

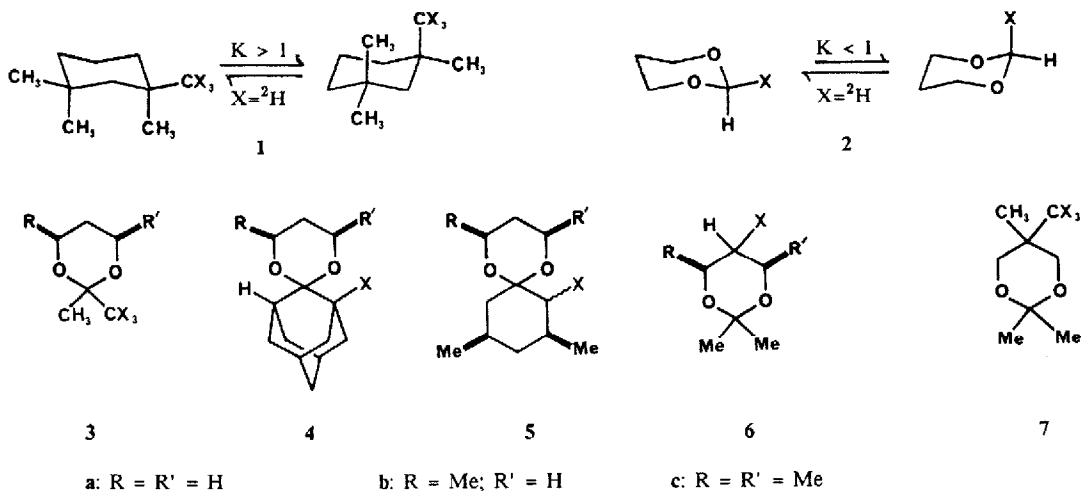
DIVERSE ORIGINS OF CONFORMATIONAL EQUILIBRIUM ISOTOPE EFFECTS FOR HYDROGEN IN 1,3-DIOXANS

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Abstract:--Conformational equilibrium isotope effects in derivatives of 1,3-dioxan are consistent with *four* distinct origins: (i) steric hindrance, (ii) the anomeric effect, (iii) orbital interactions between C-H bonds and *either* non-bonding electrons through three or more coplanar bonds or (C-O) σ^* orbitals, and (iv) a difference in polarity between C-H and C-D.

Two origins for conformational equilibrium isotope effects (CEIEs)^{1,2} have been postulated previously. In saturated hydrocarbons with strongly hindered hydrogen, eg, **1** (X=²H),^{3,4} CEIEs are almost independent of the polarity of the solvent used^{1,4} and appear to originate mainly from non-bonding repulsions increasing vibration frequencies for C-H bonds at hindered sites.⁵ When a conformational equilibrium exchanges ¹H and ²H between hindered and unhindered sites ¹H is expected to prefer the *less* hindered site,⁵ ie, ¹H is effectively larger than ²H. In compounds with non-bonding electron pairs where steric hindrance is not important, eg, [²H₁-methyl]methylamine,⁶ [2-²H]-1,3-dioxan (**2**: X=²H),⁷ and *N*-methyl-[2-²H]piperidine⁸ CEIEs are explained by interactions between non-bonding electrons and antiparallel vicinal C-H σ^* orbitals, ie, the anomeric effect.^{9,10} We now show that CEIEs in derivatives of 1,3-dioxan may not only be observed for unhindered 'anomeric' hydrogen (as in **2**) but also for (i) strongly hindered hydrogen (in **4**, X=²H, and **5eq**, X=²H), (i) weakly hindered hydrogen *three or more bonds distant from the oxygen atoms* and (iii) *vary with the polarity of the solvent*.



The CEIEs in 3-7 ($X=^2\text{H}$) were measured using ^{13}C NMR chemical shifts of carbon atoms directly attached to C-2 of the 1,3-dioxan ring at the fast exchange limit.^{1,3,4} We have used *dual series* of model compounds¹⁴ with methyl groups at C-4 or C-4 and C-6 in the dioxan rings for 3-6 in order to estimate reliably both the chemical shifts *and* the intrinsic isotope effects (IIEs)⁴ on them in the individual chair conformers by simple extrapolation from the models.¹⁴ This is essential when the site of isotopic substitution is close to the observed carbon nucleus as in 3-5 ($X=^2\text{H}$) because the IIEs may then be comparable with the conformational effect on the chemical shifts.¹⁵

