CONFORMATIONAL ANALYSIS OF CYCLOHEXANDIOLS AND RELATED COMPOUNDS

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DECLARATION

This thesis has not been nor is currently submitted for the award of any other degree or similar qualification.

J. Bacon.

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NOMENCLATURE

The I.U.P.A.C. system of nomenclature is used in conjunction with the non - I.U.P.A.C. nomenclature. Trival names are used where literature citations may cause confusion.

ABSTRACT

The conformational equilibria in disubstituted cyclohexanes containing polar groups lead to a diversity of conformational forms. In solution, the conformational preference is shown to be highly dependent upon the nature of the solvent. In the cyclohexandiol series, the formation of intramolecular and intermolecular hydrogen bonds determines the conformational preference with regard to the molecule as a whole and with respect to the rotamer conformation of the hydroxyl groups. Polar solvents capable of hydrogen bonding to the hydroxyl group have been shown to influence the position of equilibrium between the alternative chair conformations. In cyclohexanol, the equilibrium is always shifted towards the equatorial conformation. ^{13}C nmr, ^{1}H nmr, solution i.r. and matrix isolation i.r. techniques have been used to determine the conformational structures in the cyclohexandiol series and the nature of the solvent interactions. Two types of solvent interaction have been identified, a hydrogen bonded interaction and a non-bonded dipole interaction.

A Computer Graphic Simulation has been used to quantify the conformational energy differences and to rationalize the experimental results in terms of the Van der Waals repulsion energy.

The experimental results give strong evidence that in cis cyclohexan-1,3-diol, two types of internal hydrogen bond exist in the diaxial conformation. The Computer Graphic simulation supports this reasoning on thermodynamic grounds.

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INTRODUCTION

THE CONFORMATION OF CYCLOHEXYL SYSTEMS

In the cyclohexane ring system, the possession of polar groups which are capable of self-association can potentially influence the preferred conformation of the molecule.

It is a well established fact that the preferred conformation of cyclohexane is the chair form, with skew and boat forms having very low populations (fig 1.1).

fig.1.1

There are of course two chair forms, identical in cyclohexane but not in its substituted derivatives (fig 1.2).

fig 1.2

The two chair forms are fairly rigid but can be interconverted via a flexible form. The process is called ring inversion and results in all equatorial substituents becoming axial and all axial substituents becoming equatorial (fig1.3).

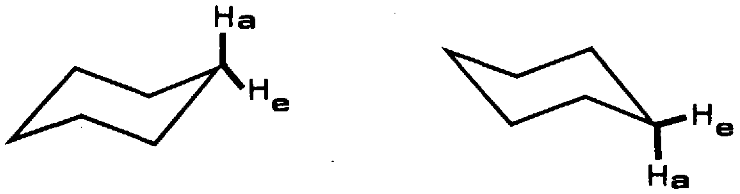


fig 1.3

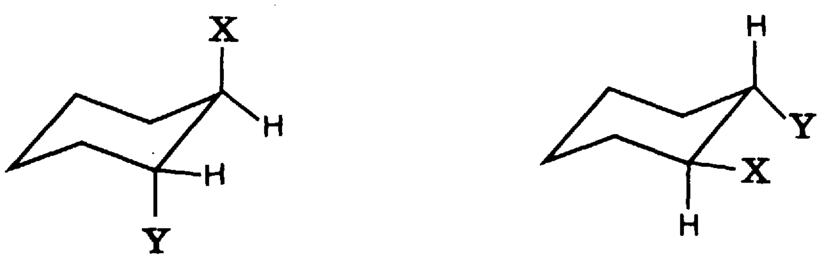
The exact geometric changes that occur in the process are not known but the energy barrier is known to be about 42kJ/mol. This is appreciable but can be overcome at room temperature, so that interconversion is frequent at 298K but has virtually ceased at 173K. This can be seen from the proton magnetic resonance spectrum of cyclohexane. At room temperature, cyclohexane stays in any one chair form for about 10^{-5} second. The nmr spectrometer "observes" the proton for about 10^{-2} second, during which period it has changed environment many times. All twelve protons therefore appear to the spectrometer to have identical averaged environments and hence the same chemical shift. The spectrum at room temperature therefore consists of a single sharp line. At 173K ring inversion is slow and the protons remain in an axial or equatorial position during the time of observation. Two lines are observed in the spectrum at different chemical shifts corresponding to protons in two distinct environments.

Monosubstituted cyclohexanes would also be expected to exist almost entirely in chair forms but now the two chair forms are different, with the substituent axial in one form and equatorial in the other. The barrier to ring inversion is still about 42KJ/mol so they are rapidly interconverting at room temperature. However, the two forms need not be equally stable. When substituent X is a carbon atom, the 1,3 X to H distance in the axial form is 2.55A^{O} whereas in the equatorial form the 1,2 X to H distance is 2.8A (fig 1.4).

fig 1.4

If X is large, Van de Waals steric compression is therefore less when X is equatorial. e.g. in methyl cyclohexane 95% is in the equatorial form.

In 1,2 disubstituted cyclohexanes steric repulsions are now possible between the two substituents themselves and if the two groups are bulky, then the diaxial conformer will be preferred (fig. 1.5).



DIAXIAL

DIEQUATORIAL

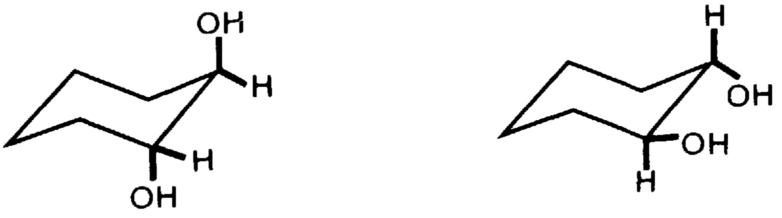
fig. 1.5

The proportion of each isomer will therefore depend upon the size and nature of the substituents X and Y.

In the cyclohexandiol series (excluding the geminal diols), each diol molecule has two configurational isomers (cis and trans) and each configurational isomer can have conformational isomers.

The stability of any particular isomer in the cyclohexandiol series will depend upon a number of factors, the chief one being the steric repulsions that occur between each hydroxyl group. However, association between neighbouring molecules or intramolecular association can be expected to have a stabilizing effect upon a particular conformation. In solution, the solvent can also be expected to have pronounced effects. Solvents of differing polarity and dielectric constant influence hydrogen bonding and hence could be expected to influence the conformation of cyclohexandiols in solution.

Taking for example, cyclohexan-1,2-diol in which there are two configurational isomers, cis and trans. The chair form of the trans isomer has two possible conformational isomers (fig 1.6).



DIAXIAL DIEQUATORIAL

fig. 1.6

Either both the hydroxyl groups are axial or both are eqatorial. In the absence of all other forces the diaxial conformer would be expected to have the larger population on steric grounds, since the hydroxyls have an anti relationship and repulsive forces are minimized. In the diequatorial conformer the gauche relationship between the hydroxyls causes steric repulsions due to Van de Waals forces and so is less favoured. However, it has been shown that in solution in an inert solvent, extensive hydrogen bonding occurs, both intermolecularly and intramolecularly (33). These association phenomena have pronounced effects upon the infrared and nmr spectra of this compound and the other diol isomers. To understand these effects, consideration must be given to the nature of the hydrogen bond and its associated effects.

HYDROGEN BONDING

The term hydrogen bonding is a general term which covers a diversity of associations. There are, however, certain criteria for hydrogen bonding:

1. Hydrogen bonding occurs between a proton donor A-H and a proton acceptor B, where A is an electronegative atom such as O, N, S, F, Br, I, Cl or C and the acceptor is a lone pair, an electronegative atom, a pi-electron orbital or a multiple bond. Generally, a hydrogen bond can be characterized by a proton shared by two lone pairs of electrons.

2. Hydrogen bonding is distinctly directional and specific in its interaction. Hydrogen bonds are planar, but considerable variation can occur in the angle A--H--B.

It is more localized than any other type of weak interaction.

3. The total hydrogen bond length R(A--B) is equal to or less than the

sum of the Van der Waals radii of atoms A and B, i.e. the total bond length contraction caused by hydrogen bond formation is equal to or greater than twice the Van der Waals radius of the hydrogen atom.

4. Hydrogen bonding is an associative phenomenon. It causes a decrease in the total number of free molecules and an increase in the average molecular weight except in the case of intramolecular hydrogen bonding.

5. In hydrogen bonding a specific A-H group interacts with a specific acceptor site. The A-H bond is therefore weakened but not broken and the properties of the acceptor group are also affected.

6. The first bond length variation rule relates the intermolecular donor-acceptor interaction to the induced intramolecular effects.

In a molecule capable of self-association, i.e. one that possesses both donor and acceptor sites, the hydrogen bond interaction causes an increase in the bond length A-H in both molecules. This results in an increase in the acceptor properties of A and the donor properties of H ie., A becomes a stronger electron donor whilst H becomes a stronger electron acceptor.

In dimeric hydrogen fluoride, H-F----H-F, the H-F bonds are longer than in the monomeric molecules, and hence the acceptor properties of the terminal hydrogen atoms, as well as the electron donor properties of the terminal fluorine atoms are greater than in the monomeric species.

All molecules can be conveniently classified into four types with reapect to their ability to participate in hydrogen bonding (table 1). Hydrogen bonding molecules can be divided into types 1 to 3, while molecules incapable of hydrogen bonding form type 4. The latter include compounds which are used as so called inert solvents in studies of hydrogen bonded molecules.

Type 1 and 2 molecules form hydrogen bonded complexes, frequently in a simple ratio (1:1). The strength of the hydrogen bond depends primarily on the relative acidity of 1, and the relative basicity of 2 (e.g. chloroform/acetone).

TABLE 1

TYPE	DESCRIPTION	EXAMPLES
1	Molecules with one or more donor groups and no acceptor groups	Haloforms, highly halogenated compounds, alkynes.
2	Molecules with one or more acceptor groups and no donor groups.	Ketones, ethers, esters, alkenes, aromatics, tert.amines nitriles and isonitriles.
3	Molecules with both donor and acceptor groups.	Alcohols, water, phenols, acids, primary and sec. amines.
4	Molecules with neither donor or acceptor groups.	Alkanes, carbontetrachloride, carbondisulphide.

(Type 3 molecules can self-associate by hydrogen bonding with themselves.)

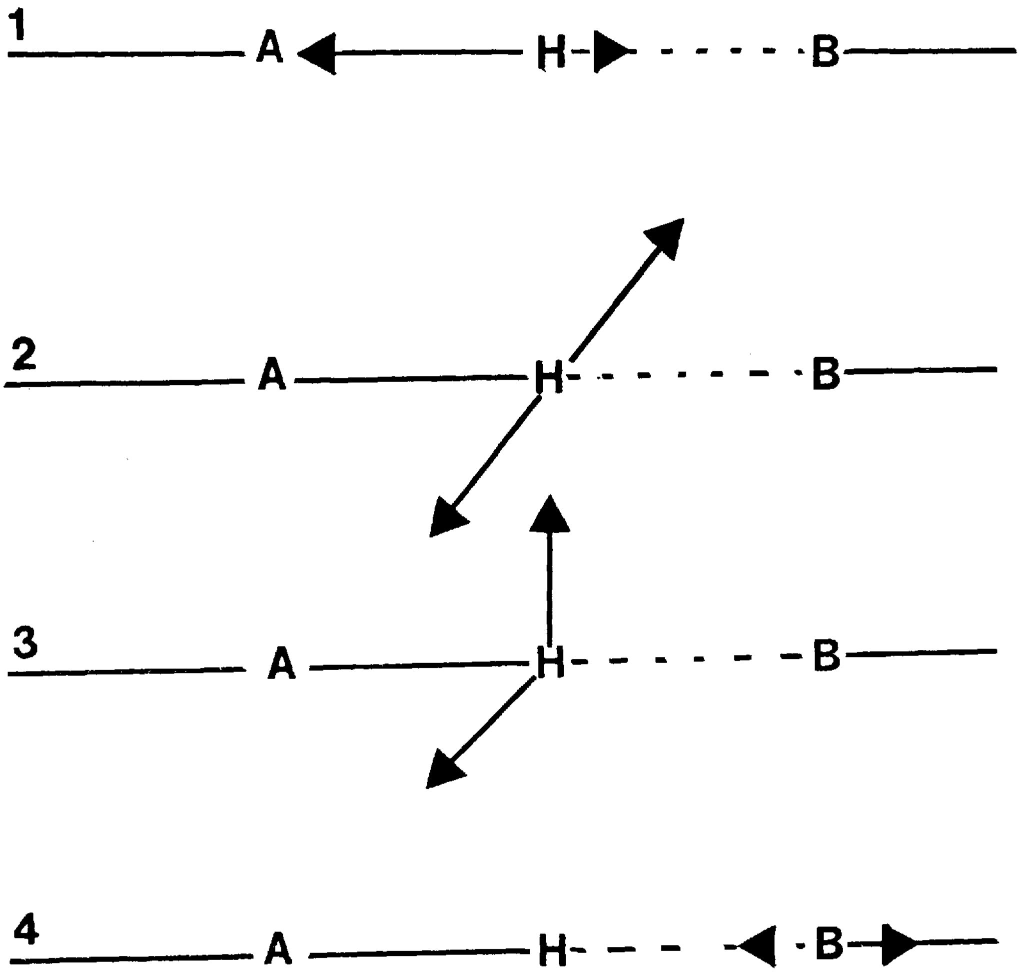
Two types of hydrogen bonded complexes may be formed.

a. Intermolecular, involving two or more separate molecules.

b. Intramolecular, involving donor and acceptor sites within the same molecule.

The strength of the hydrogen bond depends not only upon the relative acidities of the donor and acceptor sites, but also, in the case of intramolecular hydrogen bonding on the spatial arrangement present. Self association through intermolecular hydrogen bonds can form

fig.1.7



1.The fundamental A-H stretching frequency (A-H).

2.The A-H in plane deformation (bending) frequencies (A-H).

3.The A-H out of plane deformation (bending) frequencies (H---B).

4.The AH---B fundamental stretching frequencies (H---B).

a large variety of open/linear and cyclic/closed polymers.

INTRAMOLECULAR HYDROGEN BONDS

An intramolecular hydrogen bond occurs only when one proton donor and one proton acceptor site on the same molecule are in favourable spatial configuration i.e. when the distance between the hydrogen of the donor group and the acceptor site is between 1.4 and 2.5Å , and when the angular orientation of the acceptor site does not deviate greatly from the bond axis of the donor group A-H.

Typical molecules which exhibit intramolecular hydrogen bonding are monoanions of 1,2 dicarboxylic acids, ortho-halogenophenols, orthohydroxyphenols and ketones.

VIBRATIONAL SPECTROSCOPY OF HYDROGEN BONDED MOLECULES

A molecular model may be considered as consisting of point masses joined together by springs. The model is flexible and the point masses may vibrate with respect to each other.

In general, in the case of n atoms there are 3n degrees of freedom, of which three are translational, and in a non-linear molecule 3 are rotational leaving 3n-6 vibrational degrees of freedom. These vibrations consist of various stretching and deformation (bending) modes which are restricted to certain permitted energies.

Several vibrations of the complex A-H---B are useful in hydrogen bonding studies (fig. 1.7).

When hydrogen bonding occurs between a proton donor group A-H and an acceptor group B, i.e. a hydrogen bond complex A-H---B is formed, several effects are usually found in the infrared region;

1. The absorption bands due to the A-H stretching vibrations (fundamental and overtones) are shifted to lower frequencies. These shifts range from about 30cm^{-1} to several hundred cm^{-1} or more. This effect is due to the weakening of the force constant of the A-H stretching mode caused by formation of the hydrogen bond.

2. The shifted absorption bands due to the hydrogen bonded A-H stretching vibrations are much broader than the corresponding bands of the non-hydrogen bonded A-H groups. The change in the half-band width $(\Delta \nu_{\frac{1}{2}})$ varies from 30cm^{-1} to 100cm^{-1} or more. The breadth and structure of the hydrogen bonded A-H stretching vibrations are affected very little by change in phase or temperature.

3. In addition to broadening, the integrated intensity of fundamental A-stretching bands increases, sometimes up to factors of ten or more. However, the corresponding overtone decreases slightly in integrated intensity. The reasons for these striking intensity effects are thought to be due to the fact that hydrogen bonds have substantial electrostatic character and that the intensity of absorption due to infrared active vibrations is directly proportional to the rate of the electrostatic dipole with internuclear distance.

4. The A-H deformation modes are shifted to higher wavenumbers. These shifts are appreciably smaller than those found for the A-H stretching

vibrations. Formation of hydrogen bonds constrains the deformation vibrations and therefore increases the force constants for these modes.

5. The A-H deformation modes do not show any substantial line broadening or intensity change when hydrogen bonding occurs.

6. New vibrational modes, corresponding to H---B stretching and deformation, are found at low frequencies in the far infrared region.

7. The vibrational modes of the hydrogen bond acceptor, B, are shifted by hydrogen bonding. These shifts may be to either longer or shorter wavelength, and are generally much smaller than those found for the donor A-H vibrations.

The A-H stretching modes have been more widely investigated in hydrogen bond studies than any other experimental effect. The shift in the A-H stretching vibration is easily observed and measured. Band contour broadening and increase in integrated absorption intensity of the A-H stretching vibration are simple to observe but difficult to quantify. Frequency shifts and changes in band intensities are also observed on changing the phase or the solvent and may not be ascribed unambiguously to hydrogen bonding without additional supporting evidence. For example, the relatively weak dispersion forces between the non-polar symmetric molecules of methane produce small but easily detectable shifts in the C-H stretching vibrations frequencies with change in state. in more polar molecules such as hydrogen chloride the intermolecular interactions are much stronger, leading to greater shifts caused by change in state. Similarly, large solvent effects on the stretching vibration frequency are observed even in the so-called inert solvents. Thus, a frequency shift alone cannot identify an intermolecular interaction mechanism, although the magnitude of the shift may be a guide to the energy of interaction. Correlations of frequency shifts with the strength of hydrogen bonds have frequently been made but there are exceptions (12).

Some of the simplest examples of shifts in ν(A-H), that can be attributed to hydrogen bonding, are shown by the C-H band in halogenated hydrocarbons dissolved in proton acceptor molecules (3). In all cases, the introduction of the proton acceptor solvent produces a new, broad, more intense absorption at lower wavenumbers (3). The shift to lower wavenumbers is due to a decrease in the force constant of the bond.

Similar manifestations of hydrogen bonding occur in the spectra of self associated compounds. The broadening of the A-H stretch bands in a hydrogen bonded complex and the structure of the broadened band (if any) can be attributed to the superposition of absorption bands due to several different hydrogen bonded molecular species, e.g. dimer, trimer....polymer, or by one of two hypotheses:

1.Frequency modulation, anharmonic coupling of the ν(H---B) absorption giving a series of sum and difference bands ν(A-H) nν(H---B).

2.Occurence of Fermi resonance between the ν_{0-1}(A-H) and overtone or combination bands which are of similar frequency to the fundamental and are of the same symmetry class. In cases where only a 1:1 complex is known to exist, band broadening cannot be caused by the superposition of bands from several different hydrogen bonded species.

Hydrogen bonding causes large infrared band intensity changes. However, "inert" solvents cause changes in intensity of the donor and acceptor group vibrations which are also substantial, and in some cases of the same order of magnitude as those due to hydrogen bonding. Due to the breadth of the band it is not usually possible to decide whether the increase in intensity is real or due to the presence of sub-bands. Integrated intensities are much more difficult to obtain accurately than are frequency shifts and they have therefore been relatively neglected as a source of quantitative information on hydrogen bonding.

Many of the problems encountered in hydrogen bond studies can largely be overcome by the use of the matrix isolation technique which eliminates the requirement for a solvent.

THE MATRIX ISOLATION TECHNIQUE

Matrix isolation is a technique for trapping species as isolated entities in an inert solid, in order to investigate their properties by spectroscopic methods. A suitable matrix at the temperature of the experiment, must be a solid which is inert, rigid with respect to diffusion and transparent in the spectral region of interest. The noble gases and nitrogen are ideally suited as matrices because of their inertness and their own spectral simplicity.

