10] for which the dual model method[7] is not applicable and which will be included in a full paper.
10. C.A. Carr, M.J.T. Robinson and A. Webster, unpublished measurements.
11. The *trans* coupling $^3J_{CD}$ is an average of the large di-axial and small di-equatorial couplings in the two chair conformers, while the smaller, *cis*, coupling is the average of two small axial-equatorial couplings. Related $^3J_{CH}$ couplings are given by J.L. Marshall, *Carbon-Carbon and Carbon-Proton Couplings*, Verlag Chemie International, Deerfield Beach, Florida, 1983.
12. Prepared from 4,4-dimethylcyclohexenone and $^2H_2$ over Pd/C; the predominant *cis*-isotopomer **7** was accompanied by small amounts of **6** and **8**; quantitative measurements on **6** were made using an isotopomerically pure sample.
13. Synthesised stereospecifically in seven steps from 4-hydroxy-[^{13}C-*carboxyl*]benzoic acid: A. Webster, *B.A. Part II Thesis*, Oxford, 1986
14. W.D. Cotterill and M.J.T. Robinson, *Tetrahedron Lett.*, 1963, 1833.
15. D.C. McKean, *J.C.S. Chem. Commun.*, 1971, 1373.
16. Eg, $^1J_{CD}$ is 20.4 Hz for *eq*-C(6)-D and 18.8 Hz for *ax*-C(6)-D in 3,3,5-trimethylcyclohexanone.[10]
17. J.C.J. Barna and M.J.T. Robinson, *Tetrahedron Lett.*, 1979, 1459.
18. We have not yet studied the CEIE in [3-$^2H_1$]1,1-dimethylcyclohexane, required for comparison with **2**, but it seems likely that steric effects will be dominant.
19. F.A.L. Anet, *J. Am. Chem. Soc.*, 1986, **108**, 1355.
20. I.H. Williams, *J.C.S. Chem. Commun.*, 1986, 627.
21. See, eg, M.R. Giddings, E.E. Ernstbrunner, and J. Hudec, *J.C.S. Chem. Commun.*, 1976, 954.
22. B. Rickborn, *J. Am. Chem. Soc.*, 1962, **84**, 2414.
23. If the molecules had ideal geometries with tetrahedral bond angles and equal carbon-carbon bond lengths then the relation of H_b (or H_c) and 3(eq)-H (or 3(ax)-H) to the C=O group would be the same. We assume that the non-ideal geometry will change the effects quantitatively but not qualitatively.

(Received in UK 15 June 1989)