The CEIEs ($\Delta G^\circ = -RT \ln K$) in each of 3-5 ($X=^2\text{H}$) were derived from the difference d between the chemical shifts of natural abundance ^{13}C attached to C-2 (Figure 1) in the isotopically normal, eg, 3a, and isotopically substituted species, eg, 3a($2\text{-}^{13}\text{CH}_3$), using equation 1:

$$K = \{D + 2(d - I_E)\} / \{D - 2(d - I_A)\} \quad (1)$$

where D is the difference in chemical shifts, $\delta_E - \delta_A$, for equatorial and axial $2\text{-}^{13}\text{C}$ in $^2\text{H}_0$ -isotopomers and I_E and I_A are the IIEs in the E and A conformers of the compound.^{15,16}

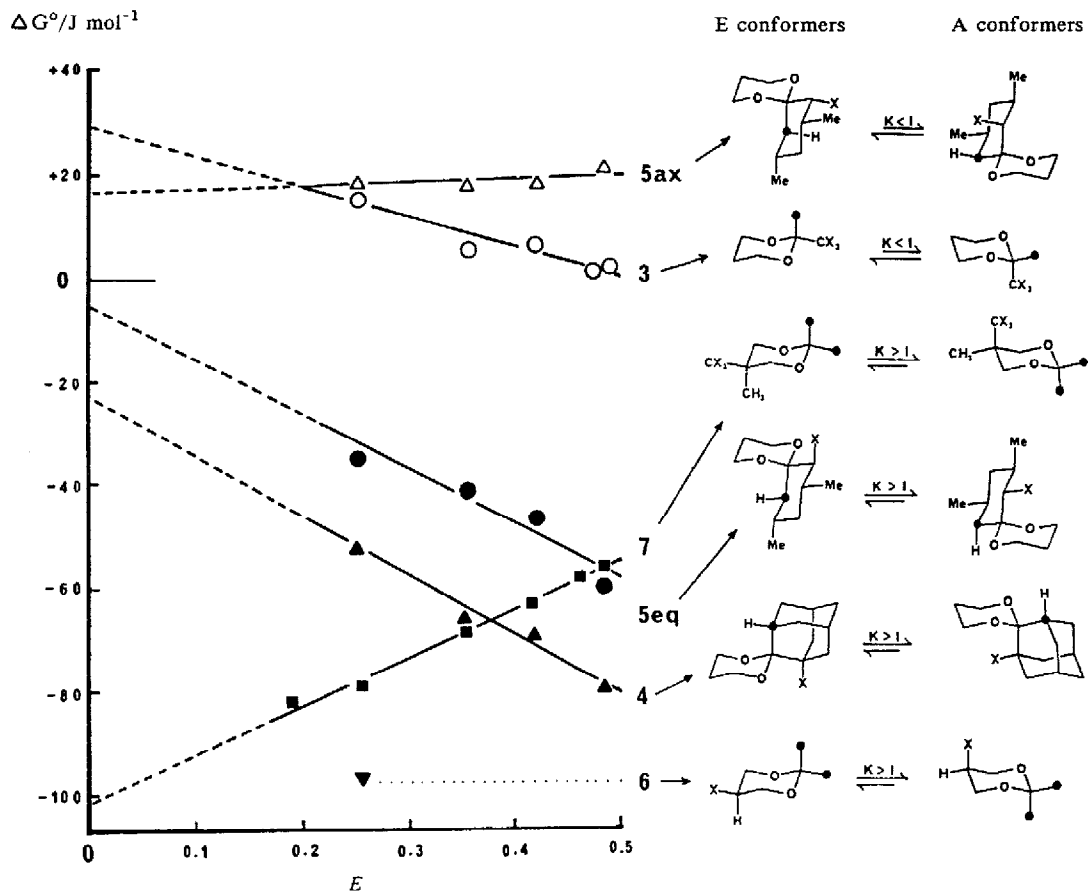


Figure 1. CEIEs in 3-7 ($X=^2\text{H}$) as a function of $E = (e - 1) / (2e + 1)$, where e is the dielectric constant of the solvent (e is taken as an approximation to the dielectric constant of the solution). (●: site of ^{13}C used for chemical shifts in equations 1 and 2)