The technique involves the rapid condensation of a mixture of the absorbing species (S) and a diluent gas (M) at cryogenic temperatures, usually 4K (liquid helium temperature) or 20K (liquid hydrogen temperature). With high matrix:absorber (M/S) ratios the solute may be expected to be isolated in the rigid matrix and thus supported in a convenient environment for spectroscopic examination. Under conditions of perfect isolation, the species under study is subject only to solute-matrix interactions. Such conditions are only achieved (and not necessarily so then) at very high M/S ratios, usually greater than 1000. At low M/S ratios interactions between the molecules become more important and molecular aggregates may be formed and trapped in addition to monomers. Molecular association will be greatest for molecules capable of forming hydrogen bonds.

The basis for the utility of the technique of matrix isolation lies in the fact that isolation of monomeric species in an inert environment at cryogenic temeratures greatly reduces intermolecular interactions, resulting in considerable sharpening of solute absorptions compared with other phases. With the exception of a few small hydrides, e.g. hydrogen chloride and ammonia, rotation does not occur in matrices, hence much narrower bands are observed than in the vapour phase. Thus half-band widths are typically one-fifth (or less) of those of similar concentrations in liquid solutions at ambient temperatures and it is possible to resolve features separated by as little as $1\mathrm{cm}^{-1}$ and to measure their wavenumbers with a precision of about half a wavenumber. This has been well illustrated by the ability of the method to distinguish features due to energetically-similar molecular conformers (4).

The same advantages apply to matrix trapped multimers, many well known broad features, in ambient temperature spectroscopy showing quite a drastic resolution into bands due to "isolated" dimers, trimers etc. Furthermore, the association process can be controlled and followed in a very elegant manner by depositing a very low concentration mixture (i.e. high M/S ratio) and allowing the matrix to warm up slightly and thus soften. The trapped monomers then diffuse forming dimers and higher multimers and the process can be monitored spectroscopically. The results are far more informative than corresponding studies in other phases.

In all matrix isolation studies it is assumed that the molecular energy levels are not significantly perturbed by the matrix environment. Perturbations do of course occur and are reflected in a wavenumber shift which is analogous to a solvent shift, and, for stretching modes it is usually to a lower wavenumber (17). In noble gas matrices, however, the shifts are usually relatively small.

It is further generally assumed that the quenching process freezes out the vapour-phase equilibrium mixture;

$$nA \rightleftharpoons (A)_n$$

However, this is little understood and various other parameters have been implicated.

A more serious disadvantage is the difficulty in making quantitative intensity measurements on solid state systems. This is extenuated in the case of solid matrices, since although accurate concentrations (M/A), can be made up in the gas phase and known quantities sprayed onto the low temperature support window, there is always uncertainty as to how much has actually condensed within the aperture of the optical beam. Similarly when the solute is a low volatile liquid or a solid, it has to be vapourized prior to mixing with the inert gas and its concentration in the mixture cannot be accurately known. This disadvantage however, is largely overcome by the use of growth curves based on an internal standard, usually a vibrational wavenumber unaffected by hydrogen bonding.

NMR SPECTROSCOPY

^{1}H NMR SPECTROSCOPY

During a hydrogen bond association, a proton donor A-H exerts an attractive force on a base B containing electron pairs, and forms a hydrogen bond complex with a defined A to B distance and a defined angle.

$$AH + B \rightleftharpoons AH{-}{-}{-}B$$

In solution, the solvent S may act as a base, which leads to hydrogen bonding with the solvent;

$$AH + S \rightleftharpoons AH{-}{-}{-}S$$

If the molecule has basic properties then self-association occurs;

$$nAH \rightleftharpoons (AH)_n$$

In accordance with the first bond-length variation rule (above), the electron acceptor properties of the hydrogen involved in the hydrogen bonding are enhanced, consequently its nucleus becomes deshielded. The process results in a shift of the proton nmr signal to lower magnetic fields or higher Lamor frequencies (13). The typical shifts are in the order of 100-1000Hz. However, the rates of interconversion between the species are much higher, and it is a general spectroscopic rule that only an averaged spectrum is observed for a molecule in different environments when the interconversion rates between the environments are higher than the frequency differences between the corresponding lines. Therefore, only one line or group of lines is observed for the associating A-H molecule.

If δ_i is the chemical shift of the nucleus in environment i, and χ_i the mole fraction of this environment, the average chemical shift of the nucleus is given by the Gutowsky and Saika equation (16).

$$\delta = \Sigma \chi_i \delta_i$$

However, hydrogen bond substitution reactions of the type;

$$B' + AH{-}{-}{-}B \rightleftharpoons AH{-}{-}{-}B' + B$$

are in a few cases so slow that AH---B and AH---B' can be observed directly by nmr spectroscopy. However, there are very few literature citations of observation in different competing hydrogen bond states.

The nmr spectra of proton donors are not only influenced by the formation and breaking of hydrogen bonds but also of A-H bonds i.e by proton exchange reactions;

$$AH + BH^* \rightleftharpoons AH^* + BH$$

Fast proton exchange influences the chemical shift as well as the hydrogen bond formation. The proton transfer has to take place in a complex which has to be formed beforehand. The study of proton exchange kinetics, therefore gives information either on the proton motion along hydrogen bonds or on the hydrogen bond formation process, depending upon the rate determining step.

The effects of proton exchange have been known for a long time (16), and have been used to study mainly proton exchange in protic solvents (15). These effects are the apparent loss of spin-spin coupling of the A-H proton to the nuclei in group A and the averaging of the chemical shifts of the AH and BH protons.

The AH self exchange rate of AH with BH can be obtained from nmr lineshape analysis, using quantum mechanical density matrix formalism (22). However, most of the methods require knowledge of the reaction mechanism.

Limbach and Seiffert (25) applied these methods to the acetic acid/methanol/tetrahydrofuran system. Their theoretical results closely matched the observed changes on lowering the temperature of the system (fig 1.8).

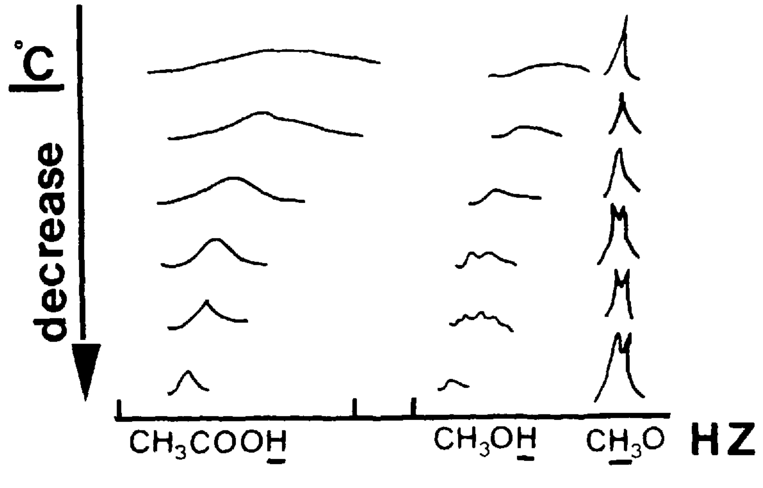


fig. 1.8

At low temperatures the case of slow proton exchange was reached with separate OH and COOH lines and spin-spin coupling of the methanol signals. At higher temperatures, proton exchange between acetic acid and methanol is faster, the methyl doublet coalesces and the OH and COOH lines broaden. The actual chemical shifts of the system depended upon the concentration and the temperature (13).

Limbach`s results show a significant case of fast hydrogen bond and slow proton exchange. They postulated that the slow proton exchange is mainly due to the hydrogen bond formation of the reactants with the solvent, which hinders the formation of an encounter complex.

The absence of hydrogen bonding to the solvent leads to very fast proton exchange between the reactants in methylcyclohexane-d_{14} (MCH) and coalescence of the OH/COOH signals as found by Limbach (25).

These workers highlighted the possible effect of the presence of small amounts of impurities that may undergo fast proton exchange e.g. water, which affects the line positions.

The chemical shift of a non-exchanging proton depends linearly on temperature because of a temperature dependant A-H distance in the hydrogen bond associates and because of changes in thermodynamic parameters of the association equilibria (13).

The work of Grunwald (15) has shown that there are two proton transfer mechanisms which can operate alone or together. One mechanism involves dissociation whilst the other is non-dissociative.

The non-dissociative mechanism consists of a series of single proton transfer steps in hydrogen bonded intermediates involving the formation of ions;

$$AH + BH \rightleftharpoons A^- + BH_2^+$$

$$AH + BH_2^+ \rightleftharpoons AH_2^+ + BH$$

$$AH + B^- \rightleftharpoons A^- + BH$$

These single proton transfers are however accompanied by self-exchanges.

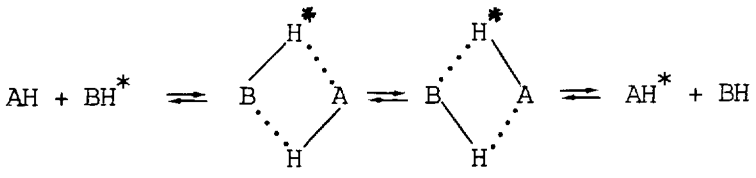
$$AH + A^- \rightleftharpoons A^- + AH$$

$$BH + B^- \rightleftharpoons B^- + BH$$

$$AH + AH_2^+ \rightleftharpoons AH_2^+ + AH$$

$$BH + BH_2^+ \rightleftharpoons BH_2^+ + BH$$

The non-dissociative mechanism consists of a double proton transfer in a cyclic hydrogen bonded intermediate;



In the buffered protic solvent system studied by Grunwald the ionic exchange predominates, the ions being provided by the buffer(15).

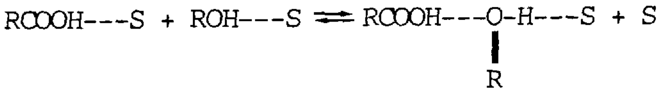
Generally, the rate constants for such processes are very fast and in the order of $10^{10}s^{-1}$. However, in pure methanol the ions A^- and AH_2^+ which catalyze the exchange have to be formed first by autoprotolysis, which yields a proton lifetime of about 10^{-1}s.

The cyclic proton exchange has been found as a side reaction of the ionic exchange reaction between carboxylic acids and alcohols (15,11).

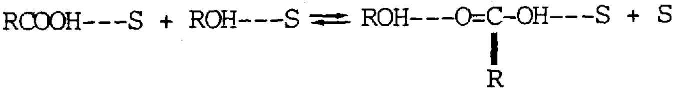
The characteristic feature of this process is the transfer of two or more protons during the encounter of the reactants. No dissociation into free solvated ions is necessary for this exchange to occur. The non-dissociative mechanism should therefore be dominant in aprotic solvents of low dielectric constant.

Cyclic proton exchange mechanisms have been postulated in a number of kinetic studies of proton exchange involving alcohols and carboxylic acids in aprotic solvents (25). However, small traces of bases or acids as well as water are able to catalyze the ionic proton exchange, even in aprotic solvents, which leads to low energies of activation. Consequently it has been very difficult to prove a cyclic proton exchange mechanism.

For the system acetic acid/methanol, Limbach et. al. (25) calculated thermodynamic parameters of a 1:1 association from experimental results. They proved the existence of two linear associates which are still hydrogen bonded to the solvent S;

1. 

$$\mathrm{RCOOH{-}{-}{-}S + ROH{-}{-}{-}S \rightleftharpoons RCOOH{-}{-}{-}\underset{\displaystyle R}{\underset{|}{O}}{-}H{-}{-}{-}S + S}$$

2. 

$$\mathrm{RCOOH{-}{-}{-}S + ROH{-}{-}{-}S \rightleftharpoons ROH{-}{-}{-}O{=}\underset{\displaystyle R}{\underset{|}{C}}{-}OH{-}{-}{-}S + S}$$

During this association the number of hydrogen bonds is retained and therefore the enthalpies are very small (below 4KJ/mol) and consequently also the entropies. The high solvent concentration however, shifts the equilibrium far to the left hand side. The formation of the cyclic dimer in which the proton exchange takes place no longer affects the chemical shifts because of its low concentration.

Many workers have observed retardation of the proton exchange process by molecular association in dimethyl sulphoxide (DMSO) and occasionally in acetone (33,8). Cairo et. al. (22) pointed out that within defined concentration limits of an associating alcohol in DMSO or acetone, simultaneous observation of both fast and retarded proton exchange is possible.

Studies of various alcohols have been made in these solvents and attempts to correlate the spin-spin coupling constant with the dihedral angle have been made (30).

COUPLING CONSTANTS

Spin-spin coupling is the interaction of the magnetic moments of two (or more) nuclei through the bonding electrons. This coupling is independent of the applied magnetic field but is dependent upon the electronic structure and is thus a constant for a particular arrangement of atoms and electrons. The constant is designated as J (in Hertz). The sign of the coupling constant refers to whether the two interacting nuclei are in a low energy state when their magnetic moments are parallel (-J) or antiparallel (+J). The sign makes an observable difference only in complex (second order) spectra.

VICINAL COUPLING CONSTANTS

Vicinal coupling is defined as the interaction of nuclei across three bonds such as H-C=C-H, H-C-C-H or H-C-O-H. The coupling in the saturated system has been found to be highly dependent upon the angle between the carbon-hydrogen bonds, i.e. the dihedral angle (fig 1.9).

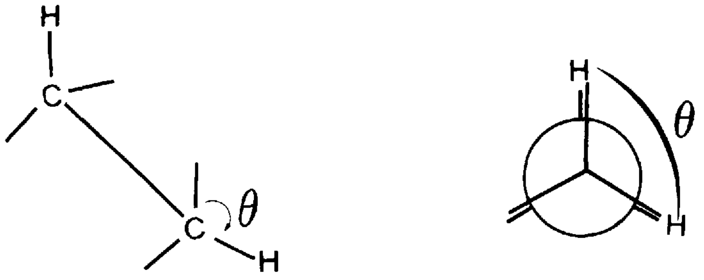


fig 1.9

This dependence has been described in terms of the valence bond theory by Karplus (21) and was found approximately to fit the equation

$$J_{vic} = A + B \cos\theta + C \cos 2\theta$$

where A = 4, B = -0.5 and C = 9.5 HZ, from empirical studies. This treatment is only approximate and deviations occur due to:

1) Change in electronegativity (X) of substituents,

$J_{vic} = J^{o}_{vic}$ (1 - 0.07 X), where J^{o}_{vic} is the vicinal coupling constant in ethane (+8.0) and X is the difference in electronegativity for hydrogen and the substituent.

2) Change in C-C bond lengths, where an increase results in a decrease

in coupling constant.

3) Variation in hybridization of the carbon atom.

4) Change in H -C -C bond angles, where an increase generally results in a decrease in coupling constant.

The variation of vicinal and allylic coupling with dihedral angle according to the Karplus equation is shown below (fig 1.10).

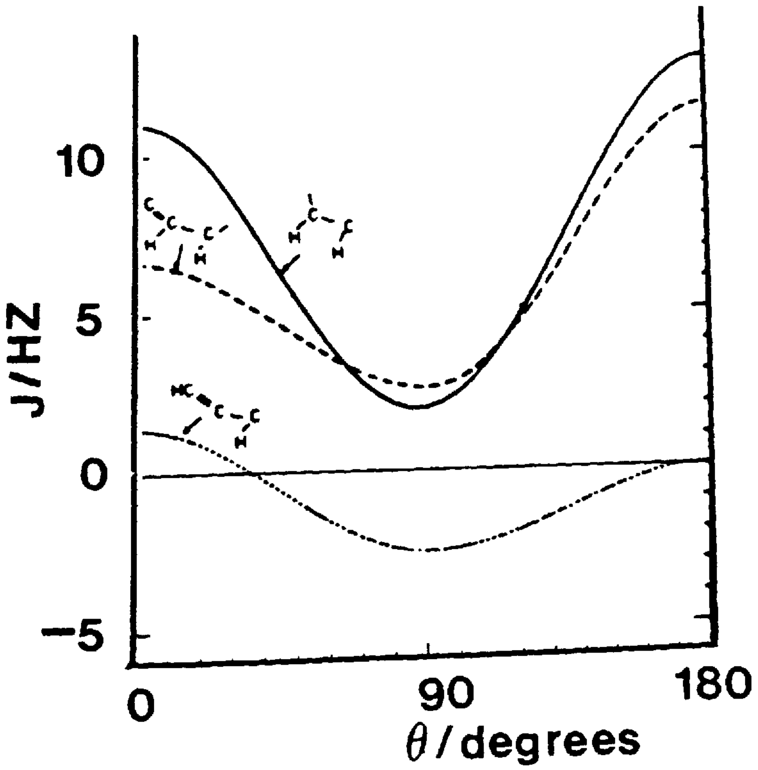
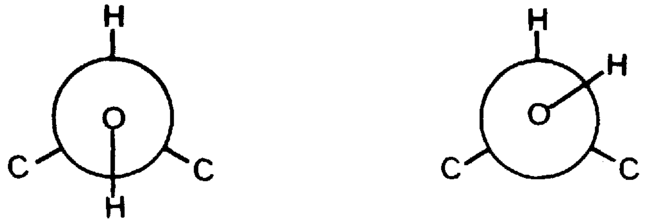


fig 1.10

Vebel and Goodwin (38) have showed that for an epimeric cyclohexanol J_{HCOH} is greater for the equatorial epimer due to the existence of a significant population of the anti rotamer (fig. 1.11).



ANTI GAUCHE

fig.1.11

Classically, hydrogen bonding shifts are clearly revealed when the pmr spectra of hydrogen bonded compounds such as alcohols are measured as a function of temperature and concentration in "inert" solvents. Typically, the pmr spectra of pure ethanol and dilute solutions in carbontetrachloride reveal a number of interesting features (fig. 1.12).

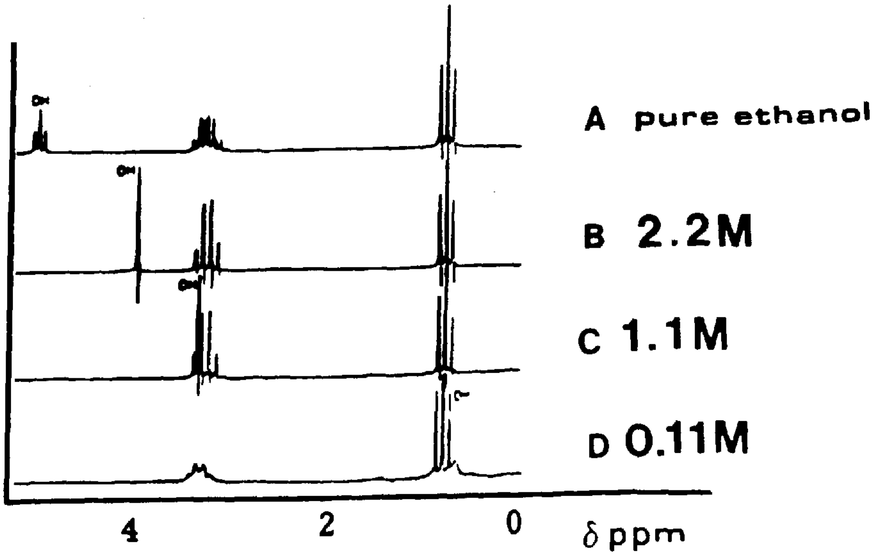
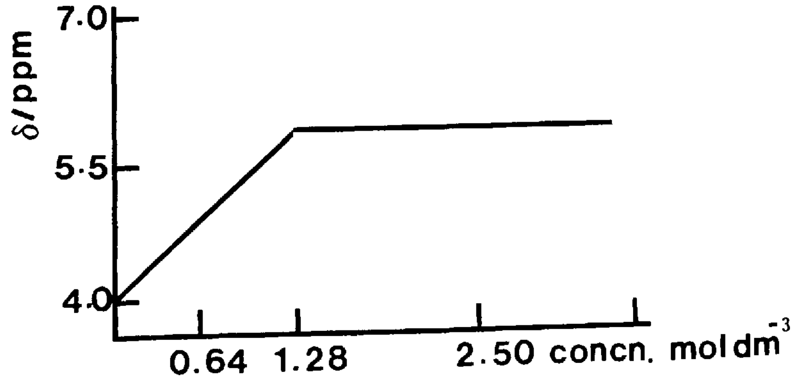


fig.1.12

The positions of the methyl triplet at about 1.2ppm and the methylene quartet at about 3.6ppm are affected very little by dilution . The OH signal moves from 5.13ppm in pure ethanol to about 1ppm in 0.11M solution of ethanol in CCl_4. In pure ethanol the OH resonance is a triplet and the CH_2 resonance is more complex than a quartet, because of coupling between OH and CH_2 protons. The increase of shielding of the OH proton, indicated by the shift of the OH resonance to higher magnetic fields with decrease in concentration, is due to dissociation of the hydrogen bonded (self-associated) alcohol complexes, the actual chemical shift being given by the Gutowsky/Saika equation (above).

