Conformational Analysis by Nuclear Magnetic Resonance. Interpretation of Solvent Effect on Standard Enthalpy and Entropy Differences between Conformations of Cyclohexanol

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THE conformational analysis of cyclohexanol is not yet completely finished. Many $\Delta G°$ values are known[1] but the interpretation of the effects observed at different concentrations in various solvents is not yet understood. Using the modified Eliel method[2-5] we have determined $\Delta G°$, $\Delta H°$, and $\Delta S°$ in a more extensive series of solvents than previously[2] (Table 1), and also for given solvents, at different concentrations (Table 2).

It seems that the variation of $\Delta H°$ and $\Delta S°$ with solvent, obtained from n.m.r. measurements, even if not exact in absolute values, is significant on a relative scale. It also appears that the unfortunate parallel between errors in $\Delta H°$ and $\Delta S°$[6] does not

TABLE 1* (ref. 7)

Solvent (c *ca.* 2 $\mathrm{Ml^{-1}}$)	$\Delta G^{\circ}_{\mathrm{conf}}(25^{\circ})$	$\Delta H^{\circ}_{\mathrm{conf}}$	$\Delta S^{\circ}_{\mathrm{conf}}$
cis-Decalin	-904	-1250 ± 14	$-1{\cdot}16 \pm 0{\cdot}03$
cis-Decalin	-879	-1228 ± 42	$-1{\cdot}17 \pm 0{\cdot}12$
Iso-octane[2]	-879	-1240 ± 30	$-1{\cdot}21 \pm 0{\cdot}09$
3,5-dimethylhexan-3-ol[2] ..	-938	-1219 ± 14	$-0{\cdot}97 \pm 0{\cdot}05$
Cyclohexanone	-809	-892 ± 15	$-0{\cdot}28 \pm 0{\cdot}04$
Pyridine	-935	-1033 ± 25	$-0{\cdot}33 \pm 0{\cdot}07$
Dimethylformamide	-1000	-1203 ± 28	$-0{\cdot}68 \pm 0{\cdot}08$
Dimethyl sulphoxide ..	-838	-725 ± 18	$+0{\cdot}38 \pm 0{\cdot}06$

TABLE 2* (ref. 7)

Solvent	$\Delta G^{\circ}_{\mathrm{conf}}$ (25°)	$\Delta H^{\circ}_{\mathrm{conf}}$	$\Delta S^{\circ}_{\mathrm{conf}}$
cis-Decalin ($c = 2{\cdot}15\mathrm{Ml^{-1}}$)	-879	-1228 ± 42	$-1{\cdot}17 \pm 0{\cdot}12$
cis-Decalin ($c = 0{\cdot}32\ \mathrm{Ml^{-1}}$)	-725	-912 ± 130	$-0{\cdot}64 \pm 0{\cdot}40$
$\mathrm{CCl_4}$ ($c = 2\mathrm{Ml^{-1}}$)† ..	-768		
$\mathrm{CCl_4}$ ($c = 0{\cdot}67\mathrm{Ml^{-1}}$) ..	-722		
$\mathrm{CCl_4}$ ($c = 0{\cdot}40\mathrm{Ml^{-1}}$) ..	-683		
$\mathrm{CCl_4}$ ($c = 0{\cdot}22\mathrm{Ml^{-1}}$) ..	-691		
$\mathrm{CCl_4}$ ($c = 0{\cdot}13\mathrm{Ml^{-1}}$) ..	-654		

* The indicated errors (least-squares treatment of van't Hoff plot) concern precision and not accuracy which is, unfortunately, not perfectly known. However, as we have said previously, the discussion here is based on relative and not absolute results. The variation of ΔH° and ΔS° with solvents and concentrations seems significant because the experimental errors are minimised by the technique used.[4,5] In particular, all the cyclohexanolic compounds used during this work are $\alpha\alpha'$-tetradeuteriated.

