Conformational Analysis. Part 21.† Conformational Isomerism in *cis*-Cyclohexane-1,3-diol

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cis-Cyclohexane-1,3-diol (CHD) has been isolated from a *cis/trans* isomeric mixture by first synthesizing the cyclic acetal 2,4-dioxabicyclo[3.3.1]nonane (**D**). The ^{1}H NMR spectra of CHD, **D**, *cis*- and *trans*-4-*tert*-butylcyclohexanol and *tert*-butylcyclohexane are reported. ^{1}H NMR parameters obtained have enabled calculation of the Gibb's free energy change ($\Delta G°$) for the diequatorial $\rightleftharpoons$ diaxial equilibrium of CHD in 14 solvents. Values for $\Delta G°$ range from 0.1 kcal mol^{-1}‡ in CCl_4 to 2.7 kcal mol^{-1} in aqueous solution in favour of the conformation in which both hydroxy groups are equatorial. Similar measurements on cyclohexanol show that the $\Delta G°$ value of the hydroxy group in inert solvents CCl_4 and $CDCl_3$ has a significant concentration dependence. The value of 0.9 kcal mol^{-1} for $\Delta G°$ characteristic for protic solvents in 1 mol dm^{-3} solutions decreases to the lower value of 0.7 kcal mol^{-1} characteristic of a free OH group in $<10^{-2}$ mol dm^{-3} solutions. There was no concentration dependence of the $\Delta G°$ value (0.80 kcal mol^{-1}) in acetone solution.

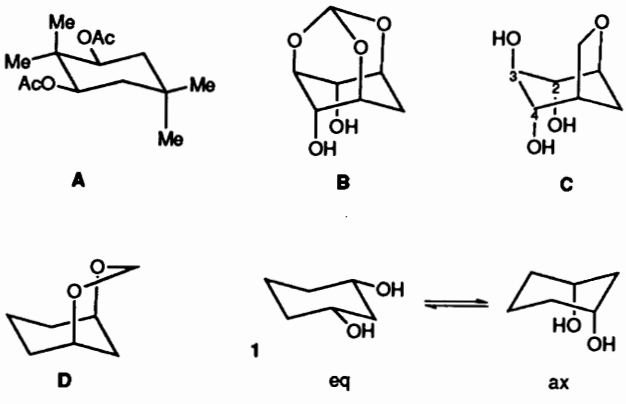
These results when considered with the results for CHD show: (i) there is no intramolecular hydrogen bonding in CHD in water, alcohols or strong hydrogen bond acceptor solvents *e.g.* acetone or DMSO. The differences in the observed $\Delta G°$ values in these solvents can be attributed to (a) the varying polarity of the solvent and (b) to increased preferential solvation of the diequatorial isomer in HBD solvents. (ii) An intramolecular hydrogen bond of *ca.* 1.6 kcal mol^{-1} energy is formed in CHD in CCl_4 solution. This hydrogen bond may be present in the more polar solvents, but its effect is much less noticeable.

In previous parts of this series[1,2] it was noted that two hydroxy groups in a *syn* di-axial arrangement resulted in a high energy conformation in solution. This was observed for the C^4–C^6 hydroxy groups in both glucose and galactose, in which the conformations with *syn* di-axial arrangements of the hydroxy groups were *ca.* 2 and 1 kcal mol^{-1} higher in energy than the most stable conformer. This unfavourable interaction is well known in crystal studies of monosaccharides and is referred to as the Hassel-Ottar or 1,3-diaxial effect.[3] It was of interest to determine whether this effect predominates in the parent compound, *cis*-cyclohexane-1,3-diol: CHD, (**1**), Scheme 1, or whether intra-molecular hydrogen bonding between the oxygen atoms in the di-axial conformer would overcome this repulsion.

We present here the analysis of the NMR spectrum of CHD in a variety of solvents from which the conformer populations and energies can be accurately determined.

Previous studies of the CHD equilibrium have been performed by IR spectroscopy. Kuhn[4] observed a free O–H band at 3619 cm^{-1} and an intramolecularly hydrogen bonded band at 3544 cm^{-1} in the IR spectra of a dilute solution of CHD in CCl_4, indicating that the conformational equilibrium is balanced in this solvent. In recent studies by Bacon *et al.*[5] three bands were observed in $CHCl_3$ solution at 3628, 3546 and 3612 cm^{-1}. The band at 3612 cm^{-1} was assigned to a free equatorial OH band. In a low temperature matrix in argon they observed one band at 3640 cm^{-1} and concluded that a substantial portion of the di-equatorial conformer was present.