Figure 1.13 shows the affect of concentration on the OH resonance of phenol in CCl_4. A simple extrapolation of the curve yields the chemical shift at infinite dilution to be 3.93ppm, whereas experiments with more dilute solutions have given a value of 2.8ppm. The example illustrates the difficulty of obtaining an accurate value for the shift at infinite dilution, i.e the chemical shift of the non-hydrogen bonded proton donor group.

fig.1.13



(The hydroxyl proton chemical shift of phenol as a function of concentration of CCl_4.)

^{13}C NMR SPECTROSCOPY

Conformationally mobile systems, for which the observed shieldings are averaged on the nmr timescale because of rapid intercoversion between two (or more) non-equivalent forms, lend themselves to study by ^{13}C nmr spectroscopy. Geometrical changes have a pronounced effect upon the ^{13}C shieldings and it follows that ^{13}C results extend the scope of ^{1}H methods. The theory involved in the conformational methods is discussed later along with the objections that have been put foward.

Hydrogen bonding is a highly complex association phenomenon, its effects on conformation can be pronounced and difficult to observe using standard nmr and i.r. techniques. The analysis and development of the slow proton exchange condition in pmr spectroscopy coupled with supportive observations from solution and matrix isolation i.r. spectroscopy have been the foundation of this study in conformational analysis.

RESULTS AND DISCUSSION

SOLVENT - SOLUTE INTERACTIONS

The study of any equilibria involving associating phenomena has inherent complications in its study. For molecules capable of forming hydrogen bonded species, the complications are multiplied, not least because of the uncertain nature of the associated species.

In the majority of equilibria systems in solution, the solvent may play a role in determining either the mechanism and (or) the position of equilibria. In a hydrogen bonding association equilibrium, the solvent may either act in the above manner(s) or it may itself generate a new equilibrium by direct hydrogen bonding with the solute.

Classically, studies of the hydrogen bonding phenomena are carried out in the so-called "inert" solvents such as hexane and carbontetrachloride. However, if true inertness was the criteria for choice of solvent then the solute would be insoluble. Inertness in the sense of minimal effect relies on the fact that a solvent possesses no dipole effects and no bulk effects, criteria which of course cannot be met. Even an isotropic solute such as TMS will be affected by the Van der Waals term in an "inert" solvent.

Broadly, the effects of non-inert solvents can be considered under three categories:

(a)The polar solvent effect.

This is an electric field effect as any polar solute will set up a reaction field in a polar solvent. This will occur even for solute molecules with no net dipole moment if they contain polar groups. The reaction field then causes electron drift in the solute; for polar solutes this occurs so as to reinforce the shielding or deshielding inductive effect associated with the original electric dipole. This results in changes in shielding. Thus polar solvents usually tend to augment the inductive effect of electronegative substituents in solutes.

(b) Solvent magnetic anisotropy

Molecules which have a pronounced anisotropy e.g. benzene, will cause inductive effects, due to the ring current effect. For solutes in benzene the effect is averaged over all possible solvent/solute molecular orientations, but, because of the disc shape of benzene there is still a net effect, even for spherically symmetrical molecules such as TMS.

Most molecules are not spherically symmetrical, and consequently further more marked differential shifts will occur. Moreover, chemically distinct nuclei in the same molecule may be affected differently. Note that this may imply that there is a certain preferred orientation between solute and solvent, but it does not necessarily imply any positive attraction between the molecules, simply, there may be steric repulsions.

It is frequently possible to make use of such solvent effects in nmr spectra to spread out a spectrum. A good example, although somewhat unusual is 1,2,3,4,5,6-hexachlorocyclohexane (fig. 2.1).

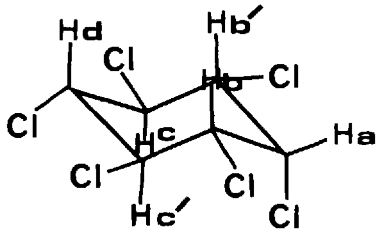


fig 2.1

In benzene solution the molecule exhibits a markedly different ^1H NMR spectrum to that in an inert solvent. The resonances of the hydrogens A, B and D are shifted by 1ppm, but the C resonance by only 0.25ppm. Clearly benzene molecules can approach closer to one side of the molecule than the other, due to the chlorine atoms. The result is the unusual feature of the spectrum of the benzene solution that the axial proton (C) resonates to a higher frequency than an equatorial proton (A). It is also notable that such preferred orientation effects will be enhanced if there are weak solvent-solute chemical interactions.

(c) Specific Interactions.

Chemical interaction between solute and solvent will clearly cause chemical shift changes. It is this specific type of solvent interaction which is most readily understood (although most difficult to study) in hydrogen bonding systems, and numerous studies have identified vast numbers of solute-solvent hydrogen bonded associates.

The vast majority of molecules capable of hydrogen bonding either through intra or inter self association or through solvent association are conformationally mobile whether it be rotational mobility as in simple alkanols or whether it is both ring inversions and rotational mobility as in the cyclohexanol type systems. Whatever type of conformational mobility may be present there will be a preferred conformational composition under specific conditions. The composition of the system will of course be dependent upon ΔG which in turn is a function of the enthalpy, entropy and the absolute temperature.

Any attempt to change the solvent in a hydrogen bonding system must have profound effects upon the thermodynamic parameters and consequently, if there is a net change in ΔG, there will be a change in the composition of the conformers at equilibrium. The enthalpy of the hydrogen bond ΔH will obviously change if the solute hydrogen bonds to the solvent, and, if the association is much stronger than the self-association hydrogen bond, the number of conformational possibilities may be restricted. However, this will affect the entropy term and so a net effect may be difficult to predict.

Polar solvent interaction which does not involve hydrogen bond formation, will have an effect which is far more difficult to interpret, since any possible effects on the enthalpy or the entropy terms can either be speculative or at best intuitive.

SOLVENT INTERACTIONS AND CONFORMATIONAL ANALYSIS

This study in conformational analysis outlines the complexity involved and has identified the role of the solvent as being a major contributing factor to the preferred conformation of the molecules studied. No single part of the thesis can be considered without first considering the general conclusions of solvent participation. It is for this reason that the solvent associated effects from all the methods used for the conformational analyses are considered first and of primary importance. The following studies have identified the nature of the solvent effects involved:

i) ^{1}H nmr αhydrogen chemical shifts.

ii) ^{1}H nmr hydroxyl proton chemical shifts.

iii) ^{13}C nmr chemical shifts.

iv) Infrared solution spectra of the OH stretch region.

i) ^{1}H nmr αhydrogen chemical shifts.

Compared to hydroxyl proton chemical shifts, the shift of the alpha hydrogen of secondary alcohols (fig. 2.2) changes relatively little with change in concentration.

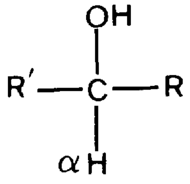
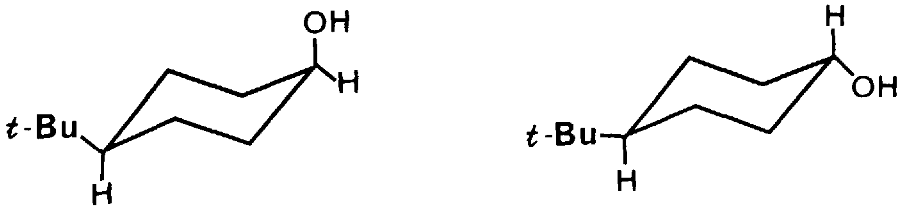


fig 2.2

However, changes in the shielding do occur and this method of analysis was utilized for the determination of conformational preference of cyclohexanol in various solvents. In common with most studies of conformational analysis of cyclohexyl systems, the conformationally rigid 4-tert.butyl cyclohexanols were used as the reference standards for axial and equatorial cyclohexanols (fig.2.3)



cis 4-tert.butylcyclohexanol
(axial hydroxyl)

trans 4-tert.butylcyclohexanol
(equatorial hydroxyl)

fig 2.3

The steric bulk of the tert.butyl group ensures that the hydroxyl group remains axial in the cis isomer and equatorial in the trans isomer.

Chemical shift measurements were carried out at a concentration of 0.2M in the solvents CCl_4, CS_2, DMSO, $CDCl_3$ and $(CD_3)_2CO$. For CCl_4 and CS_2 an external CD_2Cl_2 lock was used and all measurements were referenced to TMS as external standard. Measurements were performed on JEOL FX90Q, 90MHz F.T. Spectrometer at spectral band width of 900Hz and pulse delay of 100ms, using a 10mm tube.

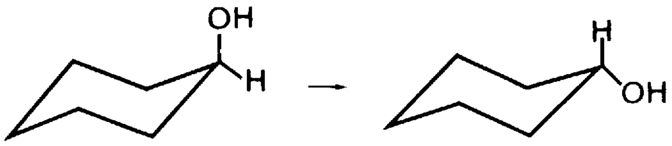
Due to the complexity of the αH signals caused by coupling with vicinal protons of the ring and hydroxyl proton, direct measurement of the chemical shift is difficult. However, the addition of a trace of dilute hydrochloric acid (see above) causes the onset of very fast proton exchange and hence apparent loss of coupling to the hydroxyl proton. The vicinal coupling was destroyed by the technique of homonuclear decoupling. The α hydrogen is removed from the resonances of the other ring protons and consequently a high power decoupling frequency applied at the centre of these resonances does not perturb the chemical shift of the α hydrogen, but does however remove the coupling. Consequently, under these conditions it was possible to record accurate chemical shifts for the α hydrogens. Table II gives the chemical shifts for the α hydrogens of cis and trans 4-tert.butyl.cyclohexanol together with cyclohexanol.

TABLE II

Solvent	δ cis(ppm) isomer	δ trans(ppm) isomer	δ cyclohexanol(ppm)
CCl_4	3.25	3.80	3.40
CS_2	3.34	3.90	3.50
$CDCl_3$	3.49	4.02	3.61

In the cis isomer (axial OH), the α hydrogen is an equatorial hydrogen, whereas in the trans isomer (equatorial OH), the α hydrogen is axial.

The equilibrium constant $K_{\alpha H}$ for the conformational change:



can be calculated using the Eliel equation (9) used in ^{13}C nmr conformational analysis which is applicable for ^{1}H nmr.

$$K_{eq\ H} = (\delta obs - \delta ax)/(\delta eq - \delta obs)$$

where δobs is the observed αH chemical shift, and δeq and δax are the observed chemical shifts for the axial αH of the trans compound and the H of the cis compound respectively. The calculated $K_{eq\ H}$ results are tabulated in table III.

TABLE III

Solvent	$K_{eq\ H}$
CCl_4	0.375
CS_2	0.400
$CDCl_3$	0.293

The calculated $K_{eq\ H}$ is the same as K_{axOH}, which must be related to K_{eqOH} by $K_{eqOH} = 1 / K_{axOH}$

then;

TABLE IV

Solvent	K_{eqOH}	% Equatorial
CCl_4	2.67	72.8
CS_2	2.50	71.4
$CDCl_3$	3.41	77.3

Any errors which are inherent in this method must be due to the assumption that the tertiary butyl group does not affect the chemical shift of the alpha hydrogen. To some degree it must, however, literature values of the equilibrium constant measured in CCl_4 compare favourably with this result (11).

The calculated equilibrium constants above show that in all the polar solvents there is an increase in the contribution of the equatorial conformer, suggesting that additional steric repulsion occurs in the axial conformation. However, it must be remembered that in the "inert" CCl_4 solutions, considerable intermolecular self-association is already present, so that the increase of equatorial population in the polar solvents could represent additional interactions and so increase the percentage of molecules which would have a large steric bulk in an unfavourable axial conformation. Consideration of the other methods gives a better understanding of this problem. DMSO and acetone solutions proved difficult to analyse, due to the presence of a strong upfield signal which overlapped the α hydrogen signals, making quantitative results erroneous.

ii) Hydroxyl proton chemical shifts.

The hydroxyl proton chemical shifts are very sensitive to changes in concentration and temperature, consequently, the error limits are very difficult to quantify.

Concentration studies showed that the errors can be appreciable and of the order of 20%. Repeated experiments showed that the conformational study of cyclohexanol was inconsistent due to this uncertainty and the method was not considered valid for comparison with the other methods. However, the hydroxyl chemical shifts for diols proved valuable in the conformational study of diols.

iii) ^{13}C nmr chemical shifts.

^{13}C nmr shifts have been widely used as a tool for conformational analysis of the cyclohexyl system (10,32). The ^{13}C nmr shifts are not very sensitive to intermolecular hydrogen bonding, whilst a conformational change has a pronounced effect on the ^{13}C nmr shieldings

(34).

In contrast to the α hydrogen chemical shifts, where the presence of the tert.butyl group in the reference compounds of 4-tert.butyl cyclohexanols could be condidered negligible, this is not the case in ^{13}C nmr. However, the concept of additive ^{13}C nmr shielding effects has been extensively used with a good deal of success in monosubstituted cyclohexyl systems (32,26). However, previous studies have paid little attention to the influence of the solvent, and literature values for K for cyclohexanol are not comparable with this study since the shielding effects of the substituents were obtained in various solvents (34,32). The principle of the method is based upon the observation that axial substituents cause an upfield shift relative to their equatorial counterpart (32,26). The γ- gauche effect (fig 2.4) between the 1,3 diaxial groups is generally held responsible for such shifts on carbon 3 and 5 (the γ carbon atoms) whilst the α and β effects are usually attributed to dipole effects.

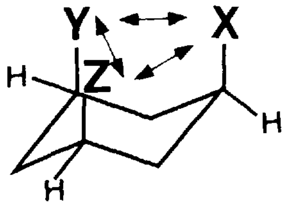


fig 2.4

The additivity principle allows the calculation of chemical shifts from experimental data. However, it was in the course of this study that it was realised that the solvent plays a considerable role in determining the conformation in a hydrogen bonded cyclohexyl system.

Calculation of cyclohexanol shifts.

Assuming complete additivity of the shielding effects, the chemical shift of a cyclohexanol bearing an axial hydroxyl and an equatorial hydroxyl can be calculated using the measured chemical shifts of cis and trans 4-tert.butyl cyclohexanols together with the chemical shifts of 4-tert.butyl cyclohexane and cyclohexane. (tables V - IX).

TABLE V

cis 4-tert.butyl cyclohexanol chemical shifts (ppm)

SOLVENT	C_1	C_2	C_3	C_4
CCl_4	64.99	33.55	20.83	48.12
CS_2	65.63	34.13	21.40	*
$CDCl_3$	65.95	33.47	20.98	47.26
DMSO-D_6	63.34	33.11	20.61	47.58
$(CD_3)_2CO$	65.76	34.79	22.18	49.50

* Uncertainty in assignment.

TABLE VI

trans 4-tert.butyl cyclohexanol chemical shifts (ppm)

SOLVENT	C_1	C_2	C_3	C_4
CCl_4	70.50	36.08	25.65	47.25
CS_2	70.84	36.71	26.23	47.68
$CDCl_3$	71.29	36.18	25.69	48.11
DMSO-D_6	69.19	35.86	25.27	46.89
$(CD_3)_2CO$	71.37	37.47	26.91	48.75

TABLE VII

cyclohexanol chemical shifts (ppm)

SOLVENT	C_1	C_2	C_3	C_4
CCl_4	69.35	35.43	23.89	25.75
CS_2	69.71	36.01	24.79	26.42
$CDCl_3$	70.41	35.64	24.22	25.54
DMSO-D_6	68.17	35.33	23.76	25.32
$(CD_3)_2CO$	70.32	36.86	25.30	26.91

TABLE VIII

tert.butyl cyclohexane chemical shifts (ppm)

SOLVENT	C_1	C_2	C_3	C_4
CCl_4	26.60	27.08	27.52	48.24
CS_2	27.45	27.94	28.08	48.68
$CDCl_3$	26.86	27.35	27.69	48.45
DMSO-D_6	26.19	26.59	27.06	47.68
$(CD_3)_2CO$	27.84	28.35	28.76	49.63

TABLE IX

cyclohexane chemical shifts (ppm)

SOLVENT	C_1
CCl_4	26.77
CS_2	27.64
$CDCl_3$	27.00
DMSO-D_6	26.30
$(CD_3)_2CO$	27.98

All measurements were recorded on a JEOL FX90Q F.T. nmr spectrometer (90 MHz) at a spectral band width of 2500 Hz, pulse delay of 2 seconds at 0.2M concentration. All spectra were fully decoupled.

For each solvent, individual calculations were performed by the following method:

1. The effect of the tert.butyl group (table X) is determined by subtraction of the cyclohexane shift from 4-tert.butyl cyclohexane.
shielding of tert butyl group = 4-tert.butyl cyclohexane - cyclohexane

2. The shift of an axial or equatoriial cyclohexanol is determined by subtraction of the tert.butyl effect (on carbon 4) from the appropriate 4-tert.butyl cyclohexanol (tables XI and XII).
Cyclohexanol shift = 4-tert.butyl cyclohexanol shift - shielding of tert.butyl group.

TABLE X

Shielding effects tert.butyl group

SOLVENT	C_1	C_2	C_3	C_4
CCl_4	-0.17	0.31	0.75	21.47
CS_2	-0.19	0.30	0.44	21.04
$CDCl_3$	-0.14	0.35	0.69	21.45
DMSO-D_6	-0.11	0.29	0.76	21.38
$(CD_3)_2CO$	-0.14	0.37	0.78	21.65

Calculated cyclohexanol chemical shifts (ppm)

TABLE XI

1) cyclohexanol (axial hydroxyl)

SOLVENT	C_1	C_2	C_3	C_4
CCl_4	65.16	33.24	20.08	26.65
CS_2	65.82	33.83	20.96	
$CDCl_3$	66.09	33.12	20.29	25.81
DMSO-D_6	63.45	32.82	19.85	26.20
$(CD_3)_2CO$	65.90	34.42	21.40	27.85

TABLE XII

2) cyclohexanol (equatorial hydroxyl)

SOLVENT	C_1	C_2	C_3	C_4
CCl_4	70.67	35.77	24.93	26.65
CS_2	71.03	36.41	25.88	26.64
$CDCl_3$	71.43	35.83	25.00	26.66
DMSO-D_6	69.30	35.57	24.51	25.51
$(CD_3)_2CO$	71.51	37.10	26.13	27.10

Additionally, the shielding effects of an axial or equatorial hydroxyl group can be calculated by subtraction of the chemical shift of cyclohexane from the calculated cyclohexanol shifts (table XIII and XIV).

TABLE XIII

1) Axial hydroxyl

Shielding effects of the hydroxyl group (ppm)

SOLVENT	C_1	C_2	C_3	C_4
CCl_4	38.39	6.47	-6.69	-0.12
CS_2	38.18	6.19	-6.68	-
$CDCl_3$	39.09	6.12	-6.71	-1.19
DMSO-D_6	37.15	6.52	-6.45	-0.10
$(CD_3)_2CO$	37.92	6.44	-6.58	-0.13

TABLE XIV

2)Equatorial hydroxyl

SOLVENT	C_1	C_2	C_3	C_4
CCl_4	43.90	9.00	-1.84	-0.12
CS_2	43.39	8.77	-1.76	-1.00
$CDCl_3$	44.43	8.83	-2.00	-0.34
DMSO-D_6	43.00	9.27	-1.79	-0.79
$(CD_3)_2CO$	43.53	9.12	-1.85	-0.88

The calculated axial and equatorial cyclohexanol chemical shifts now represent the chemical shifts for pure axial and pure equatorial cyclohexanols. In the same manner as the alpha hydrogen chemical shifts, these calculated values together for the observed cyclohexanol shift can be used to determine the equilibrium constant for the conformational change ($K_{ax \rightarrow eq}$).

$$K = (\delta obs - \delta ax) / (\delta eq - \delta obs)$$

The tabulated values for K based on each carbon atom are given in table XV.