† δ, δ_{ax}(*cis*-[$^2\mathrm{H}_4$]-4-t-butylcyclohexanol), δ_{eq}(*trans*-[$^2\mathrm{H}_4$]-4-t-butylcyclohexanol) are respectively 208·9, 234·6, and 202·1 c./sec. (Varian A 60, temperature 31°).

explain all the observed facts. It is possible to rationalise our results as follows. If X^{F}_{eq} and X^{F}_{ax} are respectively the mole fractions of the free equatorial and axial conformations, then

$$K^{\mathrm{F}}_{\mathrm{conf}} = X^{\mathrm{F}}_{eq}/X^{\mathrm{F}}_{ax} \qquad (1)$$

For the associated conformations (1 : 1 complex with a base B), we have similarly

$$K^{\mathrm{A}}_{\mathrm{conf}} = X^{\mathrm{A}}_{eq}/X^{\mathrm{A}}_{ax} \qquad (2)$$

The association constants for the axial and equatorial conformations, K^{A}_{ax} and K^{A}_{eq}, are respectively:

$$K^{\mathrm{A}}_{ax} = X^{\mathrm{A}}_{ax}/X^{\mathrm{F}}_{ax}{\cdot}X_{\mathrm{B}} \qquad (3)$$

$$K^{\mathrm{A}}_{eq} = X^{\mathrm{A}}_{eq}/X^{\mathrm{F}}_{eq}{\cdot}X_{\mathrm{B}} \qquad (4)$$

The Eliel method applied on such a system gives:

$$K = \frac{\delta_{ax} - \delta}{\delta - \delta_{eq}} = \frac{X^{\mathrm{F}}_{eq} + X^{\mathrm{A}}_{eq}}{X^{\mathrm{F}}_{ax} + X^{\mathrm{A}}_{ax}} = K^{\mathrm{F}}_{\mathrm{conf}} \cdot \frac{1 + K^{\mathrm{A}}_{eq}.X^{\mathrm{B}}}{1 + K^{\mathrm{A}}_{ax}{\cdot}X_{\mathrm{B}}} \qquad (5)$$

If $K^{\mathrm{A}}_{eq}{\cdot}X_{\mathrm{B}} >> 1$ and $K^{\mathrm{A}}_{ax}{\cdot}X_{\mathrm{B}} >>> 1$, equation (5) becomes

$$K = K^{\mathrm{F}}_{\mathrm{conf}} \cdot \frac{K^{\mathrm{A}}_{eq}}{K^{\mathrm{A}}_{ax}} \equiv K^{\mathrm{A}}_{\mathrm{conf}} \qquad (6)$$

With bases like dimethyl sulphoxide, pyridine, and cyclohexanone, at low alcohol concentration, equation (6) can be applied. For the system discussed here, equation (6) gives:

$$(\Delta G^{\circ}_{\mathrm{conf}})^{\mathrm{A}} = (\Delta G^{\circ}_{\mathrm{conf}})^{\mathrm{F}} + [(\Delta G^{\circ}_{eq})^{\mathrm{A}} - (\Delta G^{\circ}_{ax})^{\mathrm{A}}]$$

$$(\Delta H^{\circ}_{\mathrm{conf}})^{\mathrm{A}} = (\Delta H^{\circ}_{\mathrm{conf}})^{\mathrm{F}} + [(\Delta H^{\circ}_{eq})^{\mathrm{A}} - (\Delta H^{\circ}_{ax})_{\mathrm{A}}]$$

$$(\Delta S^{\circ}_{\mathrm{conf}})^{\mathrm{A}} = (\Delta S^{\circ}_{\mathrm{conf}})^{\mathrm{F}} + [(\Delta S^{\circ}_{eq})^{\mathrm{A}} - (\Delta S^{\circ}_{ax})^{\mathrm{A}}]$$