Previous NMR investigations of CHD derivatives have been limited to the analysis of the spectra of 1,1,4,4-tetramethylcyclohexyl *cis*-2,6-diacetate (A, Scheme 1), by Musher[6] and the recording of the 60 MHz spectrum of CHD by Finegold and Kwart.[7] Musher obtained vicinal couplings for **A** of $J_{2a,3a}$ = 12.4 and $J_{2a,3e}$ = 4.3 Hz, indicating a predominance of the di-equatorial conformer. The 60 MHz proton spectrum of CHD was insufficiently resolved for any proper analysis.[7]



Scheme 1

Very recently, Uhlmann and Vasella[8] observed a strong intramolecular hydrogen bond between the axial OH groups in the X-ray structure of the myo-inositol derivative **B**, Scheme 1, whereas in the analogue **C** no intramolecular hydrogen bond is observed. They ascribed this to the increased separation of the axial oxygen atoms in **C** (3.299 Å) compared to **B** (2.767 Å). The latter distance is characteristic of an O–H • • • O bond.[3]

Commercial CHD is a mixture of the *cis* and *trans* diol. To obtain the pure *cis* diol it was necessary to prepare the cyclic formal derivative 2,4-dioxabicyclo[3.3.1]nonane, **D**, Scheme 1. The proton NMR spectrum of this compound, and indeed the conformation of **D** have given rise to some controversy in the past.

The ^{1}H spectrum of **D** and its 7,7-dimethyl derivative were recorded by Anteunis *et al.*[9–11] who suggested the molecule

† Part 20, see ref. 1.
‡ 1 cal = 4.184 J.

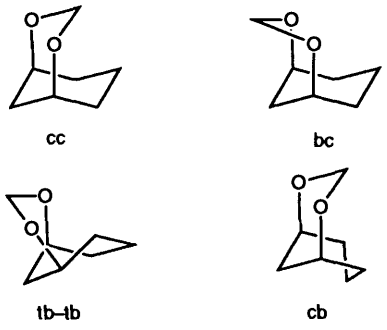


Fig. 1 Conformations of **D**; chair dioxane/chair cyclohexane ring (**cc**); boat dioxane/chair cyclohexane (**bc**); twist-boat dioxane/twist-boat cyclohexane (**tb–tb**); chair dioxane/boat cyclohexane (**cb**)

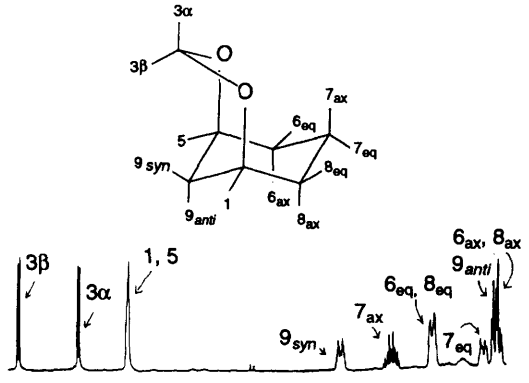


Fig. 2 400 MHz ^{1}H NMR spectrum of **D** in $CDCl_3$

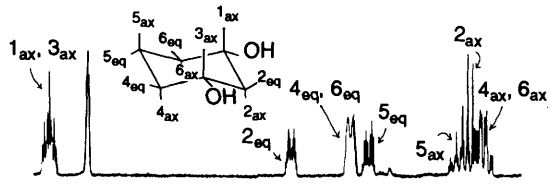


Fig. 3 400 MHz ^{1}H NMR spectrum of *cis*-cyclohexane-1,3-diol in [$^2H_4$]methanol

existed in a flattened chair-chair or twist-boat-twist-boat conformation (Fig. 1). Subsequent investigations by Peters *et al.*[12,13], using NOE difference experiments gave a very different assignment of the ^{1}H NMR spectrum of **D** in benzene solution which was consistent with a preferred boat-chair conformation. A long range ^4J(9*syn*,6e) coupling of 2 Hz characteristic of a W arrangement of the coupling nuclei, and NOE between 9*syn* and 3β provided strong evidence for the boat-chair conformation.

We present the complete assignment of the ^{1}H spectrum of **D** in $CDCl_3$ solution, in which the chemical shifts differ considerably from those in benzene. Our assignment and conclusions fully support those of Peters *et al.*[12]

Experimental

A mixture of *cis*- and *trans*-cyclohexane-1,3-diol was obtained commercially (MTM Research Chemicals/Lancaster). From the ^{1}H NMR spectrum the mixture was found to be *ca.* 65 mol% *cis*-cyclohexane-1,3-diol. The *cis*-isomer was isolated by chemical means. Since only the *cis*-diol can undergo a cyclic acetalisation, 2,4-dioxabicyclo[3.3.1]nonane (**D**) was prepared from the mixture, subsequent acid hydrolysis of this providing the *cis*-diol.