TABLE XV

Equilibrium constants

SOLVENT	C_1	C_2	C_3	C_4
CCl_4	3.17	6.44	3.77	-5.14
CS_2	2.95	5.45	3.83	-
$CDCl_3$	4.24	13.26	5.04	-0.24
DMSO-D_6	4.18	10.46	5.21	-4.63
$(CD_3)_2CO$	3.71	8.93	4.70	-4.95

The equilibrium constants calculated from the alpha carbon shifts show a similar trend to that of the values calculated from the alpha hydrogen shifts. However, they all have noticeably greater magnitudes. The alpha hydrogen calculations are however more in line with the literature values for the solutions in CCl_4. The calculations based on the beta, gamma and delta chemical shifts fail completely, suggesting that errors involved in the additivity approximation are too great for carbons other than the alpha carbon.

The equilibrium constants for the alpha carbon atom again show that the polar solvents favour the equatorial conformation.

Since different parameters are held responsible for the shielding of the various carbons relative to a functional group, consideration must be given to some of the possible factors involved. Roberts et.al. (32) attempted a qualitative description of the shielding effects of axial and equatorial substituted cyclohexane and identified, at least in part, some independent contributary factors:

(1) An inductive effect.

This was assumed to be functional group specific and independent of conformation, but dependent upon whether the substituent was primary, secondary or tertiary. An inductive effect would be expected to be entirely dependent upon the electronic distribution in the functional group.

(2) A resonance effect.

This relates to stereochemical relationships between pairs of atoms on vicinal carbons and is assumed to affect only the shifts of carbons directly involved and is expected to be sensitive to conformation.

(3) Steric effects.

These are expected to be important in the cyclohexyl system due to the different interactions involved in alternative conformations.

The overwhelming problem is the sorting out of which factors are involved at specific carbons, since a composite effect will undoubtedly exist.

On a simple basis, the alpha carbon shift for an equatorial substituent can be ascribed to some combination of substituent parameters, but the axial conformation must involve, in addition, the steric effect of the gamma carbons and their axial hydrogens on carbon 1 operating backwards through the hydroxyl group.

The difference between the axial and equatorial shifts could arise from this additional steric interaction (fig.2.5)

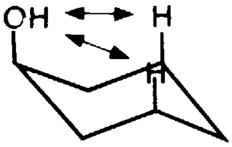


fig.2.5

The beta carbon shift in cyclohexanols is large and not easily comprehensible and there appears no clear interpretation of the shift differences.

The gamma shift is generally thought to be caused solely or predominantly by the steric factors, the 1,3 diaxial interaction being held responsible for the upfield shift of an axial cyclohexanol.

A clearer view of the effect of the solvent can be obtained by considering the shielding effect of the axial and equatorial hydroxyl in a particular solvent, this can readily be calculated by subtraction of the bulk shifts for cyclohexane from the calculated axial and equatorial cyclohexanols. Tables XIII and XIV give the shielding effects for the axial and equatorial shifts for the alpha, beta and gamma carbons. Both for the axial and equatorial hydroxyls, the order of deshielding of the carbon is:

$$\mathrm{DMSO} > (\mathrm{CD_3})_2\mathrm{CO} > \mathrm{CS_2} > \mathrm{CCl_4} > \mathrm{CDCl_3}.$$

CCl_4 can be assigned as the "inert" solvent, then it can be considered that the only type of hydrogen bonding present in this system is through self association of the type:

$$nROH \rightleftharpoons (ROH)_n$$

so that the shielding effect contains some contribution from intermolecular hydrogen bonding. In the absence of any association, it would be expected that the alpha carbon would become more shielded.

In DMSO solutions, there is a pronounced deshielding relative to that in CCl_4. The enhanced deshielding of the nucleus is indicative of a higher degree of association. In DMSO, strong solvent-solute hydrogen bonding will occur, and the deshielding effect can be attributed to this additional interaction. Theoretically, in a solution of DMSO, at least two association equilibria are possible.

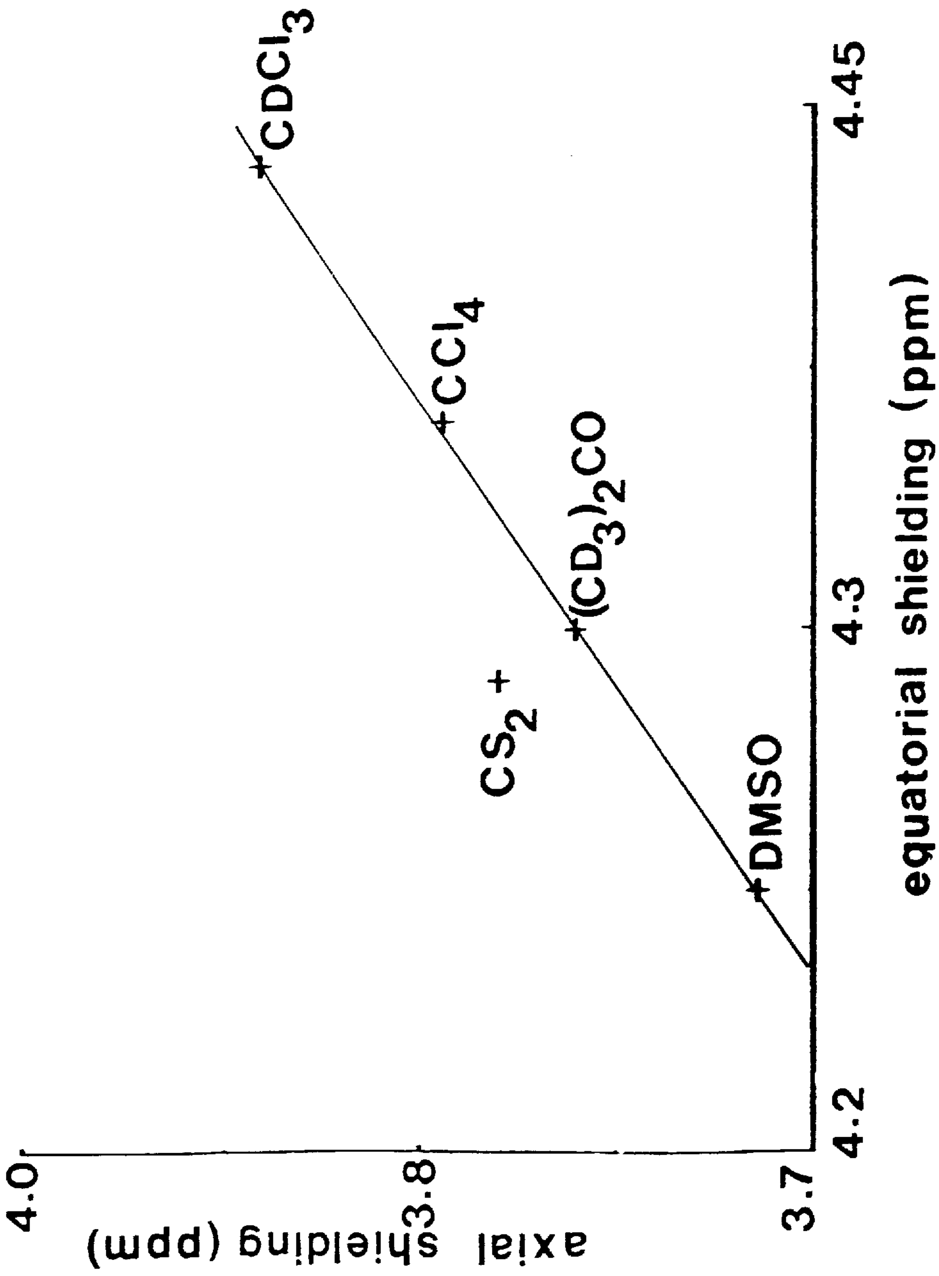
$$\text{(i) } nROH \rightleftharpoons (ROH)_n$$
$$\text{(ii) } ROH + DMSO \rightleftharpoons DMSO\text{----}ROH$$

The actual composition of such a solution at equilibrium is therefore very difficult to determine.

Similarly, in $(CD_3)_2CO$ solutions there is an enhanced deshielding compared with the CCl_4 solutions. However, the effect is less than in DMSO. This is in accordance with the fact that $(CD_3)_2CO$ is a weaker hydrogen bonding solvent than DMSO and consequently, the second equilibrium lies further to the left than with DMSO;

$$\text{(i) } nROH \rightleftharpoons (ROH)_n$$
$$\text{(ii) } ROH + (CD_3)_2CO \rightleftharpoons (CD_3)_2CO\text{---}ROH$$

fig.2.6



4.0
3.8
3.7
axial shielding (ppm)
4.2
4.3
4.45
equatorial shielding (ppm)
$CDCl_3$
CCl_4
$(CD_3)_2CO$
CS_2
DMSO

For $CDCl_3$, the α carbon is more shielded than in CCl_4, and a direct inference is that there is less association present than in CCl_4 solution. The CS_2 solution however, shows an increased deshielding.

Similarly, the gamma carbon shows the same trend as the alpha carbon, and the same arguments will apply. However, due to the obvious errors involved in the determination of conformational equilibria from the other carbon shifts, it is not considered valid to incorporate them further in this discussion.

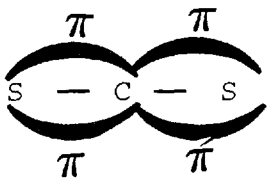
The relationship between the alpha carbon shieldings for equatorial and axial hydroxyls is clearly shown by a simple graphical method. Figure 2.6 shows the plot of equatorial shielding against axial shielding for the alpha carbons in the various solvents. Clearly a straight line relationship exists, with the exception of CS_2. The significance of a linear relationship is however quite remarkable, and a number of conclusions can be drawn:

(i) With the exception of CS_2, the ratio of equatorial to axial hydrogen bonding is constant, irrespective of the solvent i.e. it appears that the steric effect of hindrance (i.e. the 1,3 diaxial interactions) are constant and do not have a differential effect on solvent association. This conclusion however, was quite unexpected since the relative size of the solvent molecule would be expected to influence its accessibility to the hydroxyl group for association.

(ii) For CS_2, there is a differential effect. The molecule possesses no dipole moment and i.r. studies show that it does not form an intermolecular hydrogen bond with the alcohols under study.

The solvation of the hydroxyl group by CS_2 is evidently influenced by the conformation of the hydroxyl group. Such a differential effect must mean that CS_2 has anisotropic properties. Although it possesses no dipole moment, the bonding involved is through p orbital overlap, i.e. a π electron system;

S = C = S or



For π electron systems there is always an anisotropic effect, since the electron density is concentrated at the p orbital overlap. This effect gives all π bonded systems a directional effect. c.f.benzene, i.e. the p orbitals in any intermolecular interaction are positioned in the same plane as the functional group under attack.

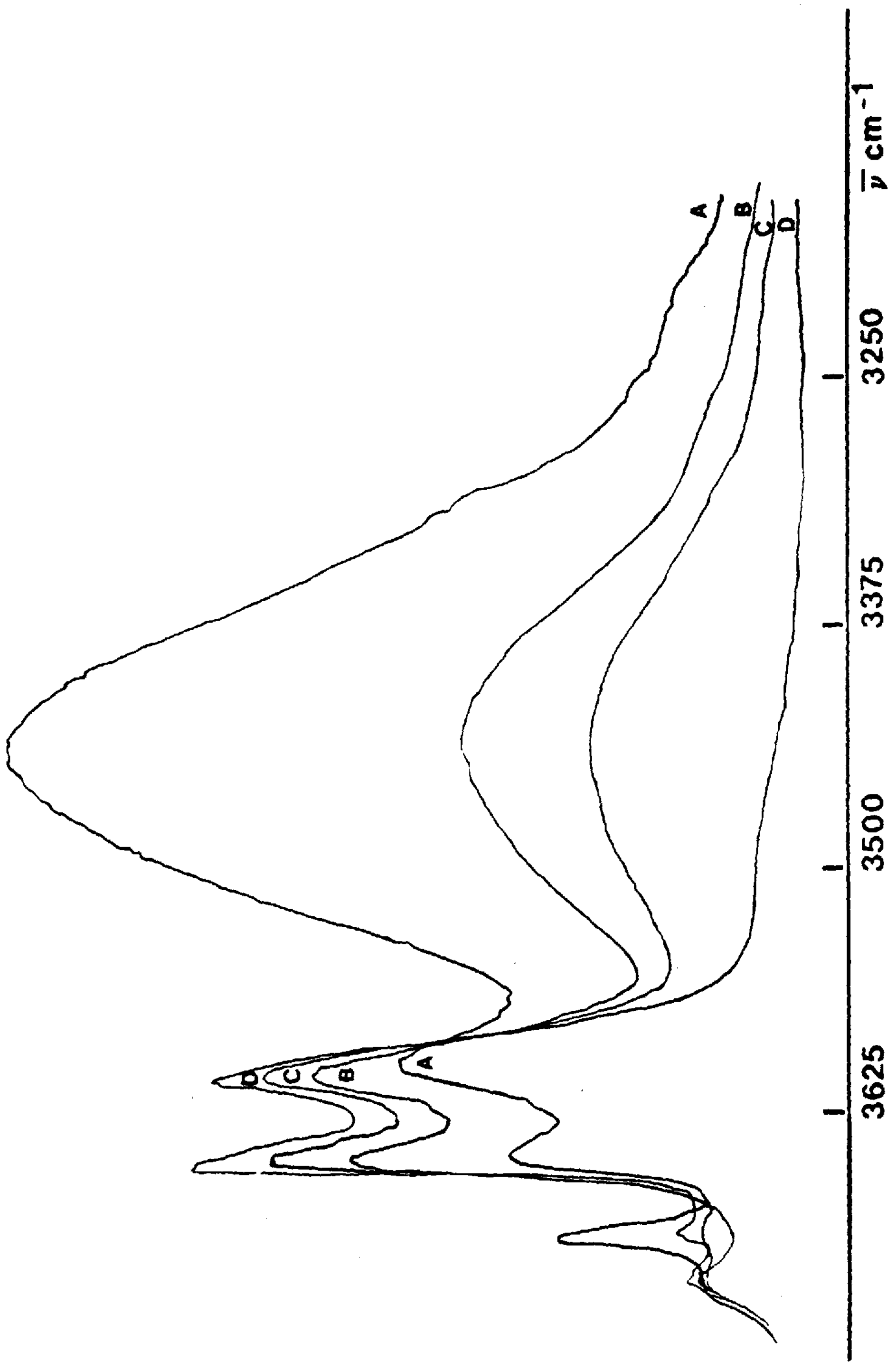
In the axial position, it is foreseeable that the steric hindrance of the axial hydrogen restricts the orientation of the CS_2 molecule and so a differential effect should not be unexpected.

I.R. SOLUTION SPECTRA OF THE OH STRETCH REGION.

The i.r. solution spectra of various monohydroxy and dihydroxy alcohols was determined at various concentrations. The measurements were carried

fig. 2.7

.2.7



out on a Perkin Elmer PE 883 i.r. spectrometer with a PE 3600 data station, with maximum resolution of $2cm^{-1}$. For all measuremenats quartz "infrasil"" 1cm path length cells were used. All solvents were previously dried over molecular sieves 3A for at least 24 hours.

DMSO solutions.

The effect of DMSO was demonstrated by the addition of small (microlitre quantities) of thoroughly dried DMSO to a dilute (0.004M) solution of trans cyclohexan-1,2-diol in CCl_4. Figure 2.7 shows (D) the infrared spectrum of trans cyclohexan-1,2-diol in the hydroxyl stretch region. Spectra (C), (B) and (A) show the affect of adding 2, 5 and 10 microlitres of DMSO per $3cm^3$ of solution. The free hydroxyl stretch band at $3632cm^{-1}$ and the intramolecular hydrogen bond band at $3598cm^{-1}$ diminish greatly on addition of DMSO, whilst a new band for the intermolecular hydrogen bond association between DMSO and the alcohol appears at c.a. $3400cm^{-1}$.

The experiment also shows that the free hydroxyl band diminishes to a lesser degree than the intramolecular hydrogen bond band. However, in pure DMSO solution no free or intramolecular hydrogen bond bands were observed. These results show that the alcohol-DMSO association is very strong, the equlibrium may lie so far to the right so as to be almost quantitative:

$$\text{ROH} + \text{DMSO} \rightleftharpoons \text{DMSO---ROH}$$

FIG. 2.8

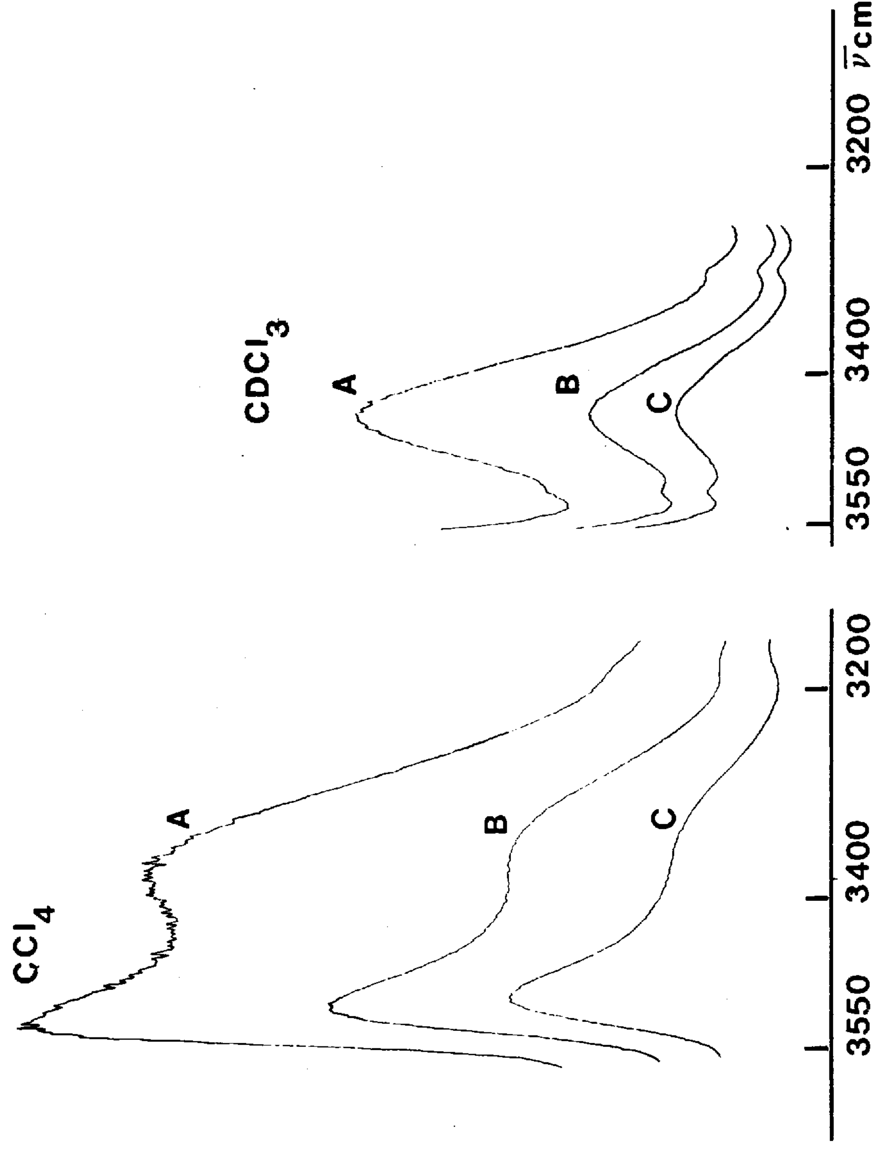
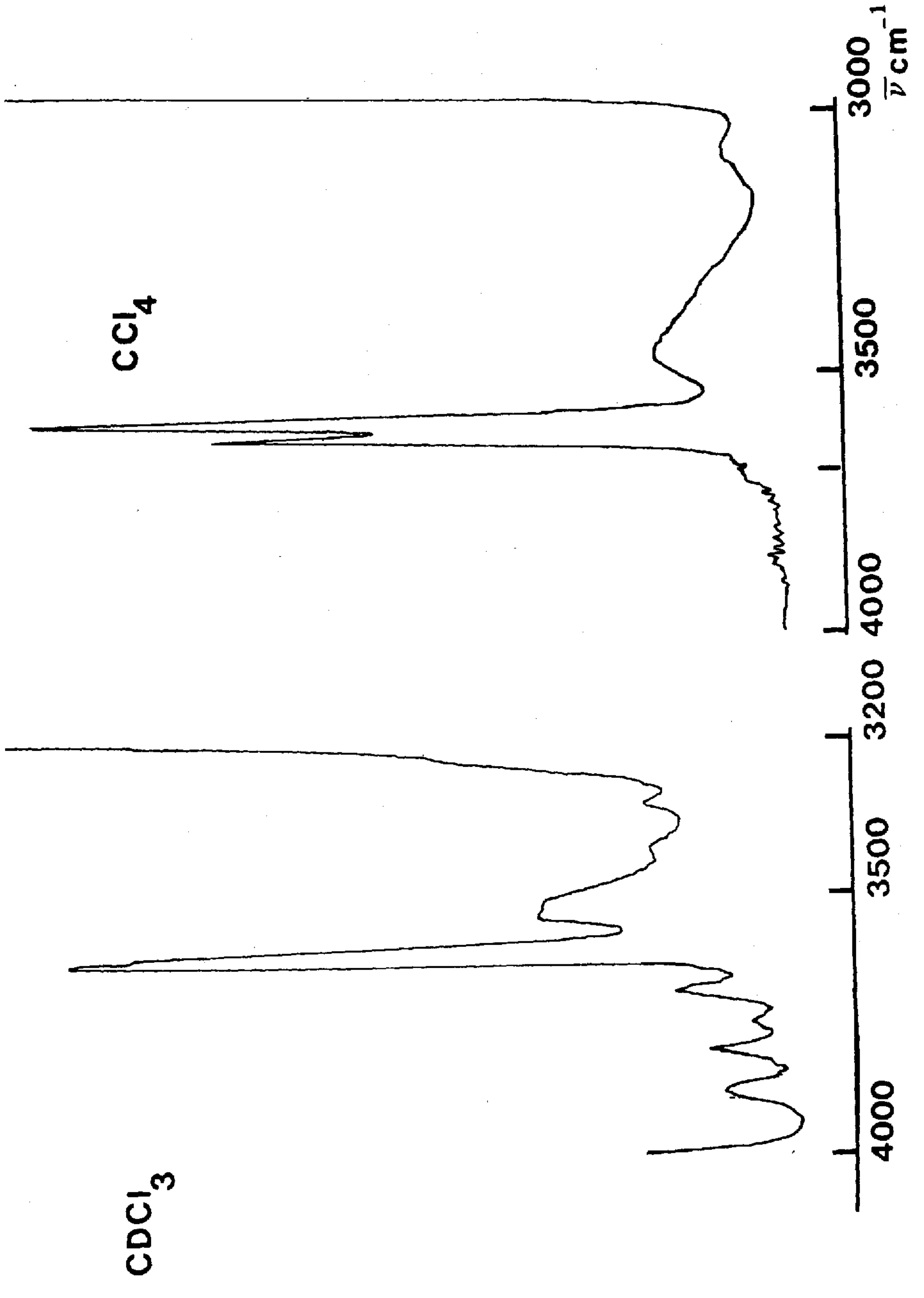


FIG.2.9



$CDCl_3$ solutions.