When equation 1 was applied to ^1H chemical shifts for 5-H in 6 and 5-Me in 7 the data were good enough to give the *signs* of the CEIEs unambiguously but the accuracy was low. Knowing the sign of the CEIE in 6 or 7, however, allowed us to infer the sign of the *difference* in chemical shifts, $d = d(\text{cis}) - d(\text{trans})$, for ^{13}C in the diastereotopic 2-methyl groups *cis* and *trans* to ^2H in 6($\text{X}=\text{H}$) or C^2H_3 in 7($\text{X}=\text{H}$) and so determine the *magnitude* of each CEIE using the equation:

$$K = (D + d)/(D - d) \quad (2)$$

At present upper limits only to the very small IIEs in 6 and 7 can be estimated from model compounds and these have been used in estimating errors, which are approximately indicated by the size of the symbols in Figure 1.¹⁶

Figure 1 shows how the CEIEs vary with solvents. Except for 5eq, for which the solvent dependence of the CEIE appears either to be non-linear or to have greater scatter than for the other data and for 6, which has as yet been studied in one solvent only, there are linear correlations between the CEIE and the dielectric function $E = (e - 1)/(2e + 1)$,¹⁷ where e is a dielectric constant, for so-called 'normal' solvents. This is consistent with equilibria between pairs of species differing in the orientation of two electric dipoles. One dipole is clearly the resultant of the two ether groups C-O-C in the ring and the other must be the *difference* in polarity of C-H and C-D bonds.¹⁸ The approximately 'orthogonal' relationship between the axial 2'-C-H(D) bond and the ring dipole in both of the two chair conformers of 5ax¹⁹ accounts for the *virtual absence* of a solvent effect in this one instance. In the other systems the C-H(D) bond dipole is approximately parallel to the ring dipole in one conformer and approximately antiparallel in the other.²⁰

The CEIEs observed in 5ax, 6, and 7 are surprisingly large for unhindered or slightly hindered hydrogen atoms.²² These CEIEs are consistent with *weakened* C-H(D) bonds in the conformers in which the C-H(D) and a pair of non-bonding electrons are at the ends of a planar zig-zag array of bonds²⁵ (Figure 2), i.e. these CEIEs result from an analogue of the anomeric effect. In each case the other chair conformer does not have any comparable bond pathways between the C-H and non-bonding electron pairs. An alternative explanation for the CEIEs in 5ax and 6, but not in 7, is interaction between antiparallel (C-H) σ and (C-O) σ^* orbitals, weakening the former. At present there is no independent evidence for C-H bond weakening in 5ax and 7, in contrast to 2($\text{X}=\text{H}$)⁷ and methylamine,⁶ but $^1J_{\text{CH}}$ is lower for the *equatorial* (123.5Hz) than for the *axial* (127.5Hz) 5-C-H in ananomeric analogues of 6.²⁶

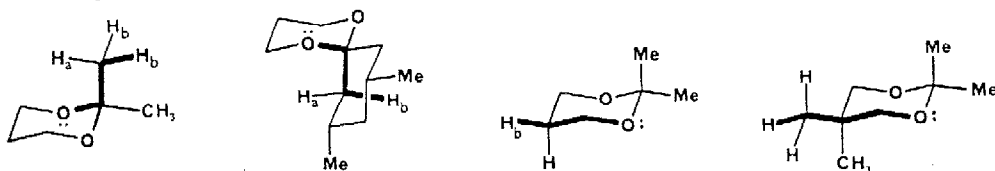


Figure 2. Planar zig zag pathways for orbital interactions in 3 and 5-7.

The contrasting CEIEs in 4 or 5eq compared with 5ax provide an explanation for the very small CEIE in 3 (Figure 2), which has a very hindered 2(ax)-methyl group.²⁷ In the latter there is one hydrogen (H_a), analogous to the hydrogen H_a in 4 and 5eq, that is strongly hindered in 5eqA, and *two* hydrogens (H_b) analogous to H_b in 5axA. Since the solvent sensitive CEIE in 4 or in 5eq is approximately twice as large but opposite in sign to the solvent insensitive CEIE in 5ax it is not surprising that the effects for H_a and the two H_b in 3 roughly cancel, yet the solvent effect for 3 is comparable with that for 4 and for 5eq.

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NOTES AND REFERENCES

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16. Measurements were made on solutions containing *all* the species required to derive the parameters use in the right hand side of equation 1, ie, a CEIE in 3 was derived from a single solution containing the *eight* species 3a-c(X=¹H), 3a(X=²H), and 3b,c(X=²H) in either eq- or ax-2-Me). Details of the model compounds used for 7 will be given later in a full paper.
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19. From molecular models.
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