2,4-*Dioxabicyclo*[3.3.1]*nonane.*[9,12]—A mixture of 60 cm^3 benzene, 10 cm^3 ethanol and 2.3 g of the cyclohexane-1,3-diol isomeric mixture, paraformaldehyde (1.8 g, 60 mmol) and some crystals of *p*-TsOH were boiled for two hours. The water formed was removed by azeotropic distillation in a Dean–Stark apparatus. The solvents were removed under reduced pressure. The residue was heated to 200 °C in a Kugelrohr apparatus for one hour, the water pump was then started and the product distilled over. The product was redistilled to yield 2,4-dioxabicyclo[3.3.1]nonane (0.57 g, 4.46 mmol).

cis-*Cyclohexane*-1,3-*diol.*—The substrate was hydrolysed by heating in a 3% dilute HCl solution for one hour. Because of its high water-solubility, the product was obtained by removing most of the water at the pump and then drying an acetone solution of the residue over anhydrous $MgSO_4$. Acetone was removed to yield the crystalline product.

cis *and* trans-4-tert-*Butylcyclohexanol.*—An isomeric mixture of 4-*tert*-butylcyclohexanol was obtained commercially (Aldrich). From its ^{1}H NMR spectrum it was found to be a mixture of *cis* and *trans* isomers in the ratio 1:3. The isomers were separated by flash chromatography using a silica gel column.[14] Using a 1:3 ethyl acetate:hexane solvent mixture the *cis*-isomer was eluted from the silica gel column first.

^{1}H *NMR Spectra.*—All spectra were obtained on a Bruker AMX 400 spectrometer. Typical conditions were: 128 transients accumulated into 16 K data points with a pulse width of 12 μs (*ca.* 83° flip angle) and a sweep width of *ca.* 2500 Hz, giving an acquisition time of 3.3 s. A Gaussian multiplication of the free induction decay (FID) was carried out using values of (LB) = −0.9 and (GB) = 0.35. The FID was zero-filled to 64 K data points giving a digital resolution of 0.075 Hz per point.

An external [$^2H_6$]benzene capillary lock was used in the acquisition of the spectra for the CCl_4, CH_2ClCH_2Cl, and piperidine solutions.

Results and Discussion

Spectral Assignments.—2,4-*Dioxabicyclo*[3.3.1]*nonane* (**D**). The assignment of **D** in $CDCl_3$ (Fig. 2, Table 1) was assisted by a ^{1}H/^{1}H COSY experiment. Our assignment of 3α and 3β follows that of Peters *et al.*[12] based on NOE experiments. The remaining chemical shifts in $CDCl_3$ differ considerably from those in benzene. For example, the signal for 9*syn* is downfield of that for 7a, the reverse of that reported by Peters *et al.* Our assignment follows unambiguously from consideration of the couplings involved (Fig. 2). The ^3J(1,9*syn*) coupling of 4.5 Hz is larger than would normally be expected for a cyclohexane ring, however, this is a consequence of the substituent effect of an oxygen *gauche* to one of the coupled protons.[15]

MM Calculations on **D** using PCMODEL[17] with the MMX force field gave the **bc** conformation as more stable than the **cc** conformation by 1.6 kcal mol^{-1}, in agreement with the value of Peters *et al.*[12,13] of 2.0 kcal mol^{-1}.

In contrast the **cc** conformation of bicyclo[3.3.1]nonane was calculated by Allinger *et al.*[18] to be 2.3 kcal mol^{-1} lower in energy than the **bc** in good agreement with experiment.

cis-*Cyclohexane*-1,3-*diol.* A ^{1}H/^{1}H COSY spectrum allowed the complete assignment of the ^{1}H spectrum of CHD in methanol solution (Fig. 3). Assigning the lowest field signal to the two C*H*(OH) protons the remaining assignments are then trivial.

4-tert-*Butylcyclohexane* (**E**) *and* cis(**F**) *and* trans(**G**)-4-tert-*Butylcyclohexanol.*[a]—The ^{1}H NMR spectra of compounds **E**, **F** and **G** have been assigned from 2D COSY NMR spectra of each of the compounds, to give the assignments in Table 3. Our assignment for **E** for δ(3a) and δ(4a) follows that of Danneels and Anteunis.[18b]

Conformation of cis-*cyclohexane*-1,3-*diol* (CHD).—The two conformers of CHD, in which the hydroxy groups are either

Table 1 Proton chemical shifts (δ) and couplings (Hz) for **D**

	3β	3α	1	9*syn*	7a	6e/8e	7e	9*anti*	6a/8a
Mattinen[a]									
$CDCl_3$	5.41	—	4.31	2.64	1.81	1.82	1.40	1.32	1.39
Peters[12]									
Benzene	5.04	4.79	4.05	2.08	2.45	1.83	1.28	0.7	0.95
Anteunis[11]									
CCl_4	4.42	5.04	4.20	2.58	1.41	1.27	2.30	1.30	1.82
This work									
$CDCl_3$	5.218	4.734	4.340	2.639	2.222	1.890	1.487	1.4	1.4

	J(1,8e)	*J*(1,8a)	*J*(1,9*syn*)	*J*(1,9*anti*)	*J*(6e,7e)	*J*(6e,7a)	*J*(6a,7a)
Peters[12]	4.9	1.5	5.0	1.0	2.1	4.8	13.1
Mattinen[16]	—	1.5	5.0	0	2.3	4.8	13.3
This work	4.5	< 2	4.5	< 2	2.6	5.0	13

	J(6a,7e)	^4J(9*syn*,6e)	*J*(3a,3e)	*J*(6a,6e)	*J*(7a,7e)	*J*(9*syn*,9*anti*)	*J*(1,7e)	*J*(9*syn*,7e)
Peters[12]	5.2	2.4	−5.5	−13.4	−13.7	−14.4	—	—
Mattinen[16]	4.8	—	—	—	−13.3	−14.3	*ca.* 1	—
This work	5.0	2.6	−5.6	−14.1	−13.5	−14.4	< 2	0.45

[a] Data for 3,6-dimethyl-2,4-dioxabicyclo[3.3.1]nonane, ref. 16.