Infrared solution spectra of alkanols and cyclohexanols show that the affect of $CDCl_3$ as a solvent may be rather complex. Figure 2.8 shows the intermolecular hydrogen bond band of octan-1-ol at the following concentrations in $CDCl_3$ and CCl_4;

$CDCl_3$	CCl_4
(A) 33 microlitres/1cm^3	(A) 28 microlitres/1cm^3
(B) 17 microlitres/1cm^3	(B) 17 microlitres/1cm^3
(C) 13 microlitres/1cm^3	(C) 13 microlitres/1cm^3

The CCl_4 solution spectra show the presence of the intermolecular (self-associated) hydrogen bond band. The intermolecular band is however, composed of two sub bands. As the concentration of alcohol is increased, the second lower wavenumber band increases in intensity. The discussion of cyclic dimers attributes the higher wavenumber band to the formation of cyclic dimers. The solutions in $CDCl_3$ show that the intermolecular hydrogen bond band is far less intense compared with the same concentrations in CCl_4. Additionally, only one band is present. It is apparent that the cyclic dimer does not occur in $CDCl_3$ solutions and this confirms the nmr observations.

Comparison of the spectra of trans cyclohexan-1,2-diol at 0.004M in CCl_4 and $CDCl_3$ (fig. 2.9), shows the effect of $CDCl_3$ on the internal hydrogen bond band. In CCl_4 solution the free hydroxyl and intramolecular hydrogen bond hydroxyl stretch bands appear as sharp bands at 3632cm^{-1}

and 3598cm^{-1} respectively, the intermolecular hydrogen bond band appears at c.a. 3645cm^{-1}. In $CDCl_3$ solution the free hydroxyl stretch band shifts to 3604cm^{-1} and remains sharp. The intramolecular hydrogen bond band shifts to 3520cm^{-1} and is greatly diminished in intensity and considerably broadened. The intermolecular hydrogen bond band is almost absent. The experiment shows that $CDCl_3$ significantly reduces the population of the intramolecularly hydrogen bonded species.

CS_2 solutions.

Similar experiments in CS_2 show that no solvent hydrogen bonding occurs.

$(CD_3)_2CO$ solutions.

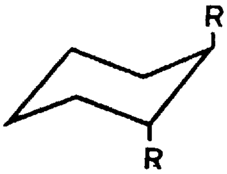
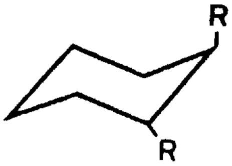
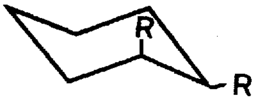
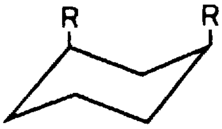
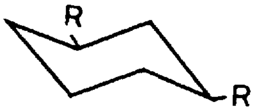
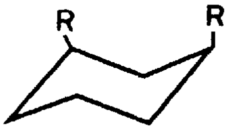
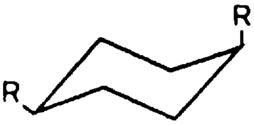
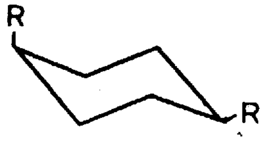
Significant studies in acetone could not be performed due to the transmission of this solvent in the region under study.

Clearly, the effect of $CDCl_3$ is that of an electronic effect, to influence the degree of hydrogen bonding there must be involved a strong non-bonded interaction. The same effect has been pointed out by Spassov and Simeonov in their study of diols (35), and it appears to be a general effect, it has also been observed in biomembrane studies (19).

However, since the conformational equilibria in cyclohexanol is shifted significantly towards the equatorial conformation, then the association, although effectively a non-bonded one does cause steric crowding around the hydroxyl group. For this effect to influence the conformational equilibrium, more than one solvent molecule is probably involved. This idea is consistent with the action of the solvent occupying the solvation sphere of the hydroxyl group. The grouping and consequently the orientating of the solvent molecules in this sphere will present a barrier to self-association. In CCl_4, dipole interactions cannot be involved since the molecule is non-polar and therefore only the much weaker Van der Waals forces are present.

In conclusion therefore, as a prelude to a more systematic discussion of conformation, the effects of solvents have been shown to be pronounced and can significantly influence any conformational equilibria that may be present.

TABLE XVI

Isomer	Conformations	
trans 1,2		
cis 1,2		
cis 1,3		
trans 1, 3		
trans 1,4		
cis 1,4		

THE CONFORMATIONAL ANALYSIS OF CYCLOHEXANDIOLS AND RELATED COMPOUNDS

THERMODYNAMIC ASPECTS OF CONFORMATION

Disubstitution in cyclohexanes leads to geometric isomerism with the formation of cis and trans isomers, each configurational isomer may have two possible chair conformations. Table XVI shows the conformational formulae of all the disubstituted cyclohexanes. From the table it can be seen that only the trans 1,2, cis 1,3, and trans 1,4 isomers can have both substituents in axial positions or both substituents in the equatorial positions. The remaining three isomers must always have one substituent in an axial position and one substituent in an equatorial position. The conformational isomers differ in energy, which follows from their interaction through space with other atoms.

In general it can be considered that the most stable isomer is the one with both the substituents equatorial; the isomer with one substituent equatorial and one substituent axial is less stable, and the diaxial arrangement is the least stable (highest energy). In the second case where both an equatorial and axial substituent coexist, it is reasonable to suppose that the equatorial position will be occupied by the substituent with the largest effective volume thereby minimising the energy.

The tert. butyl group which has a very large effective volume remains permanently in the equatorial position in the chair conformation of the cyclohexane ring. It therefore ensures that the position of the other substituents is stabilized to a considerable extent because the transition from one chair to the alternative chair is prevented. The free energy of the tert. butyl group has not been measured, but the free energy difference between a tert. butyl group in an axial and equatorial position has been calculated to be about 40 KJ mol^{-1} ($K_{ax->eq}$= 3205), and it is known that a tert. butyl cyclohexane will adopt a twist form rather than a chair form with an axial tert. butyl group. The axial form must therefore be more strained than a twist form and is at least 20 KJ mol^{-1} higher in energy than the equatorial form. The energy difference is such that in tert. butyl cyclohexane less than 0.001 % of the molecules are in the axial form.

Table XVII gives free energy differences between axial and equatorial cyclohexanes $C_6H_{11}X$ from ref (5).

TABLE XVII

SUBSTITUENT X	- G (KJ/MOL)	K	% equatorial at 298K
Me	7.1	17.6	95
Et	7.5	20.6	96
Pr^i	9.2	41.0	98
Bu^t	20.0	3205.0	>> 99
Ph	12.5	155.3	99
CN	0.8	1.4	58
COOH	5.4	2.2	69
COOEt	5.0	7.5	88
OH	2.9*	3.2*	76*
Cl	2.1	2.3	70

* literature values vary, presumably due to solvent dependency.

It is possible to apply these thermodynamic parameters to the disubstituted conformations. However, the introduction of a second substituent introduces the possibility of new steric and dipole interactions which are not allowed for in the above values. Nevertheless, the calculations are valid as a guide to the conformational preference.

trans cyclohexan-1,2-diol

Neglecting any steric or dipole interactions between the hydroxyl groups, the principle of additivity of free energies can be used to calculate the difference in free energy between the two possible chair conformations.

In cyclohexanol, $-\Delta G_{ax\to eq} = 2.9 + 2.9\ \text{KJmol}^{-1}$

$$= 5.8\ \text{KJmol}^{-1}$$

The free energy is related to the equilibrium constant K by the expression;

$$-\Delta G = RT\ \text{Ln}\ k$$

$$-5800 = 8.314 \times 298\ \ln k$$

$$\underline{k = 10.8}$$

Which gives a percentage equatorial isomer of approximately 92% at 298K.

cis cyclohexan-1,2-diol

Here both conformations are identical with axial/equatorial conformation and equatorial/axial conformation respectively. On simple reasoning and on thermodynamic grounds, ΔG should be zero, k = 1 giving a 50/50 isomeric composition at all temperatures.

trans cyclohexan-1,3-diol

Similarly in this configurational isomer, both possible chair conformations are identical in energy and so thermodynamically a 50/50 isomeric composition should be present.

cis cyclohexan-1,3-diol

A diaxial and a diequatorial conformation is possible, and based on the same arguments as trans cyclohexan-1,2-diol, the free energy difference between the conformational isomers is given by:-

$$\Delta G_{(ax. - eq.)} = 5.8 \text{ KJ/mol}$$

$$k = 10.8$$

$$\underline{\% \text{ equatorial} = 98 \text{ at } 298\text{K}}$$

cis cyclohexan-1,4-diol

An axial/equatorial and an equatorial/axial conformer are possible hence a free energy difference of 0. Therefore the expected isomeric composition is 50/50 at all temperatures.

These thermodynamic criteria should hold well for the 1,3 and 1,4 configurational isomers, however, in the trans cyclohexan-1,2-diol, the dipole - dipole interaction between the equatorial hydroxyls is expected to be large and should greatly reduce the free energy difference between the conformers (fig 3.1).

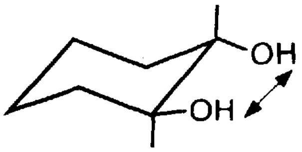


fig.3.1

In cis cyclohexan-1,3-diol the dipole - dipole repulsion between the axial hydroxyls would be expected to increase the free energy difference between the diaxial and diequatorial forms.

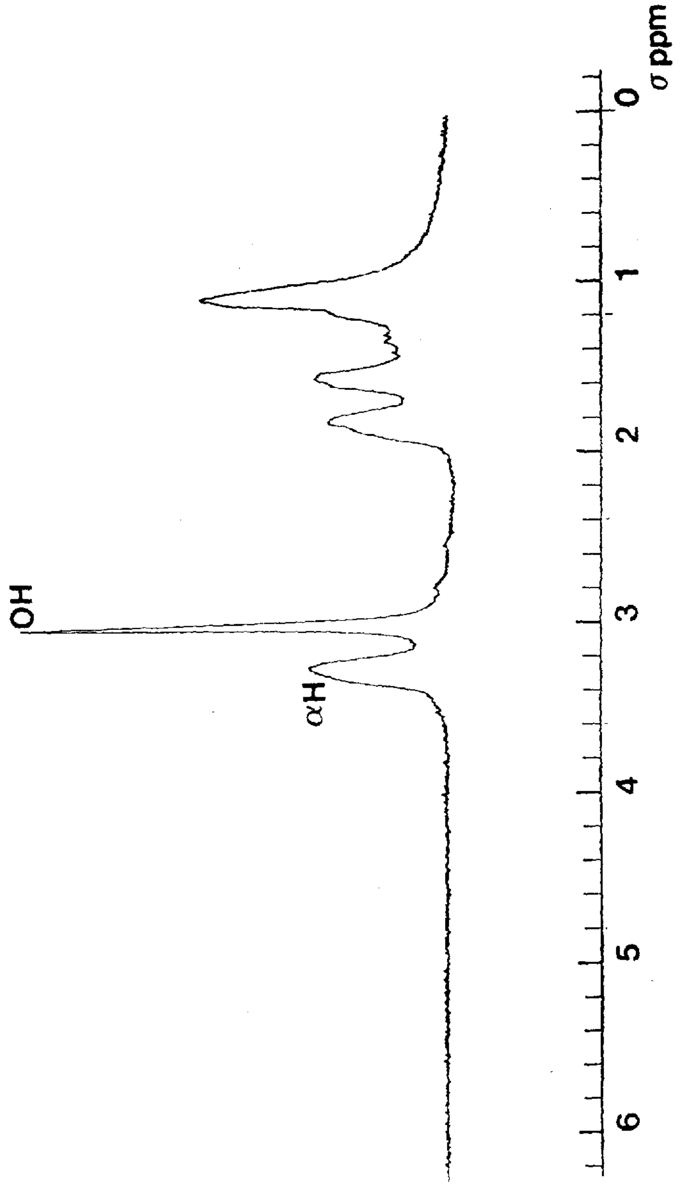
PROTON MAGNETIC RESONANCE CHEMICAL SHIFTS

THE HYDROXYL PROTON CHEMICAL SHIFT

PMR SPECTRA IN $CDCL_3$ SOLUTION

The nmr spectra of cyclohexandiols in $CDCl_3$ solution shows only a single rather sharp resonance signal for the hydroxyl proton, which on dilution moves to higher fields, consistent with the shielding of the nucleus. Monomeric free hydroxyls and hydrogen bonded hydroxyls are all coalesced and the average chemical shift is given by the Gutowsky/Saika equation. The spectra are rather uninformative with regard to hydroxyl shifts, but conformationally the presence of signals for the alpha

FIG.3.2



trans cyclohexan-1,2-diol

FIG.3.3

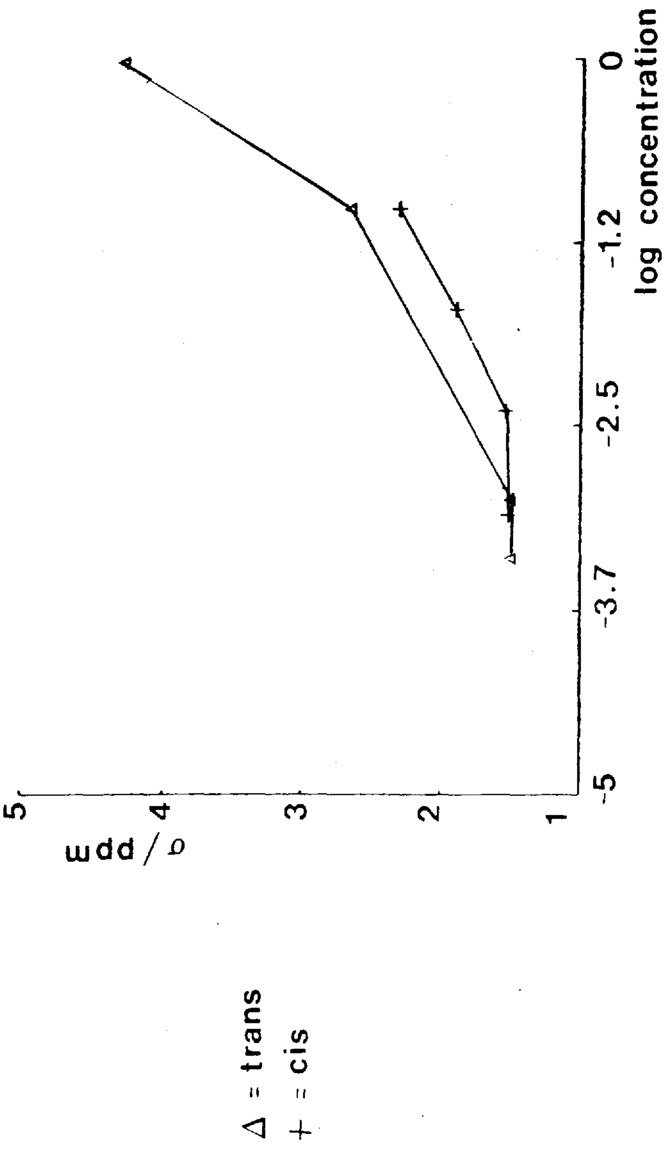
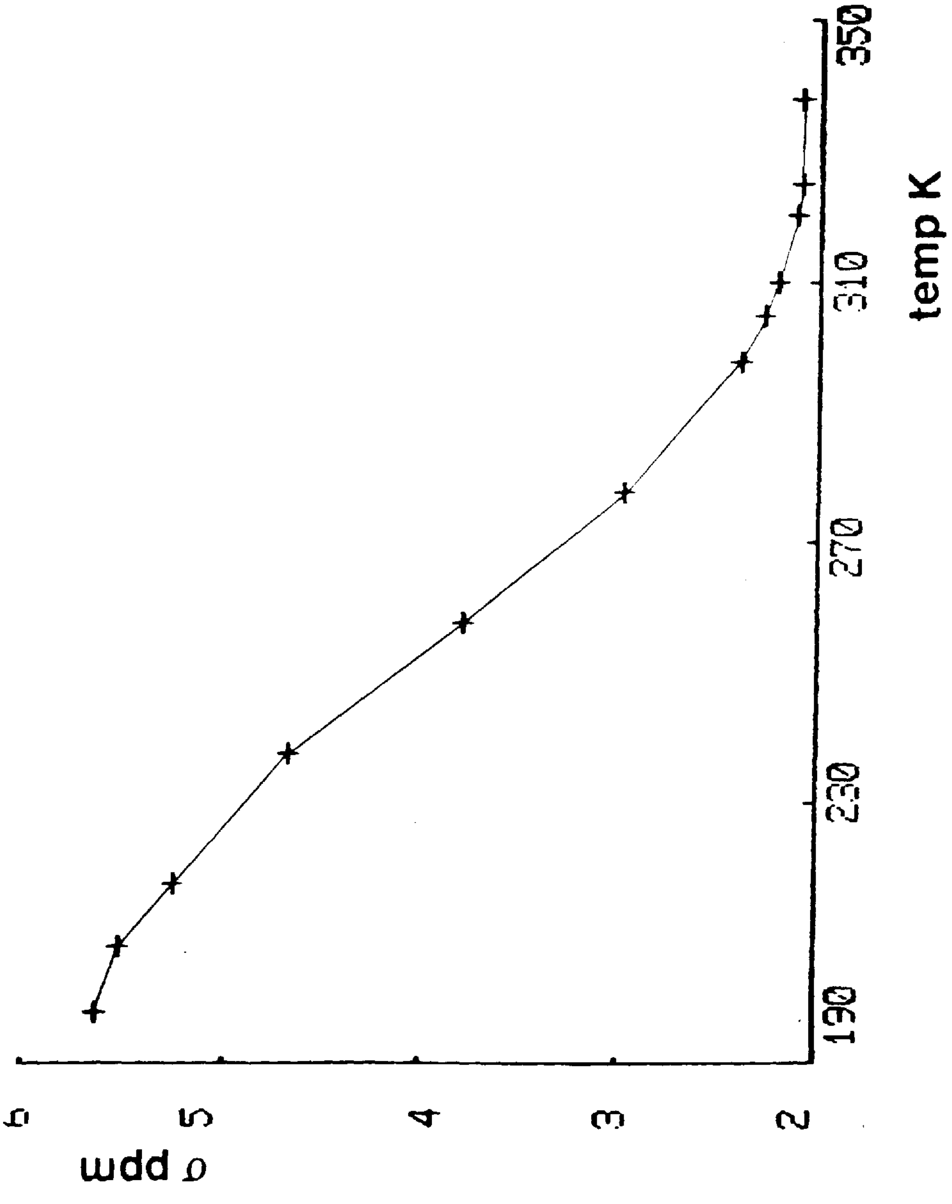


fig.3.4



carbon hydrogens are of value in the subsequent discussions.
The typical spectra of the cyclohexandiols is shown in fig.3.2, due to the conformational equilibrium the proton signals are averaged.
The effect of dilution is shown by fig.3.3 and tables XVIII and XIX. Figure 3.3 shows the change of chemical shift of cis and trans cyclohexandiol in $CDCl_3$ with decreasing concentration. In both cases a point is reached c.a. 0.004M after which no further decrease in chemical shift occurs (the limiting chemical shift). This chemical shift represents the average hydroxyl proton chemical shifts of all the free hydroxyl protons and the hydroxyls involved in internal hydrogen bonds.

