Conformational Free Energies of the Formyl, Hydroxymethyl, Acetal, and Hydroxyl Groups as Determined by the Equilibration Method

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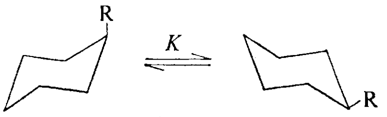
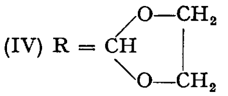
CONFORMATIONAL preferences have recently been reported for the formyl[1] (I) and hydroxymethyl[2] (II) groups on the basis of ^{1}H and ^{13}C n.m.r. spectra, respectively.



$$-\Delta G^{\circ} = RT \ln K$$

(I) R = CHO (II) R = CH_2OH
(III) R = Ac



(IV) R = $CH\begin{matrix} O-CH_2 \\ | \\ O-CH_2 \end{matrix}$

We have independently determined these preferences by a different method (*cis–trans* equilibration of 4-t-butyl-substituted compounds, Table 1). The previously reported values[1,2] and a recently determined value[3,4] for the acetyl group (III) are shown for comparison.

The *cis*- and *trans*-4-t-butylcyclohexanecarboxaldehydes were synthesized by catalytic hydrogenation of 4-t-butylbenzaldehyde diethyl ketal ($Rh–Al_2O_3$, room temp., 50 lb./in.^{2}) followed by acid hydrolysis (1 : 1 HCl, 10 min., reflux); the ethylene ketal, similarly prepared, was not readily hydrolyzed but could be equilibrated as shown in Table 1. *cis- and trans*-Acetals were enriched by fractional distillation (spinning band column) and while acid hydrolysis resulted in partial equilibration of the aldehydes, samples ranging in *cis* : *trans* composition from 1 : 1 to 1 : 4·3 were obtained, so that equilibrium (approximate position 1 : 3) could be reached from both sides. Analysis was by g.l.c.; since pure aldehydes (for determination of response ratios) were not available, some analyses were checked by reducing the aldehyde mixture to alcohols with an excess of $LiAlH_4$ and analysing the carbinol mixture.

The 4-t-butylcyclohexylcarbinols were prepared by $LiAlH_4$ reduction of the corresponding carboxylic acid,[4] *cis*, m.p. 25° (lit.[5] 25—27°), *trans*, m.p. 58° (lit.[5] 56—57°) and were equilibrated by refluxing with Raney nickel[6] and analysed by gas chromatography.

Our equilibration results for $-\Delta G^{\circ}_{CHO}$ are in poor agreement with earlier data derived from ^{1}H n.m.r. spectra[1] on the C*H*O protons (which differ by only 0·1 p.p.m. between the axial and equatorial group). Since it has recently been shown[7,8] that the introduction of a 4-t-butyl group, required for the measurements on model axial and equatorial compounds in the n.m.r. method, may cause small changes in chemical shifts, application of the method to closely placed signals in the axial and equatorial conformations may be dubious. In any case, our finding that $-\Delta G^{\circ}$ for CHO is smaller than for Ac or for CO_2R (1·2 kcal./mole) seems reasonable, since an axial CHO is less constrained than COX.

Our value for CH_2OH in a non-polar solvent

TABLE 1

Conformational free energies[a]

Compound	$-\Delta G^{\circ}$	Solvent/Catalyst/Temperature	Ref.
(I)	0·56	methanol, sodium methoxide, 25°	b
	0·73	diethyl ether, toluene-*p*-sulphonic acid, 25°	b
	0·74	cyclohexane, triethylamine, 100°	b
	0·78	dibutyl ether, triethylamine, 100°	b
	1·35 ± 0·1	CCl_4, C_6H_6, MeCN, $CHCl_3$, room temp.	1
(II)	1·65	cyclohexane, Raney Ni, 80°	b
	2·06	isopropyl alcohol, Raney Ni, 80°	b
	1·4±0·25	carbon disulphide, room temp.	2
(III)	1·5	acetic acid, HBr, 25°	3
	1·52	methanol, sodium methoxide, 25°	4
(IV)	2·2	chloroform, toluene-*p*-sulphonic acid, 25°	b

[a] In kcal./mole; [b] this work.

TABLE 2

Equilibration of 4-t-butylcyclohexanols (cis ⇌ trans)

Solvent	$-\Delta G^\circ$ (kcal./mole)	$-\Delta H^\circ$ (kcal./mole)	ΔS° (cal./degree-mole)
Cyclohexane	0·61 ± 0·02	0·62 ± 0·01	−0·02 ± 0·02
Isopropyl alcohol	0·95 ± 0·02	1·09 ± 0·01	−0·46 ± 0·03
t-Butyl alcohol	0·95 ± 0·03	1·18 ± 0·02	−0·76 ± 0·04
$MeOCH_2{\cdot}CH_2{\cdot}OMe$	0·74 ± 0·02	0·83 ± 0·01	−0·30 ± 0·03

agrees, within limits of experimental error, with that obtained by ^{13}C n.m.r.[2] In this case the span of chemical shifts was rather sizeable (4·6 p.p.m.) and a small effect of the t-butyl group on these shifts would be of minor importance.

The $-\Delta G^\circ$ value for CH_2OH in the hydrogen-bonding solvent isopropyl alcohol is enhanced to an unexpected extent, in view of the remoteness of the OH group from the ring, and the somewhat smaller enhancement (ascribed to stabilization of the equatorial conformation by preferential hydrogen bonding) observed[6] for an OH group directly attached to the ring. Data more recently obtained in the equilibration of the 4-t-butylcyclohexanols by Raney nickel (Table 2) indicate that the effect is more pronounced for hydrogen-donating solvents (isopropyl alcohol, t-butyl alcohol) than for a hydrogen-accepting solvent (ethylene glycol dimethyl ether) and that, as one might expect, the enthalpy advantage of the equatorial hydroxyl group is to some extent offset by an entropy disadvantage, since hydrogen bonding leads to a restriction in (translational) degrees of freedom.

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[1] G. W. Buchanan and J. B. Stothers, *Chem. Comm.*, 1967, 179; G. W. Buchanan, J. B. Stothers, and S.-T. Wu, *Canad. J. Chem.*, 1967, **45**, 2955.

[2] G. W. Buchanan and J. B. Stothers, *Chem. Comm.*, 1967, 1250.

[3] A. Heymes and M. Dvolaitzky, *Bull. Soc. chim. France*, 1966, 2819.

[4] E. L. Eliel and M. Reese, *J. Amer. Chem. Soc.*, 1968, **90**, in the press.

[5] N. Mori, *Bull. Chem. Soc. Japan*, 1961, **34**, 1567.

[6] E. L. Eliel and S. H. Schroeter, *J. Amer. Chem. Soc.*, 1965, **87**, 5031.

[7] S. Wolfe and J. R. Campbell, *Chem. Comm.*, 1967, 872.

[8] E. L. Eliel and R. J. L. Martin, *J. Amer. Chem. Soc.*, 1968, **90**, 682.