Table 2 ^{1}H NMR chemical shifts of *cis*-cyclohexane-1,3-diol

Solvent[a]	δ(1)	δ(2a)	δ(2e)	δ(4a)	δ(4e)	δ(5a)	δ(5e)
D_2O	3.647	1.208	2.223	1.128	1.886	1.251	1.776
DMSO[b]	3.364	1.018	2.006	0.960	1.706	1.112	1.601
CD_3CN	3.554	1.23[f]	2.091	1.23[f]	1.80[f]	1.23[f]	1.80[f]
MeOD	3.514	1.182	2.181	1.108	1.848	1.243	1.746
Acetone	3.552	1.2[f]	2.106	1.155	1.777	1.2[f]	1.725
Pyridine	3.945	1.856	2.725	1.501	2.098	1.301	1.80[f]
CD_2Cl_2	3.795	1.3[f]	2.001	1.383	1.751	1.493	1.852
$CDCl_3$	3.820	1.565	2.040	1.432	1.776	1.319	1.894
Benzene[c]	3.642	1.592	1.888[e]	1.406[e]	1.640[e]	1.197[e]	1.9[f]
CCl_4[d]	3.921	1.705	2.098	1.605	1.85[f]	1.477	1.85[f]

[a] 298 K unless indicated otherwise. [b] 313 K. [c] 296 K. [d] 323 K. [e] Assignment uncertain. [f] Peak obscured by other peaks.

Table 3 Chemicals shifts (δ) and couplings (Hz) for 4-*tert*-butylcyclohexane (**E**) and *cis*(**F**) and *trans*(**G**) 4-*tert*-butylcyclohexanol

^{1}H NMR parameter	Compound E	F	G
δ(1a)	1.084	—	3.512
δ(1e)	1.635	4.026	—
δ(2a)	1.191	1.490	1.218
δ(2e)	1.745	1.831	2.006
δ(3a)	0.913	1.353	1.042
δ(3e)	1.745	*ca.* 1.54	1.783
δ(4a)	0.944	0.993	0.963
δ(Bu^t)	0.830	0.862	0.848
J(1,2a)	12.6[b]	2.7	11.0
J(1,2e)	3.4[c]	2.7	4.4

[a] $CDCl_3$ solutions. [b] $J_{3a,4a}$. [c] $J_{3e,4a}$.

diaxial (**ax**) or diequatorial (**eq**), Scheme 1, are in rapid equilibrium in solution at room temperature. The mole fraction of the diequatorial conformer (P_{eq}) is given directly from the observed vicinal couplings as

$$P_{eq} = [J_{1,2}(trans) - J_{1e,2e}]/(J_{1a,2a} - J_{1e,2e}) \quad (1)$$

Alternatively, P_{eq} can be calculated from the observed peak width of the H1/H3 signal, (d) as:

$$P_{eq} = (d_{ax} - d)/(d_{ax} - d_{eq}) \quad (2)$$

or from the observed chemical shift (δ) as:

$$P_{eq} = (\delta_{ax} - \delta)/(\delta_{ax} - \delta_{eq}) \quad (3)$$

The free energy difference $\Delta G° = -RT\ln K$ and equilibrium constant $K = (1 - P_{eq})/P_{eq}$ are thus readily obtained.

For δ_{ax} and δ_{eq} values for the proton alpha to the hydroxy group in *cis*- and *trans*-4-*tert*-butylcyclohexanol, were taken, but this ignores the γ-effect of the second hydroxy group. Calculations showed that this is a significant error, and thus this method was not considered further. The population of the diequatorial conformer was therefore calculated from eqns. (1) and (2). The vicinal couplings $^3J_{aa}$, $^3J_{ae}$, $^3J_{ea}$ and $^3J_{ee}$ used in eqn. 1 were taken from the H1,H2 couplings in *cis*- and *trans*-4-*tert*-butylcyclohexanol (Table 3). These values are very similar to those obtained by Anet from low temperature measurements on hexadeuteriocyclohexanol acetate (aa, ae, ea and ee couplings of 11.4, 4.2, 2.7 and 2.7 Hz respectively).[19]

Similarly the reference values of the width of the α-H signal were also taken from the 4-*tert*-butyl compounds (axial OH 10.7 Hz, eq. OH 30.8 Hz). The conformer populations and energies for CHD in a variety of solvents are given in Table 4.