For trans cyclohexan-1,2-diol, the effect of temperature was studied down to 198K (fig 3.4 and table XX), in an attempt to reduce the rate of ring inversion and proton transfer. However, no spin-spin coupling of the hydroxyl proton was observed, but the shift of the hydroxyl proton showed a systematic decrease of shielding with decrease of temperature. The resultant curve has a sigmoidal nature and at 198K there is the end of a plateau, below which temperature the curve suggests that there is no further increase of shielding. On subsequent temperature increase there is an increase of shielding up to approximately 315K, at which point a second plateau is reached and further increase of temperature does not affect the chemical shift. The chemical shift reflects an averaged proton environment, consequently, with increase of temperature the mole fraction of the monomer species should increase until a point is reached at which only the monomeric species is present. The plateau at 315K could reflect this state, however, the solvent effect experiments show that there is an interaction between the solvent and the hydroxyl group, therefore it is

fig.3.5

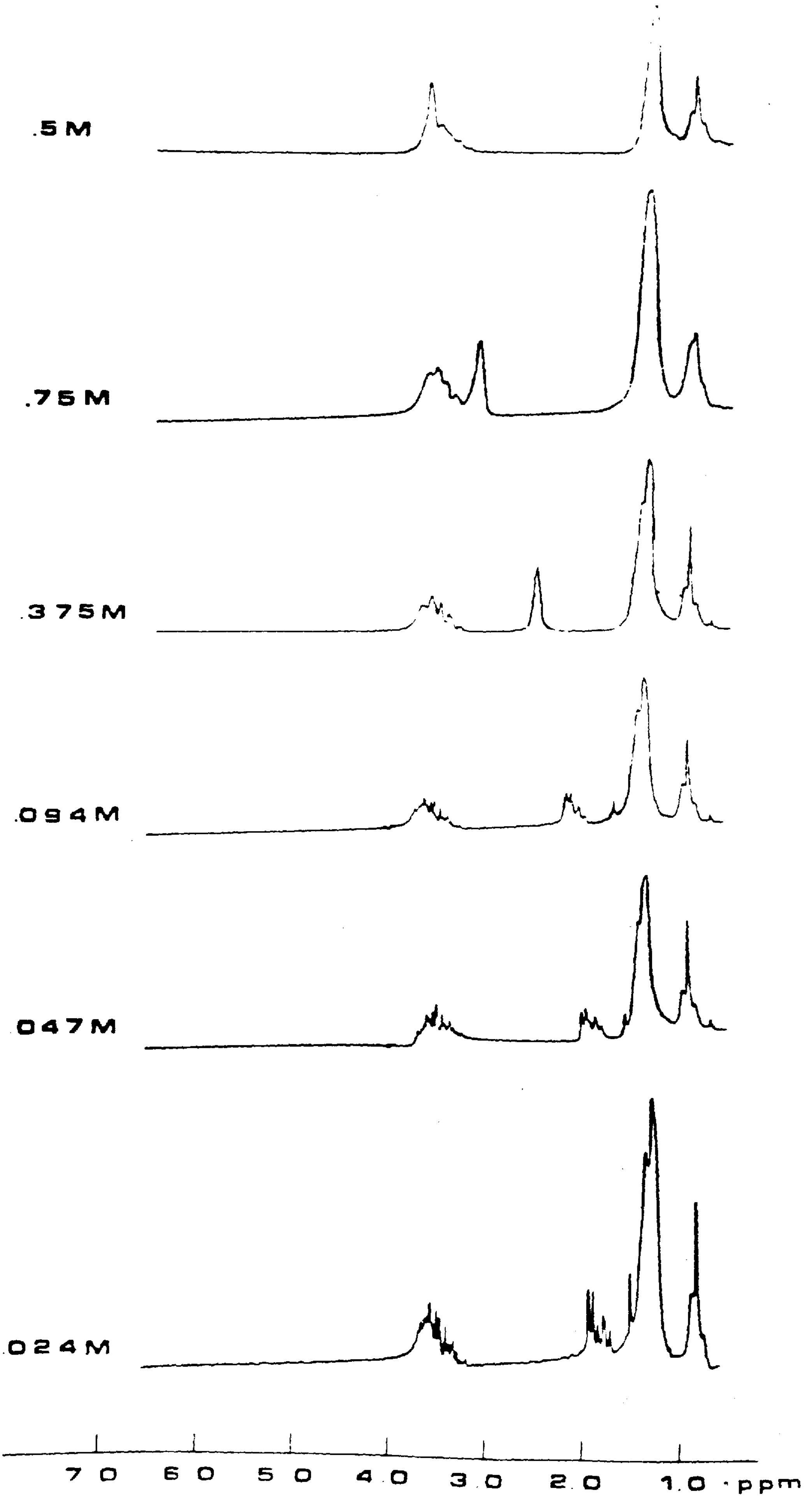
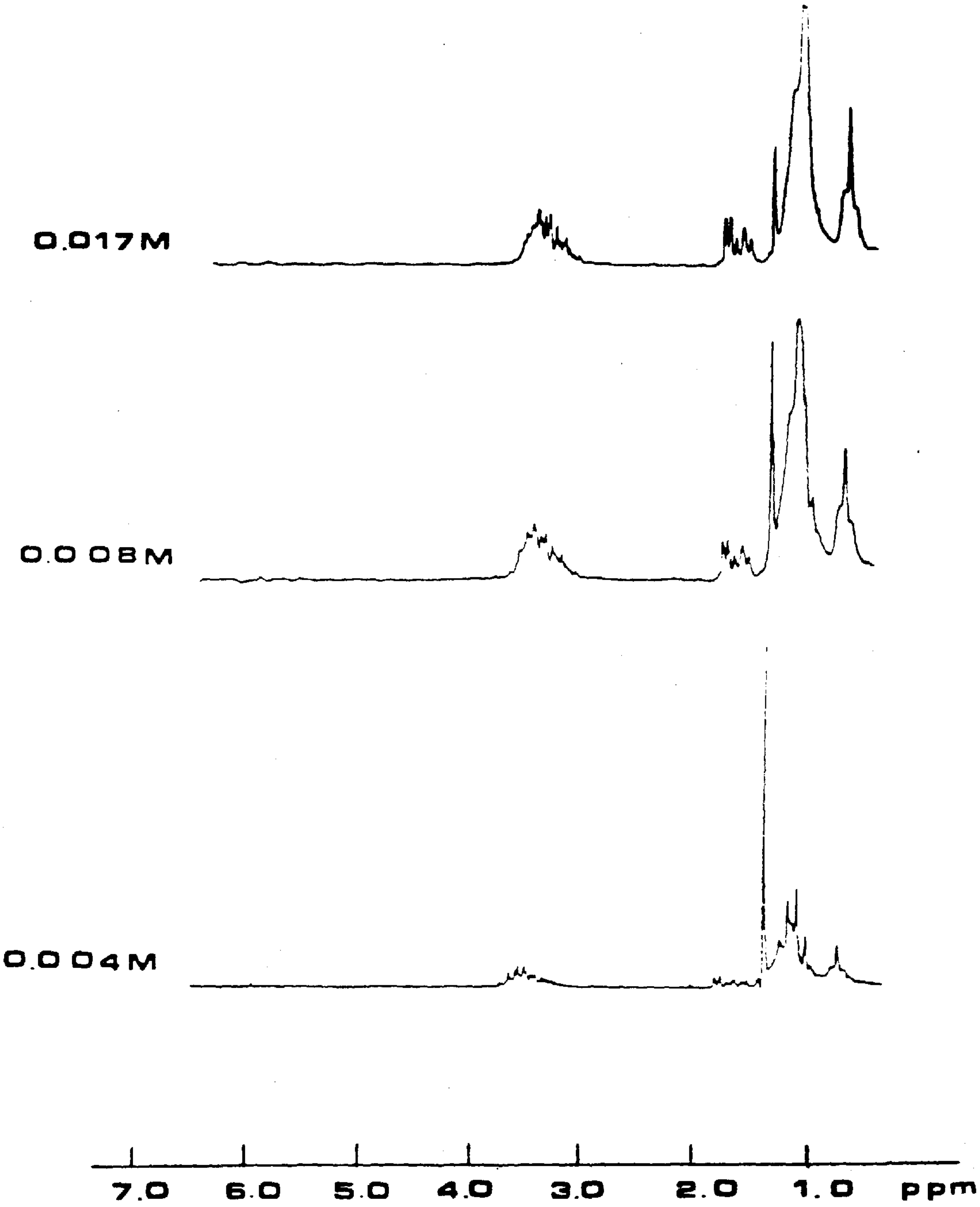


fig.3.5 contd.



more likely that this plateau reflects complete "dissociation" of solvent interaction from the solvation shell of the molecule. However, this explanation is rather doubtful and the probable explanation is that the plateau represents the dissociation of the internal hydrogen bond.

PMR SPECTRA IN CCl_4 SOLUTION

In contrast to $CDCl_3$, the solubility of these compounds in CCl_4 is very small, e.g. 0.001M compared with 3.0M for the trans-1,2-diol. This obviously reflects a much reduced solvent interaction in CCl_4 solution.

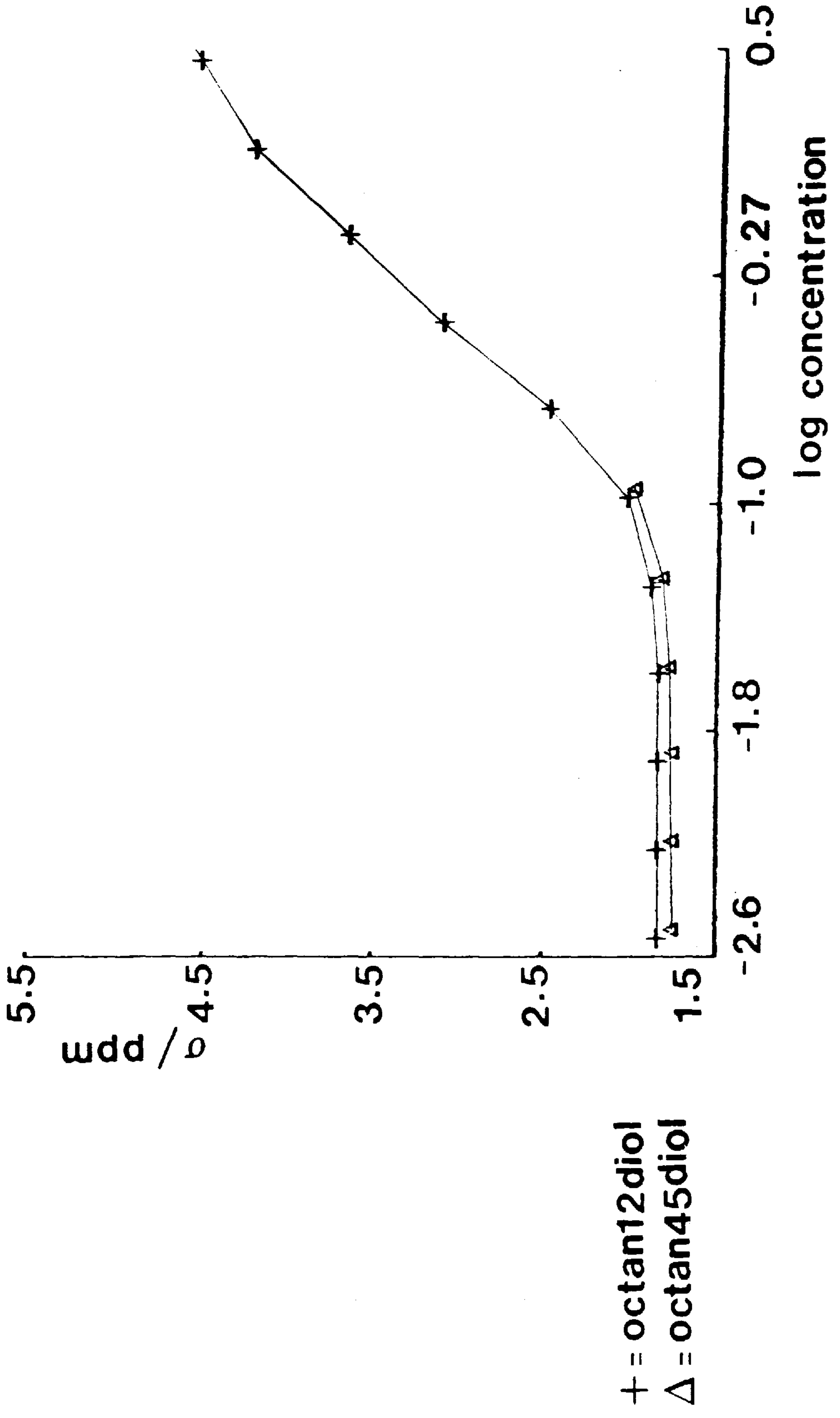
It was expected that an averaged hydroxyl proton signal would be observed, which would vary with concentration. However, on dilution, and on temperature elevation no shift of any of the signals was observed. It was therefore apparent that the concentration was low enough to permit only the unassociated species and a possible internally hydrogen bonded species, neither of which would cause a chemical shift on dilution. The presence of a rapid conformational equilibrium does not however permit the study of these species separately. Consequently, it was decided to study some typical straight chain diol systems as an aid to interpretation.

The solubility of the octandiols was such that a wide concentration range could be studied, octan-1,2,-diol and octan-4,5-diol were chosen, with regard to the symmetry of the molecules i.e. the 4,5-diol has two identical hydroxyl groups, whilst the 1,2-diol possesses two non-equivalent hydroxyls.

OCTAN-1,2-DIOL

The pmr dilution study in deuterated chloroform revealed some very interesting features (fig 3.5).

fig.3.6


σ / ppm
5.5
4.5
3.5
2.5
1.5
-2.6
-1.8
-1.0
-0.27
0.5
log concentration
+ = octan12diol
Δ = octan45diol

1.On dilution the hydroxyl signal shifts upfield, which is consistent with the deshielding of the nucleus.

2.At concentrations of about 0.01M, the hydroxyl signals begin to split and show evidence of spin-spin coupling, On further dilution down to approximately 0.002M, the multiplet is clearly discernable as a doublet and a triplet centered at 1.8ppm.

3.Coincident with the advent of spin-spin coupling is the appearance of a second signal upfield of the multiplet at 1.4ppm. On dilution, this second signal increases, until at 0.004M, only vestiges of the multiplet are evident, and the second signal is very intense.

The triplet arises from the coupling of the hydroxyl proton with its two alpha hydrogens and the doublet from the coupling of the hydroxyl group with the single alpha hydrogen (carbon 1).

The hydroxyl proton multiplet can only exist if the condition of slow proton exchange is met. Consequently, within defined concentration limits species exist in which the proton exchange mechanism is retarded.

The effect of dilution is shown in figure 3.6 and table XXI. The plot log concentration against chemical shift compares octan-1,2-diol with octan-4,5-diol. The shape of the curve is the same in both cases and is similar to the dilution curve for cis and trans cyclohexan-1,2-diols (above).

PMR CHEMICAL SHIFTS OF HYDROXYLIC PROTONS

TABLE XVIII

trans cyclohexan-1,2-diol in $CDCl_3$

CONCENTRATION (mol dm^{-3})	Log CONCENTRATION	CHEMICAL SHIFT (OH) (ppm)
1.0000	0.0000	4.28
0.1000	-1.0000	2.64
0.0010	-3.0000	1.48
0.0004	-3.3980	1.48

TABLE XIX

cis cyclohexan-1,2-diol in $CDCl_3$

CONCENTRATION (mol dm^{-3})	Log CONCENTRATION	CHEMICAL SHIFT (OH) (ppm)
0.1000	-1.0000	2.29
0.0200	-1.6990	1.89
0.0040	-2.3980	1.54
0.0008	-3.0970	1.52

TABLE XX

TEMPERATURE EFFECTS FOR TRANS-1,2-CYCLOHEXANDIOL

TEMPERATURE (K)	CHEMICAL SHIFT (ppm)
198	5.64
208	5.52
218	5.24
238	4.66
258	3.78
278	2.96
298	2.40
305	2.28
310	2.20
325	2.10
338	2.10

TABLE XXI

octan-1,2-diol in $CDCl_3$

CONCENTRATION (mol dm^{-3})	log CONCENTRATION	CHEMICAL SHIFT (ppm)
3.0000	0.4771	4.52
1.5000	0.1761	4.20
0.7500	-0.1249	3.66
0.3750	-0.4260	3.10
0.1875	-0.7270	2.48
0.0938	-1.0280	2.00
0.0469	-1.3291	1.88
0.0234	-1.6301	1.82
0.0117	-1.9311	1.82
0.0059	-2.2322	1.82
0.0290	-2.5376	1.82

TABLE XXII

octan-4,5-diol in $CDCl_3$

CONCENTRATION (mol dm^{-3})	log CONCENTRATION	CHEMICAL SHIFT (ppm)
0.1000	-1.0000	1.96
0.0500	-1.3010	1.80
0.0250	-1.6021	1.76
0.0125	-1.9031	1.74
0.0063	-2.2041	1.74
0.0031	-2.5052	1.74

OCTAN-4,5-DIOL

The solubility of this compound in $CDCl_3$ is much less than that of the corresponding 1,2 diol, however, a dilution study was possible and a similar pattern of results was observed as for the 1,2 diol:-

1.At approximately 0.1M, the hydroxyl signal appears as a doublet at 2.1ppm.

2.Coincident with the appearance of the doublet is an upfield signal at 1.6ppm.

3.On further dilution, the multiplet intensity decreases and the upfield signal increases.

CARBONTETRACHLORIDE SOLUTIONS

In CCl_4 solution, spin- spin coupling is not observed for either compound, but a systematic shielding of the hydroxyl proton is observed on dilution. The concentration range available does not however permit concentration plots for comparison with the $CDCl_3$ solutions.

PROTON EXCHANGE AND SPIN - SPIN COUPLING

The mechanism of cyclic proton exchange put forward by Limbach et.al. (25) for carboxylic acids and alcohol association, involves the formation of a cyclic dimer in which the proton exchange takes place.

If the mechanism of cyclic proton exchange is applicable to alcohol self-association in aprotic solvents, this would then necessitate the formation of a self-associated dimer.

Consequently, any factor which tends to inhibit the formation of a cyclic dimer will result in a decrease of the rate of proton transfer.