$(\Delta H^{\circ}_{\mathrm{conf}})^{\mathrm{F}}$ and $(\Delta S^{\circ}_{\mathrm{conf}})^{\mathrm{F}}$ are unknowns, the first of which is certainly negative $[(H^{\circ}_{\mathrm{conf}})^{\mathrm{F}}_{eq} < (H^{\circ}_{\mathrm{conf}})^{\mathrm{F}}_{ax}]$ while the second is probably positive $[(S^{\circ}_{\mathrm{conf}})^{\mathrm{F}}_{eq} > (S^{\circ}_{\mathrm{conf}})^{\mathrm{F}}_{ax}]$.[8]

The sign of the difference $[(\Delta H^{\circ}_{eq})^{\mathrm{A}} - (\Delta H^{\circ}_{ax})^{\mathrm{A}}]$ is unknown but would be negative in some solvents.[8] Thus, if we assume that, the decrease of enthalpy accompanying association is larger for the equatorial than for the axial form, $(\Delta H^{\circ}_{\mathrm{conf}})^{\mathrm{A}}$ must be more negative (larger in absolute value) than $(\Delta H^{\circ}_{\mathrm{conf}})^{\mathrm{F}}$.

Generally,[9–11] a relation seems to exist between $(\Delta H^\circ)^A$ and $(\Delta S^\circ)^A$ in a series of proton donors or acceptors. If $|(\Delta H^\circ_{eq})^A| > |(\Delta H^\circ_{ax})^A|$, then $|(\Delta S^\circ_{eq})^A| > |(\Delta S^\circ_{ax})^A|$, in the same basic solvent.† Then the variation of $(\Delta H^\circ_{conf})^A$ and $(\Delta S^\circ_{conf})^A$ with the solvent must be more important than the variation of $(\Delta G^\circ_{conf})^A$ (*cf.* Table 1).

From equation (6), if $K^A_{eq}/K^A_{ax} \simeq 1$, it follows that $K^A_{conf} \simeq K^F_{conf}$. This situation seems to be realised, within experimental error, in dimethyl sulphoxide at normal temperature.[12] However, the ΔG° value obtained in this solvent is probably more negative than $(\Delta G^\circ_{conf})^F$ (see Table 2). In our experiments, the alcohol concentration is certainly too high to prevent self-association even in a basic solvent, but the results obtained with different solvents can be explained on the above basis.

Strictly speaking, the form developed here does not adapt to the case of self-association, in solvents like hydrocarbons. The conformational problem of self-associated cyclohexanol is difficult to treat quantitatively even in the case of a 1 : 1 complex, because several possibilities exist for the associated species *eq–eq*, *ax–ax*, *eq–ax*. In Table 2, when the concentration is lowered the conformational values approach the free cyclohexanol conformational values and the ΔH° and ΔS° values become less negative. ΔH° and ΔS° cannot be determined experimentally for lower concentrations (< 0·32 Ml^{-1} in *cis*-decalin as solvent). Furthermore, it is difficult to obtain ΔH° and ΔS° values in CCl_4 because of the low boiling point of the solvent and poor solubility of 4-t-butyl derivatives at lower temperature.

Other and better methods will certainly give more accurate measurements but it is of interest to note that our results agree qualitatively with the results of Eliel, Neilson, and Gilbert,[13] obtained by equilibration at low concentration (*ca.* 0·1 Ml^{-1}); that in tertiary alcohol is in very good agreement. In contrast, the values in hydrocarbons as solvent are very different. The concentration effect certainly plays a prominent part (*cf.* Table 2), perhaps sufficient to explain the discrepancy.

The interpretation of the solvent effect on conformational values for an associative system, independently suggested by Eliel's laboratory[13,14] and ours[7], seems very similar.

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† The experimental values are given as ΔG°, ΔH°, and ΔS° even if, in some solvents, these terms are probably equal to $(\Delta G^\circ_{conf})^A$, $(\Delta H^\circ_{conf})^A$, and $(\Delta S^\circ_{conf})^A$ respectively.

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