Discussion

The percentage of the axial conformer of CHD present in solution for each solvent is given in Table 4, from eqns. (1) and (2). These values in are in good agreement, although $\Delta G°$ is calculated taking the values from eqn. (1), as these are probably the more accurate. In low dielectric solvents such as carbon tetrachloride $\Delta G°$ is just a few tenths of a kilocalorie and the ax conformer is significantly populated. In contrast, in high dielectric solvents $\Delta G°$ is > 1 kcal mol^{-1} and CHD exists largely as its eq conformer. If dipole–dipole solvent–solute interactions are dominant one might have expected the reverse trend, *i.e.* the more polar axial conformation would be stabilised in high dielectric media (from *ab initio* calculations $\mu_{eq} = 2.01$ D and $\mu_{ax} = 2.96$ D).

$$\Delta G°(\text{NHB}) = 0.13 + 0.0248\varepsilon \ (r^2 = 0.984)$$

Alternatively, in terms of solvation the equatorial OH groups are more exposed than the axial OH groups to solvent molecules. As the solvent molecules become more polar they are better able to solvate the diequatorial form of CHD.

Table 4 Conformer populations and Gibb's free energy differences for the diequatorial and diaxial conformations of *cis*-cyclohexane-1,3-diol in solution

Solvent[a]	ε[e]	d/Hz	$J_{1,2}(cis)$	$J_{1,2}(trans)$	P_{eq} d	P_{eq} $J(trans)$	$\Delta G°$(eq→ax)[g]/ kcal mol^{-1}
D_2O	78.54	30.1	4.14	10.91	96.5	98.9	2.66
DMSO[b]	46.68	28.7	4.27	10.26	89.6	91.1	1.62
CD_3CN	37.50	27.7	3.94	9.93	84.6	87.1	1.13
CD_3NO_2[h]	35.87	26.9	3.87	9.61	80.6	83.3	0.95
MeOD	32.70	29.7	4.10	10.73	94.5	96.7	2.00
EtOD	24.5	*f*	4.07	10.29	—	91.4	1.40
Acetone[h]	20.70	27.1	4.14	9.88	81.6	86.5	1.10
Pyridine	12.4	28.6	4.0	10.3	89.1	91.6	1.41
CH_2ClCH_2Cl	10.36	23.8	4.1	8.1	65.2	65.1	0.37
CD_2Cl_2	8.9	unresolved		8.08	—	64.8	0.36
Piperidine	5.80	28.2	3.9	10.2	87.1	90.4	1.33
$CDCl_3$	4.81	23.1	3.85	7.78	61.7	61.2	0.27
Benzene[c]	2.28	22.8	3.81	7.65	60.2	59.6	0.23
CCl_4[d]	2.24	21.8	4.35	7.30	55.2	55.4	0.14

[a] 298 K Unless indicated otherwise. [b] 350 K, J(H1,OH) subtracted from peak width. [c] 296 K. [d] 323 K. [e] Solvent dielectric constant. [f] Peak obscured by solvent peak. [g] Calculated from $J_{1,2}(trans)$. [h] D_2O droplet added to remove J(H1,OH).

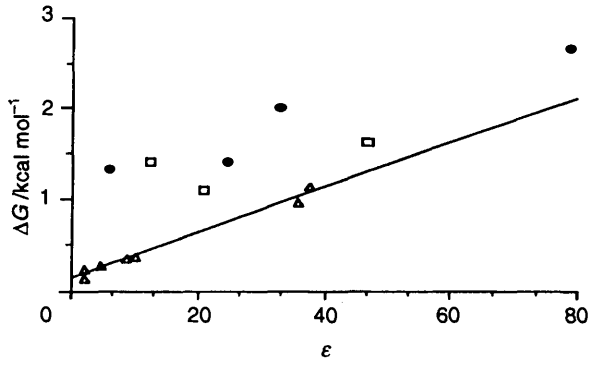


Fig. 4 Plot of the Gibbs free energy change against solvent relative permittivity for the equatorial/axial equilibrium of *cis*-cyclohexane-1,3-diol in non-hydrogen bonding (NHB), hydrogen bond acceptor (HBA) and hydrogen bond donor and acceptor (HBD) solvents. △; NHB, ●; HBD, □; HBA.

The correlation of $\Delta G°$ with solvent dielectric constant (ε) is poor (cor. coef. = 0.676) (Fig. 4). If intermolecular and intramolecular hydrogen bonding play a role in this equilibrium then this is to be expected. For the solvents: CCl_4; benzene; $CDCl_3$; CD_2Cl_2; CH_2ClCH_2Cl; CD_3NO_2 and CD_3CN, which are largely unable to hydrogen bond (NHB solvents) the $\Delta G°/\varepsilon$ correlation is good (cor. coef. = 0.984).

The hydrogen bonding solvents all occur above the NHB line of Fig. 4, so that intermolecular solvent–solute hydrogen bonding makes the equatorial conformer in these solvents more favourable than for NHB solvents of the same dielectric. The $\Delta G°/\varepsilon$ correlation for the HB solvents is poor (cor. coef. = 0.762). This is perhaps not surprising as these solvents have differing hydrogen bonding abilities. Sub-division of the HB solvents into hydrogen bond acceptor (HBA) solvents (*i.e.* pyridine, acetone, and DMSO) and hydrogen bond donor (HBD) solvents (*i.e.* piperidine, ethanol, methanol and water) improves the $\Delta G°/\varepsilon$ correlation, for HBD solvents cor. coef. = 0.912. There are too few data points for the HBA solvents for any meaningful correlations.