However, the formation of cyclic dimers in alcohol associations has been the subject of much discussion. Luck (27) points out that there is

fig.3.7

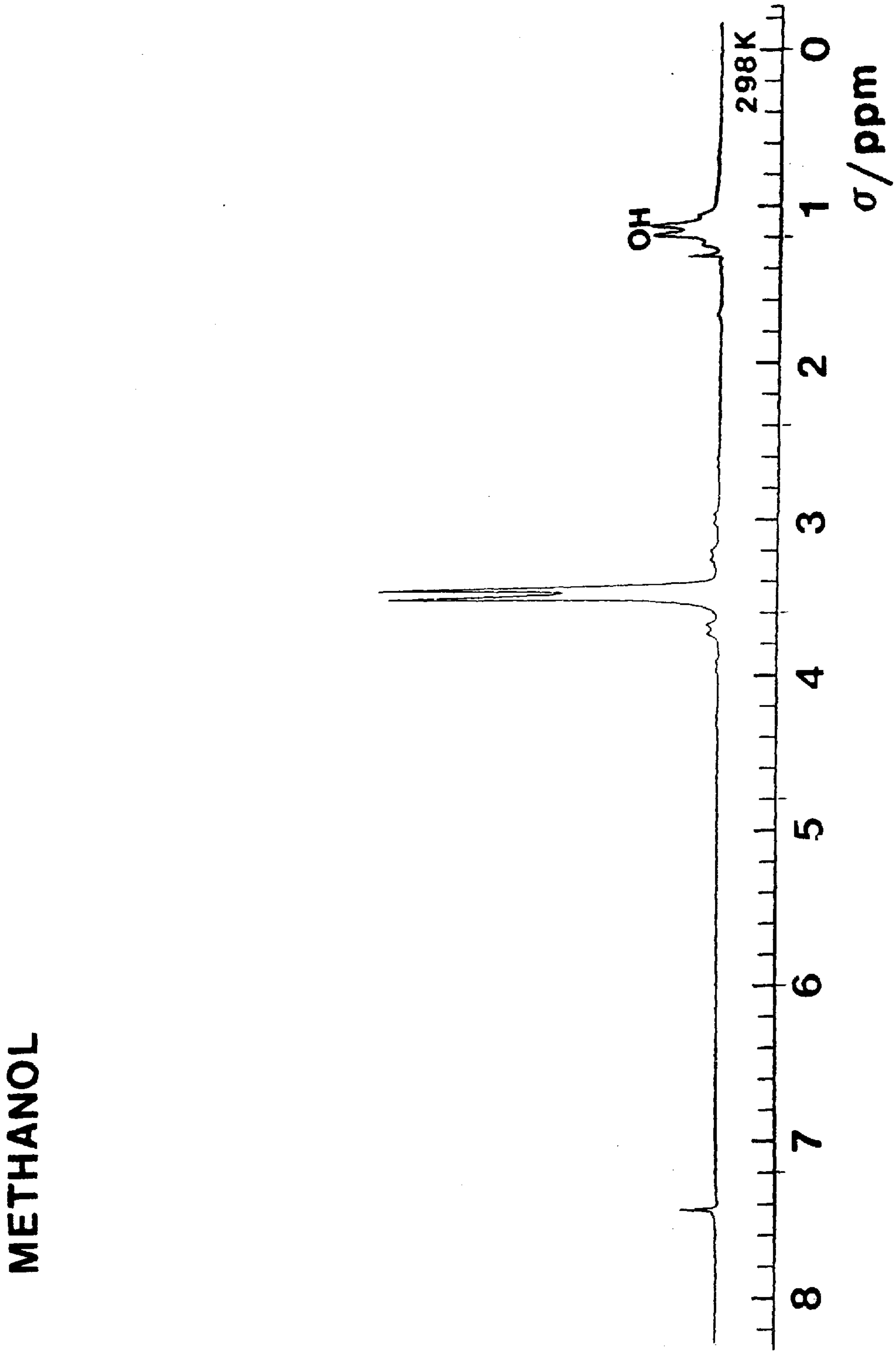


fig.3.8

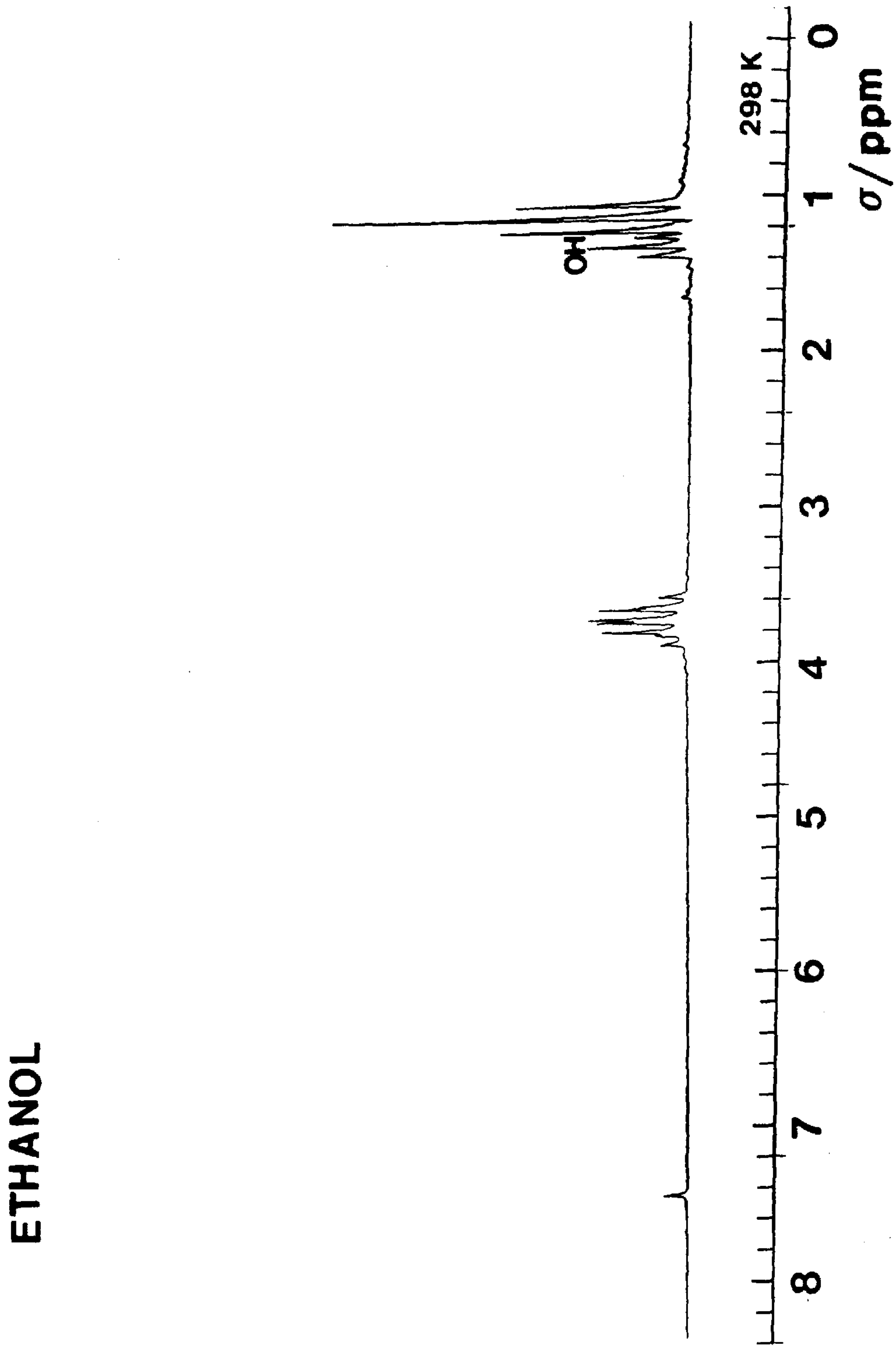


fig.3.9

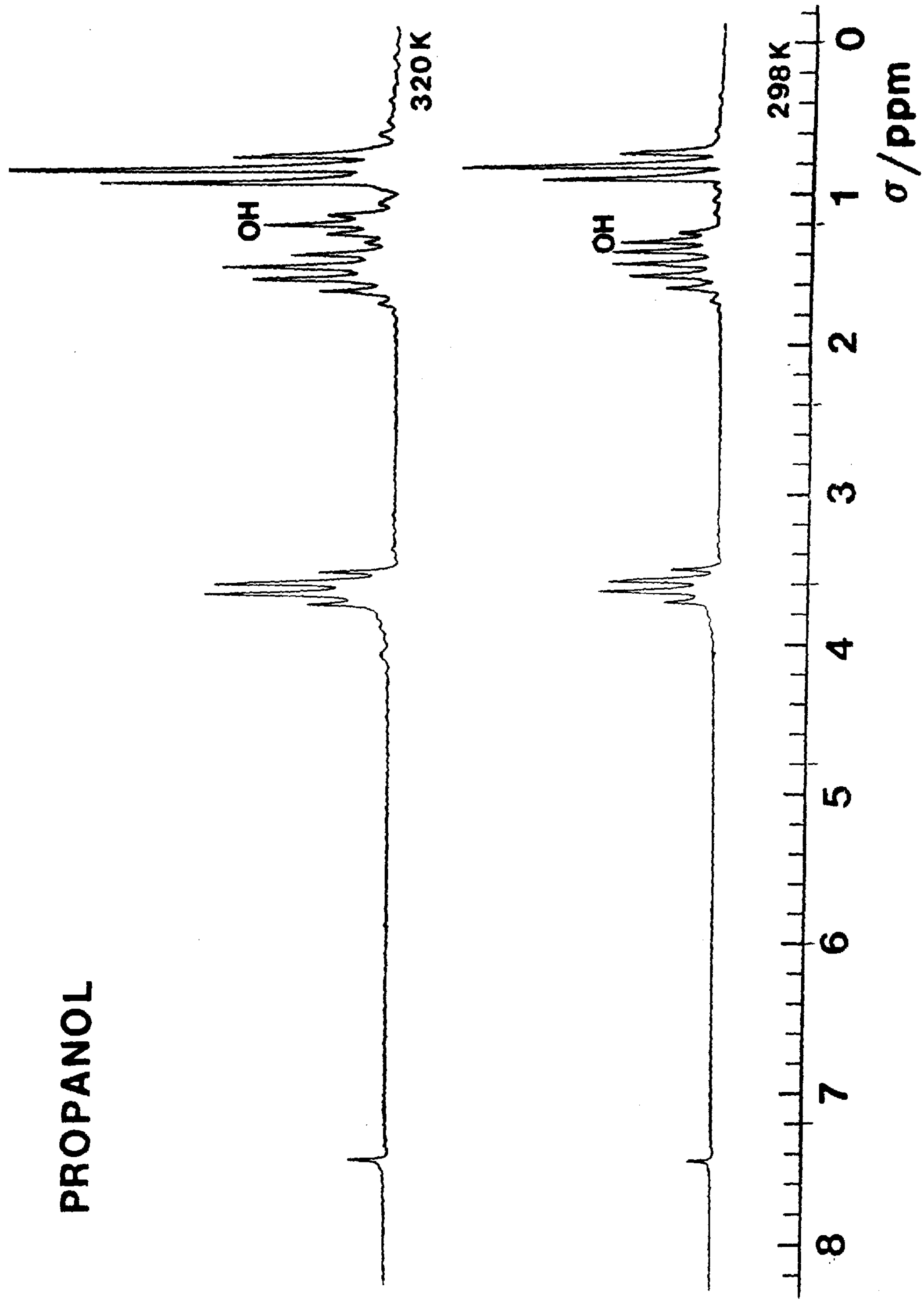
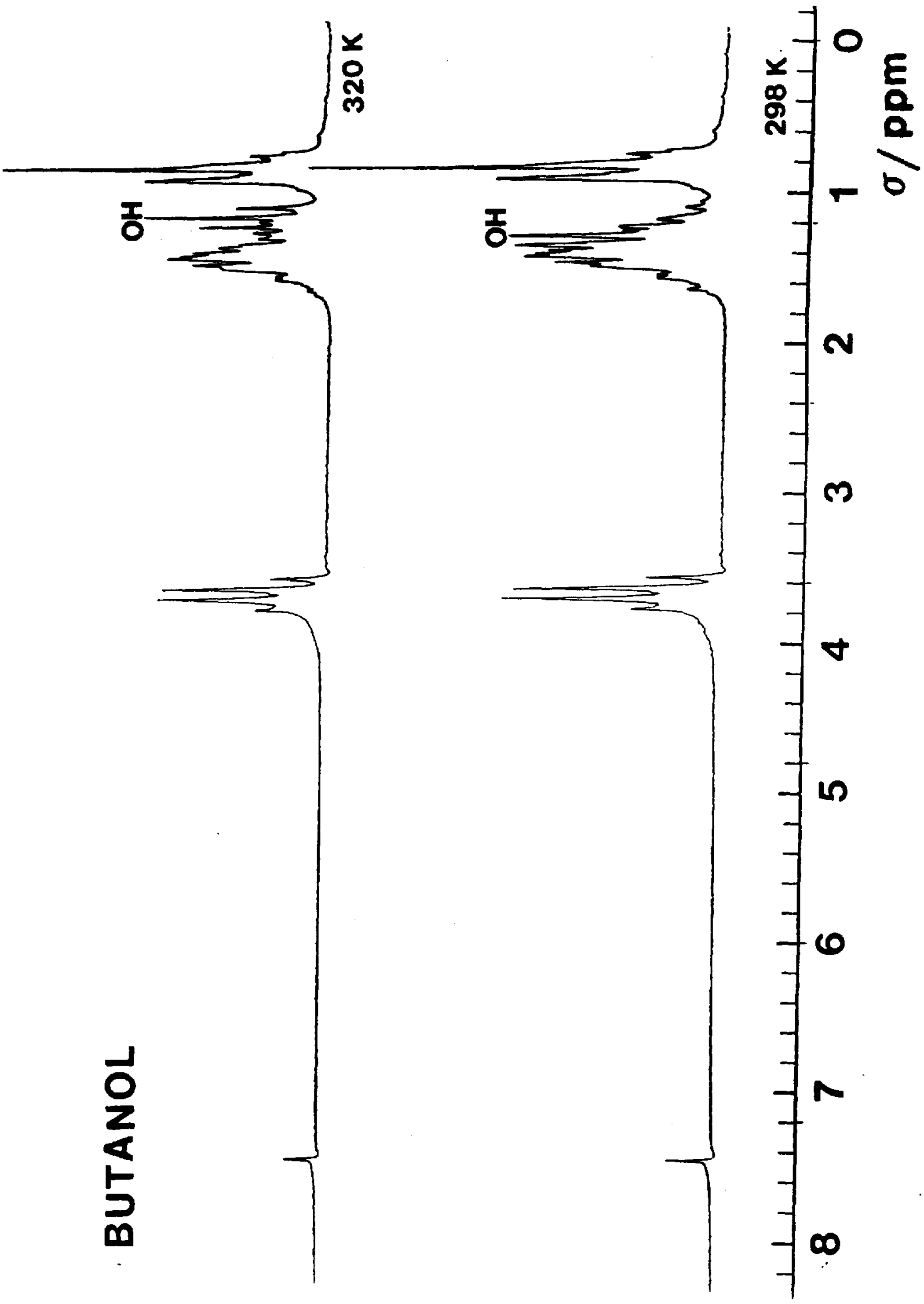


fig.3.10



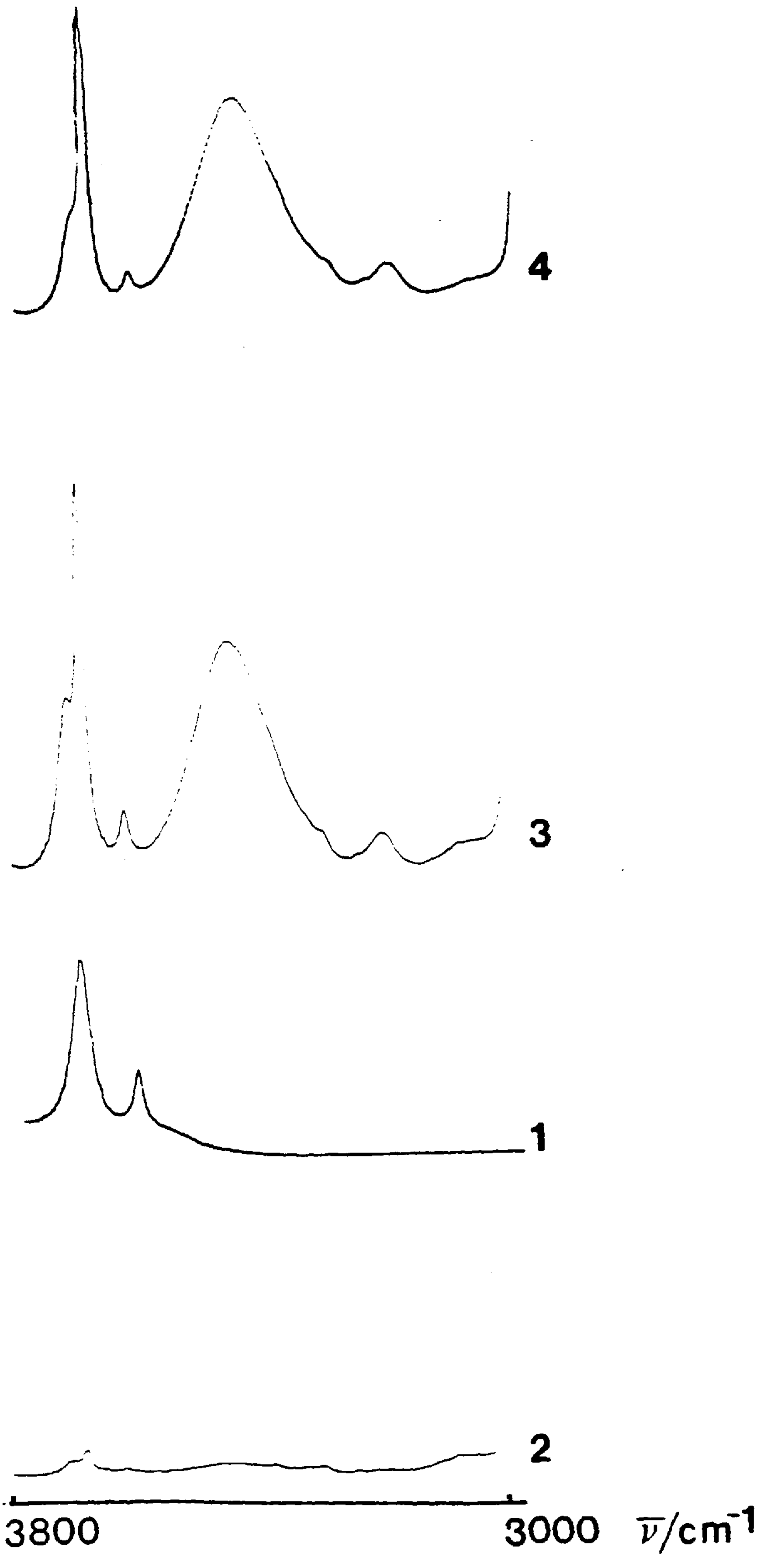
no convincing argument against the assumption of cyclic structures and generally it is assumed that these structures are formed in conjunction with linear forms but predominate at lower concentrations. In the i.r. spectra therefore, they are assumed to appear as a transient band which is engulfed by a broader intermolecular band on concentration increase.

The solvent studies (above) have shown that alcohol solutions in $CDCl_3$ show a lesser degree of intermolecular hydrogen bonding than a comparable solution in CCl_4. This being the case,the mechanism of proton transfer retardation is readily explainable since cyclic dimer formation will be inhibited. The presence of an intramolecular hydrogen bond in the alkandiols does not cause the loss of spin-spin coupling. Therefore, the intramolecular bond does not contribute towards proton transfer in these compounds.

With careful drying and precautions to remove all acidic impurities from the solutions, the pmr spectra of alkanols from n=1 to n=10 were studied. In all cases, spin - spin coupling could be observed at concentrations of up to about 0.1M in $CDCl_3$ In the cases of methanol and ethanol, the coupling is easily observed since it is not overlapped by the CH_2 and CH_3 resonances (figs 3.7,3.8). In the higher alcohols, the OH multiplet is obscured but can be identified by its shift to higher field on temperature increase (figs. 3.9,3.10).