A multi-regression analysis of the $\Delta G°$ values for all the solvents in Table 4 against the solvation parameters of M. H. Abraham[19b] *et al.* gave eqn. (4) where π_1^* is the solvent

$$\Delta G = -0.72 + 1.46\pi_1^* + 1.03\alpha_1 + 1.17\beta_1 \quad (4)$$

dipolarity/polarisability, α_1 is a measure of the solvent hydrogen bond donor ability, and β_1 is a measure of the solvent hydrogen bond acceptor ability. The regression has a correlation coefficient of 0.936 and standard deviation of 0.32 kcal mol^{-1}.

In order to quantify and explain the interactions in the *cis*-1,3-diol it is necessary to know the corresponding free energy differences of the single OH group in cyclohexanol.

Eliel, in a seminal paper, both comprehensively detailed previous determinations of the cyclohexanol free energy difference and also accurately measured this equilibrium by equilibration methods in a range of solvents.[20]

He noted an incredibly diverse range of previous determinations (*e.g.* in CCl_4 solution the ΔG values ranged from 0.3 to 1.0 kcal mol^{-1}), but recommended values of 0.90 (± 0.05) kcal mol^{-1} for hydroxylic solvents and smaller values of 0.6–0.7 kcal mol^{-1} for aprotic and NHB solvents.

He attributed the difference in the hydroxy ΔG values to an equatorial hydroxy being more exposed to hydrogen bonding by the solvent than an axial OH thus conferring extra stability on the equatorial conformation.

Eliel also considered the possibility that intermolecular hydrogen bonding between the solute molecules in the relatively concentrated solutions used (*ca.* 0.1 mol dm^{-3}) may affect the ΔG values. This possibility can now be easily checked by NMR spectroscopy with the vastly increased sensitivity of modern NMR spectrometers, and Table 5 records the chemical shifts of the C-1 proton of cyclohexanol with increasing dilution in CCl_4, $CDCl_3$ and [$^2H_6$]acetone together with the corresponding ΔG values obtained directly from eqn. (3) using the corresponding protons of the *cis* and *trans* 4-*tert*-butyl compounds as references.

The results are of interest and confirm and refine Eliel's conclusions. In both CCl_4 and $CDCl_3$ there is a significant change in the C-1 proton chemical shift with concentration, which contrasts with the absence of any observable change for the chemical shifts of the 4-*tert*-butyl reference compounds. This is therefore clearly due to a change in the conformer populations with dilution, reflected in the derived ΔG values.

For solutions sufficiently dilute to preclude intermolecular hydrogen bonding between the solute molecules ($< 10^{-2}$ mol dm^{-3}),[21] the ΔG values agree completely with Eliel's values. The slight increase in ΔG in $CDCl_3$ compared to CCl_4 is to be expected as $CDCl_3$ is a weak hydrogen bond donor.

For the concentrated solutions, the ΔG values obtained are those characteristic of hydrogen bond donor solvents, again to be expected as all the solute hydroxy groups are intermolecularly hydrogen bonded at these concentrations.

Table 5 Variation in ΔG for the equatorial/axial equilibrium of cyclohexanol with solute concentration[a]

Concentration/ mol dm^{-3}	δ(CHOH)	K	ΔG/ kcal mol^{-1}
$CDCl_3$[b,c]			
1.0	3.5893	6.24	−1.08
0.1	3.6090	4.67	0.91
0.01	3.6141	4.37	0.87
0.005	3.6135	4.40	0.88
0.0005	3.6154	4.30	0.86
0.0001	3.6153	4.30	0.86
0.000 025	3.6153	4.30	0.86
CCl_4[b,c]			
1.0	3.4879	4.22	0.85
0.1	3.5033	3.55	0.75
0.001	3.5197	3.01	0.65
0.0001	3.5197	3.01	0.64
0.000 01	3.5194	3.01	0.65
CD_3COCD_3[b,c]			
0.1	3.5081	3.82	0.79
0.001	3.5031	4.05	0.83

[a] 298 K. [b] For *cis*-4-*tert*-butylcyclohexanol δ(CHOH) = 4.0337 ($CDCl_3$), 3.9301 (CCl_4) and 3.9260 (CD_3COCD_3). [c] For *trans*-4-*tert*-butylcyclohexanol δ(CHOH) = 3.5181 ($CDCl_3$), 3.3832 (CCl_4) and 3.3986 (CD_3COCD_3).

In [$^2H_6$]acetone again as expected there was no concentration dependence of the C-1 proton chemical shift, and the ΔG value obtained agrees with Eliel's value for HBA solvents (*e.g.* THF 0.69, dimethoxyethane 0.63 kcal mol^{-1}).

Note also that the value of ΔG for cyclohexanol in aqueous solution is recorded in ref. 20 as *ca.* 1.0 (±0.1) kcal mol^{-1}.

One intriguing question arising from these results is why inert solvents and HBA solvents give the same ΔG value for cyclohexanol. This is simply explained as due to the high energy of the *endo* conformation of axial cyclohexanol (*i.e.* with the hydrogen pointing towards the ring, analogous to **7** in Fig. 5), which can be excluded from consideration. Thus axial cyclohexanol can only act as a hydrogen bond donor. HBA solvents will solvate both the axial and equatorial conformers equally, giving a similar ΔG value to that for the inert solvents. In contrast the protic solvents are HBD and HBA and they can therefore solvate the equatorial OH group, but not the axial OH group as both donors and acceptors. This gives an increased solvation energy to the equatorial conformer in these solvents.

The above discussion allows us to both quantify and explain the additional interactions of the two hydroxy groups in CHD.

In aqueous solution we would envisage essentially no intramolecular hydrogen bonding between the *cis*-1,3-hydroxy groups in axial CHD. Thus the observed ΔG value of 2.7 kcal mol^{-1} should be due to the combined steric effects of the hydroxy groups. Three unfavourable 1,3-interactions [1 × (OH ··· OH) and 2 × (H ··· OH)] would favour the eq. over the ax. conformer. From pH measurements on the complexation of various cyclitols with sodium borate in aqueous solution Angyal and McHugh[22] calculated 1,3-diaxial interaction energies $\Delta G°(H_{ax} \cdots OH_{ax}) = 0.45 \pm 0.05$, and $\Delta G°(O_a \cdots O_a) = 1.9 \pm 0.1$ kcal mol^{-1}. These are in complete agreement both with the value of cyclohexanol in aqueous solution, *i.e.* $\Delta G°(H_{ax} \cdots OH_{ax})$ 0.50 kcal mol^{-1}, and with values obtained from the relative rotamer energies for galactoses of $\Delta G°(O_{ax} \cdots O_{ax})$–$\Delta G°(H_{ax} \cdots O_{ax})$ = 1.4 kcal mol^{-1} in D_2O. Using the values of Angyal and McHugh for CHD in D_2O $\Delta G°$ is predicted to be 2 × 0.45 + 1.9, *i.e.* 2.8 kcal mol^{-1}, in excellent agreement with the observed value.

In the protic solvents recorded here (MeOH, EtOH) there is a marked decrease in the observed ΔG value for CHD compared with that in aqueous solution (Table 4), which is not observed in cyclohexanol itself. Most of this decrease may be attributed to the decrease in the solvent dielectric constant (*cf.* Fig. 4). The slope of the line through the protic (HBD) solvents (not shown in Fig. 4) is very similar to that shown for the NHB solvents. This would suggest that there is little evidence for intramolecular hydrogen bonding in di-axial CHD in these solvents. On this basis the difference in ΔG values between *e.g.* methanol and nitromethane, a solvent of comparable dielectric constant but very limited hydrogen bonding properties, of *ca.* 1.0 kcal mol^{-1}, is largely due to the extra stabilisation of the di-equatorial conformer in protic solvents of *ca.* 0.7 kcal mol^{-1} (*vide infra*).

Similar reasoning may be used to consider the ΔG values in the aprotic solvents, though here there is a clear difference in that the ΔG value for the hydroxy group in cyclohexanol in these solvents differs considerably from that in aqueous solution (0.65 *vs.* 1.0 kcal mol^{-1}). This in itself gives a decrease in the predicted ΔG value of CHD of *ca.* 0.7 kcal mol^{-1}, which combined with the decrease in the dielectric constant (*cf.* Fig. 4) accounts for most of the difference in the ΔG value between say DMSO and aqueous solution.

In the light of these findings the proposal by Uhlmann and Vasella[8] that a strong intramolecular hydrogen bond exists between the axial OHs of compound B (Scheme 1) in DMSO is most interesting. They argue the variation in chemical shift of the axial hydroxy protons in **B** with temperature, -3.6×10^{-3} ppm/K, is typical for an OH participating in intramolecular H-bonding (for the equatorial OH the variation was -7.5×10^{-3} ppm/K). For compound **C** variations of -6.2×10^{-3} (OH-C2 and OH-C4) and -6.6×10^{-3} (OH-C3) are found. Measurements of δ(OH) versus temperature for CHD in DMSO gave a slope of -6.0×10^{-3} ppm/K, a value close to that observed for OH-C3 and OH-C4 in compound **C**. This is evidence that CHD does not undergo intramolecular hydrogen bonding in DMSO, though of course, this value is the weighted mean of the values for the diequatorial and diaxial conformations. ^3J(CH,OH) is 4.7 Hz in DMSO and 4.5 Hz in acetone, these values are consistent with there being free rotation about the C–OH bonds in these solvents.

Finally it is of interest to consider the implications of the ΔG value obtained for CHD in CCl_4 solution of 0.14 kcal mol^{-1} (Table 4). The ΔG value for cyclohexanol in the same solvent (0.65 kcal mol^{-1}, Table 5) provides a value of the $H_{ax} \cdots OH_{ax}$ repulsive interaction of 0.33 kcal mol^{-1}. Furthermore from the relative rotamer energies of galactose derivatives a value of $(OH_{ax} \cdots OH_{ax})$–$(H_{ax} \cdots OH_{ax})$ of 0.5 kcal mol^{-1} in chloroform solution was found, with which Fig. 4 provides an estimate of the $OH_{ax} \cdots OH_{ax}$ repulsive interaction as 0.83 kcal mol^{-1}.

These values taken together with the ΔG value of 0.14 kcal mol^{-1} for CHD in CCl_4 provide an estimate of the hydrogen bond attractive interaction in the diaxial conformer of 0.83 + 0.65 + 0.14 *i.e.* 1.6 kcal mol^{-1}. This would appear a reasonable value for a moderately weak hydrogen bond, and compares with the value of hydrogen bonding for ethanol in CCl_4 solution of 1.5 kcal mol^{-1}.[3]

Calculated vs. *Observed Conformer Energies in* CHD.—The vapour phase free energy difference between the two conformers of CHD can be obtained by extrapolation to $\varepsilon = 1$; which gives from Fig. 4 $\Delta G°_v = 0.14$ kcal mol^{-1}. Using the theoretically more rigorous Kirkwood function $(\varepsilon - 1)/(2\varepsilon + 1)$ a good linear plot is obtained for all the NHB solvents except for nitromethane and acetonitrile and extrapolation of this line to $\varepsilon = 1$ gives $\Delta G°_v = 0.0$ kcal mol^{-1}. These values may be compared with those of −0.72 (±0.4) kcal mol^{-1} from eqn. (4). We will use the value of $\Delta G°_v$ of 0.0 (±0.2) kcal mol^{-1} henceforth.

It was of some interest to see whether this value could be

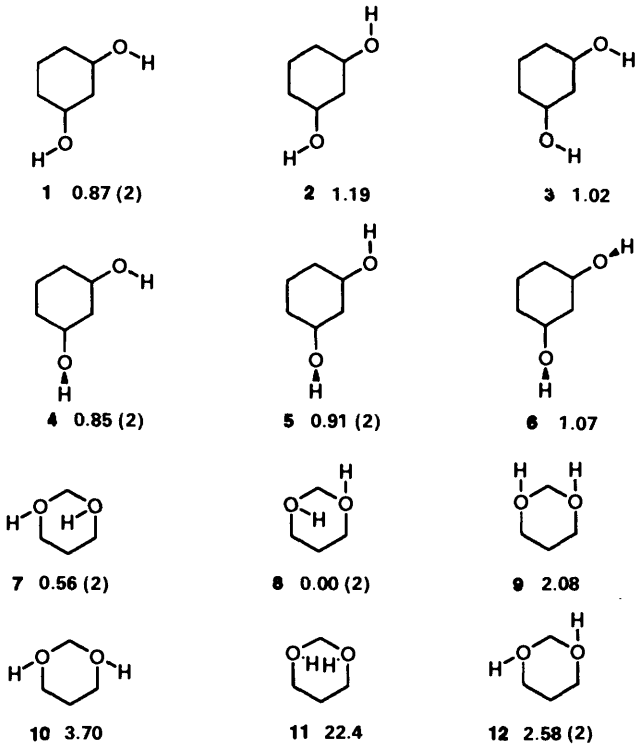


Fig. 5 Possible OH orientations of the di-equatorial (**1**–**6**) and di-axial (**7**–**12**) conformers of CHD, with their relative energies (kcal mol^{-1}) and statistical weights (in parenthesis) for the degenerate orientations

reproduced by the molecular mechanics and MO programmes available to us. These were PCMODEL,[17] in which the MMX force field used 'is loosely derived from Allingers MM2 force field', NEMESIS which uses the COSMIC force field,[23] and the GAUSSIAN-90 suite of programmes.[24]

There are nine possible orientations of the hydroxy group for both the equatorial and axial conformations, some of which are degenerate. The physically distinct orientations are shown schematically in Fig. 5, which also gives their relative energies from *ab initio* (STO-3G) calculations using standard geometries, together with their statistical weights.

The di-equatorial conformer has six orientations of roughly equal energy, three of which are doubly degenerate, giving a statistical weight of nine. In the axial conformer there are two orientations (**7** and **8**) of similar energy each being doubly degenerate. The other orientations are of much higher energy, and this gives a statistical weight of four for the axial conformer. On this analysis the diequatorial conformer of CHD has an excess entropy of $R\ln 9 - R\ln 5$ *i.e.* 1.17 cal deg mol^{-1} and therefore the observed conformer energy difference ($E_{ax} - E_{eq}$) is estimated as -0.35 kcal mol^{-1}.

The calculated energy difference ($E_{ax} - E_{eq}$) for orientations **4** (eq) and **8** (ax) was calculated as 0.29 (PCMODEL), -1.89 (NEMESIS) and -0.85 (STO-3G) kcal mol^{-1}. There is little consistency but the STO-3G calculated energy is in reasonable agreement with the observed value. The large disparity in the results of the two MM calculations reflects the difficulty in parameterising the hydroxyl group in MM programs.

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