A notable observation of the spectra of the solutions in $CDCl_3$ is the high field sharp resonance at low concentrations of diol. At first this was thought to be due to the presence of unassociated species. However, on dilution the signal intensifies to such an extent that integration shows that it does not arise from the alcohol molecule. An explanation for this result was not obtained until the work progressed to solutions in DMSO and i.r. studies were undertaken. It has now been

fig.3.11



shown that the signal arises from trace water behaving in an "abnormal" manner. Typically, water is observed in the nmr spectra as a somewhat broadened signal, not as a sharp signal as in this case. The same observation is made with solutions in DMSO, but it is more readily understood from the i.r. study.

Figure 3.11, spectrum (1), shows the infra-red spectrum between 3800cm^{-1} and 3000cm^{-1} of CCl_4 saturated with water. The free OH bands appear at 3707cm^{-1} and 3615cm^{-1} and a broad intermolecular band at 3075cm^{-1}.

The presence of two free OH bands is accounted for by the two stretching modes of the non-linear water molecule; the higher wavenumber vibration can be attributed to the asymmetric O-H stretch, whilst the lower wavenumber must be due to the symmetric O-H stretch (fig. 3.12).

asymmetric

symmetric

fig.3.12

Spectrum(2) shows the OH stretch region for DMSO, which has been thoroughly dried over molecular sieves 3A. Small bands of low intensity are evident due to the presence of trace water, but their intensity is so small that it does not interfere with the experiment.

Spectrum(3) shows the effect of adding 1 microlitre of DMSO to 3cm^3

of water saturated CCl_4. The antisymmetric stretch band at 3707cm^{-1} diminishes and a new band at 3682cm^{-1} appears. Similarly, the symmetric stretch band at 3615cm^{-1} diminishes together with the intermolecular hydrogen bond band. Simultaneously, a broad intense band appears centred at 3444cm^{-1} and a second much less intense band at 3203cm^{-1}. Spectrum(4) shows the effect of adding an additional microlitre of DMSO to the solution, the new bands intensify whilst the water bands diminish.

The intense broad intermolecular hydrogen bond band at 3444cm^{-1} can be attributed to monomeric water molecules bonded to DMSO (fig.3.13).

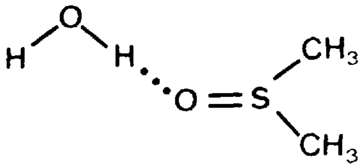


fig.3.13

The presence of the intense free OH band at 3682cm^{-1} is indicative of a free OH being present during the association.

The second intermolecular bond of much less intensity can probably be related to the following species (fig.3.14):

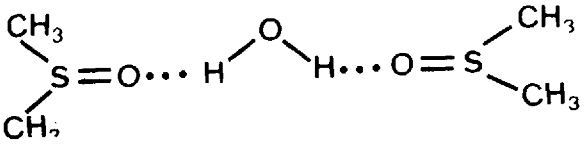


fig.3.14

However, its intensity is such that its population is probably relatively small.

These solvent bound water molecules apparently undergo rapid proton transfer, as indicated by the extreme narrowness of the OH signal in the nmr spectra. However, heteromolecular proton transfer between these species and the alcohol molecules evidently does not occur.

In $CDCl_3$ solutions, solvent - water hydrogen bonding does not occur, however, the general effect of $CDCl_3$ to decrease the amount of intermolecular association is present. Consequently, for trace quantities of water practically no intermolecular association will be present so that the free hydroxyl groups must participate in a proton transfer mechanism which is of the non- associative form i.e. ionic. Whatever the mechanism, it is very effective since no broadening of the signal is observed.

The ^1H nmr spectrum of trans 1,2 cyclohexandiol in $CDCl_3$, does not show spin-spin coupling, Presumably this can be attributed to the dynamic effect of the chair-chair equilibrium. The pmr spectra of the cyclohexandiols in $CDCl_3$ are rather uninformative as regards conformation. However, the interpretation of the spectra was profitable in the sense that it was appreciated that the solvent effects should be studied in depth.

^1H nmr SPECTRA in DMSO SOLUTIONS.

The spin-spin coupling of hydroxyl protons in DMSO solution is a general observation for all the alcohols studied. Its occurence can be readily understood from the preceding discussions. The inhibition of proton exchange by the prevention of formation of self associated species (probably cyclic dimers) is a consequence of association to the solvent. The measurment of the hydroxylic proton coupling constant and its correlation with conformation has been initiated by Rader (31) and

Sehgal (33). However, in this study an attempt has been made to correlate the coupling constant with the conformation in cyclohexandiol systems.

The solvent effect study showed that associating solvents such as DMSO shift the conformational equilibrium in cyclohexanol so as to significantly favour the equatorial conformation. In the study of cyclohexandiols, the same effect is anticipated in those isomers which are subject to change i.e. trans cyclohexan-1,2-diol, cis cyclohexan-1,3-diol and trans cyclohexan-1,4-diol. The remaining isomers are conformationally degenerate and the solvent is not expected to influence this degeneracy. Additionally, the evidence (see page 47) is that DMSO will prevent intramolecular association, the consequences of which may profoundly alter the preferred conformation of certain isomers compared with that in CCl_4

The hydroxyl proton coupling constants were determined in DMSO solution for the configurational isomers of 4-tert.butyl cyclohexanol. The concentration of all the solutions was 0.2M and the experimental conditions were the same as detailed above. The hydroxylic proton coupling constants are tabulated below (table XXIII).

TABLE XXIII

COMPOUND	J (HZ)
cis-4-tert.butyl cyclohexanol	3.08
trans-4-tert.butyl cyclohexanol	4.40

In accordance with a Karplus type relationship, the coupling constant is expected to vary with the dihedral angle (31).
The Newman projections along the oxygen to carbon bonds (fig 3.15 and 3.16) show the preferred orientations of the rotamers.

trans-4-tert.butyl cyclohexanol

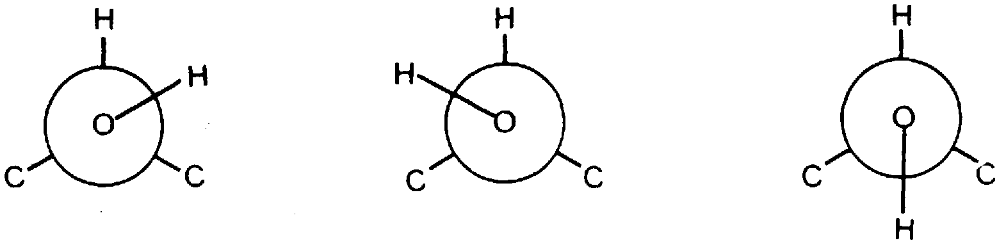


fig.3.15

Energetically, these rotamers show Van der Waal repulsion minima (see Computer Graphic p 157). The repulsion energy difference between the gauche and the anti rotamers is about 4.73 KJ mol^{-1}. However, there are two forms of the gauche rotamer and this therefore introduces an entropy factor in favour of the gauche forms. For two equipopulated identical forms, $\Delta S = R \ln 2$.

The repulsion energy differnce can be equated to the enthalpy difference between the gauche and the anti rotamers, so that:

$$\Delta G = \Delta H - T\Delta S$$

$$\Delta G = -4730 - 298 \ln 2$$

$$\Delta G = -4523.4 \text{ KJ MOL}^{-1}$$

$$\text{then } -\Delta G = R\ T \ln K$$

$$\text{and } K = 6.2$$

This represents an anti population in excess of 85 %.

cis 4-tert.butyl cyclohexanol

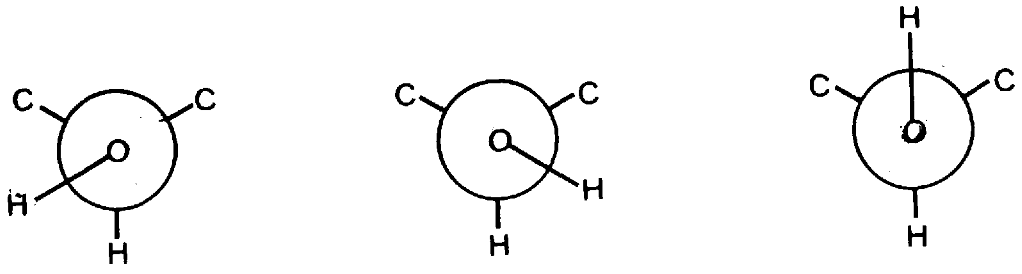


fig.3.16

Similary, the axial conformation gives rise to two gauche forms and one anti form. However, the axial form is subject to a much greater degree of repulsion than in the equatorial conformation due to the 1 - 3 interaction (fig.3.17).

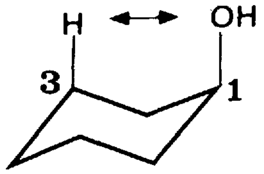


fig.3.17

This increased energy difference between the gauche and anti forms greatly favours the gauche form. This, coupled with the entropy factor ensures that $>$ 90 % of the axial conformation has the gauche conformation.

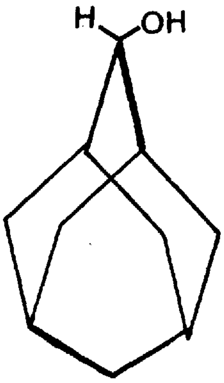
If the Karplus relationship holds, the equatorial hydroxyl of the predominantly anti rotamer population (180 degree dihedral angle) has a larger coupling constant than the axial conformation with a predominantly gauche rotamer (approx 60 degree dihedral angle). Great caution must however be observed in the application of the above calculations since the hydroxyl groups in DMSO solution are not free but associated to DMSO. This association must affect the rotamer populations, particularly the anti rotamer, and a considerable reduction of the population of this orientation is expected particularly in the axial conformation.

To test the applicability of the measured coupling constants, some conformationally fixed cyclohexanol systems were examined and their coupling constants determined in DMSO (table XXIV).

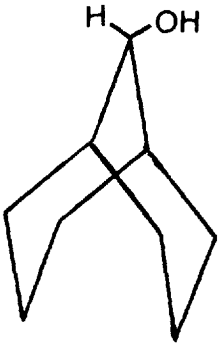
TABLE XXIV

COMPOUND	J_{OH-H} (HZ)
2-Adamantanol	3.08
bicyclo (3,3,1) nonan-9-ol	3.08
bicyclo (3,3,1) nonan-2-ol	3.08

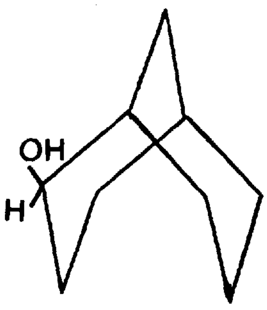
The configuration of these compounds is such that the hydroxyl group occupies an axial position with dihedral angles identical to those found in an axial cyclohexanol (fig.3.18).



2-adamantanol



bicyclo(3,3,1)nonan-9-ol



endo-bicyclo(3,3,1)nonan-2-ol

fig.3.18

In all these compounds the steric repulsions are identical to those in axial cyclohexanol and this is consistent with the observed coupling constants of 3.08 HZ. A remarkable feature of the hydroxyl proton coupling constant is its insensitivity to changes in the cyclohexyl skeleton, provided that the steric interactions are not affected.

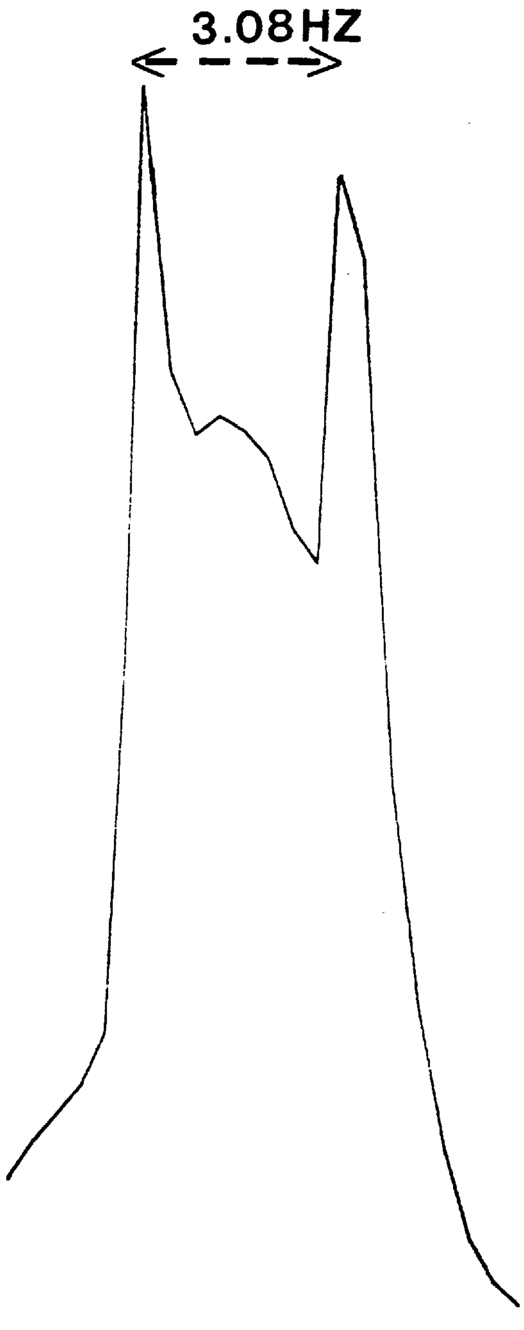
In principle, the existence of two different coupling constants for the axial and equatorial hydroxyls of the cyclohexyl system can be used for conformational analysis of a conformationally mobile cyclohexanol system. The kinetic averaging of coupling constants is analagous to the kinetic averaging of the chemical shifts. However, apparently anomalous results are obtained for cyclohexanol itself. Typically, the DMSO spectrum of cyclohexanol shows averaging of the chemical shifts, but the coupled hydroxyl doublet is apparently a composition of two superimposed doublets one of 3.08 HZ and one of 4.40 HZ.

The coupling constants determined for the cyclohexandiol series were however of immense value. Table XXV gives the observed coupling constants for all the cyclohexandiols in DMSO solution at 0.2M concentration.

TABLE XXV

CYCLOHEXANDIOL	J_{OH-H} (HZ)
trans 1,2	3.52*
cis 1,2	3.95
trans 1,3	3.96
cis 1,3	4.40
trans 1,4	4.40
cis 1,4	3.96

fig.3.19



* Two overlapping doublets are observed, the outer doublet is measured at 3.52HZ, the inner doublet cannot be measured due to the overlap (fig.3.19).

Table XXVI, shows the possible chair conformations of the cyclohexandiols using the hydroxyl groups as reference.

TABLE XXVI

CYCLOHEXANDIOL	POSSIBLE CONFORMATIONS
trans 1,2	dieq diax
cis 1,2	eq/ax ax/eq
trans 1,3	eq/ax ax/eq
cis 1,3	dieq diax
trans 1,4	dieq diax
cis 1,4	eq/ax ax/eq

As discussed above, the evidence suggests that the internal hydrogen bond is not formed in DMSO solution and so in the following discussion it will be assumed that they are be absent.

For cis cyclohexan-1,3-diol and trans cyclohexan-1,4-diol the two possible conformations are the diequatorial forms and the diaxial forms. The thermodynamic considerations above showe that the diequatorial forms are greatly favoured and should dominate the equilibria. The coupling constants for both these isomers is 4.40 Hz, which is identical with the coupling constant for the equatorial cyclohexanol. It can therefore be concluded that the conformational preference in both these compounds is almost entirely diequatorial.

For cis cyclohexan-1,2-diol, cis cyclohexan-1,4-diol and trans cyclohexan-1,3-diol, the axial/equatorial and equatorial/axial conformations are degenerate ($\Delta G = 0$) and both an axial and an equatorial hydroxyl must be present in equal amounts. Significantly, the coupling constant in these compounds is 3.96 HZ which must represent an average value for the axial and equatorial hydroxyl proton coupling constants. Since the averaging of the coupling constants is governed by the same kinetic process which governs the averaging of chemical shifts, the Gutowsky equation (16) is applicable:

$$J_{obs} = \chi_{eq} \cdot J_{eq} + \chi_{ax} \cdot J_{ax}$$

Where J_{obs} is the averaged coupling constant.

J_{eq} and J_{ax} are the coupling constants for the equatorial and axial coupling constants.

χ_{eq} and χ_{ax} are the mole fractions of the equatorial and axial conformations.

$$\text{then } \chi_{eq} + \chi_{ax} = 1$$

and since the equatorial and axial populations must be equal,

$$\chi_{eq} = \chi_{ax} = 0.5$$

The value for J_{eq} can be taken from the above results e.g. from the trans cyclohexan-1,4-diol. Therefore the axial coupling constant can be calculated:

$$3.96 = (0.5 \ . \ 4.40) + (0.5 \ . \ J_{ax})$$

$$J_{ax} = 3.52 \text{ HZ}$$

Of particular note is the fact that this calculated value of J_{ax} is identical to the observed value of the outer doublet of trans cyclohexan-1,2-diol, which is substantial evidence that the diaxial and diequatorial conformations are present in comparable amounts.

J_{ax} in the cyclohexandiol system is therefore larger than in the cyclohexanol system, whilst the equatorial coupling constant is unchanged. The cause of such a difference is not easy to explain, since if the presence of the second equatorial hydroxyl were to sterically perturb the axial hydroxyl and consequently change its rotamer population, then the equatorial hydroxyl should also be affected. However, it appears that peturbation (if any) is insignificant.

The anomalous behaviour of the non-kinetically averaged coupling constants in cyclohexanol and trans cyclohexan-1,2-diol require the examination of the factors which determine the effect of kinetic averaging. Since all forms of kinetic averaging in nmr are dependent upon the time-scale, any discussion must involve the meaning of nmr timescale.

LONGITUDINAL AND TRANSVERSE RELAXATION PROCESSES

In order to gain an understanding of the parameters which define slow and fast exchange, the processes of nuclear relaxation must be considered.

From the quantum mechanical point of view, for nuclei with a spin 1/2 such as ^1H and ^{13}C, two possible spin states are possible; m = +1/2 and m = -1/2, where the former spin state is of lower energy than the latter. When the sample is introduced into a magnetic field B_o, a Boltzmann distribution of spins occurs between the energy levels, which gives rise to a small excess of nuclei in the lower energy state which is established by means of a specific relaxation process. If, after equilibrium is attained, the nuclei are irradiated with electromagnetic energy at their resonance frequencies, the nuclei absorb energy from the field (B_1) and the populations equalize. When B_1 is removed, the nuclei tend to re-establish the equilibrium under the applied field B_0. This is established by relaxation processes and the energy acquired by the spin system is transferred to the surroundings. Such energy changes between the spin system and the lattice give rise to what is called spin-lattice relaxation. However, it must be pointed out that additional relaxation processes, which involve interactions between the spins without any change in the relative populations of the energy levels also need to be considered. These contributions are referred to as spin-spin relaxation.

A mathematical treatment of the macroscopic magnetization vector M of a set of identical nuclei has two time constants T_1 and T_2 which charecterize the exponential return to equilibrium of the longitudinal (M_z) and transverse (M_x and M_y) components respectively.

$$dM_z/dt = (M_z - M_0)/T_1$$

$$dM_x/dt = -(M_x/T_2)$$

$$dM_y/dt = -(M_y/T_2)$$

T_1 is the longitudinal or spin-lattice relaxation time and T_2 is the transverse or spin-spin relaxation time. The smaller the values of T_1 and T_2 the more efficient the relaxation.

When the B_1 field is removed after resonance the spins tend to lose their phase coherence. This dephasing leads to a statistical repartition of the magnetization components, thus M_x and M_y vanish. If complete dephasing occurs before the longitudinal component M_z has reached its equilibrium value M_0, through energy exchange with the lattice, it means that the transverse decay is faster than the longitudinal decay and T_2 is smaller than T_1. Since M_x and M_y are necessarily zero when $M_z = M_0$, the reverse situation is obviously impossible and the relationship ; $T_2 < T_1$ holds.

SLOW EXCHANGE AND FAST EXCHANGE

Magnetic site exchange of the types discussed above lead to nmr spectra which depend upon the rate of the relevant process. In particular the rate needs to be compared with the nmr timescale. The nmr timescale generally refers to lifetimes of the order of 1s to 10^{-6}s. Two extreme types of nmr behaviour can readily be distingished. If the exchange lifetime is greatly in excess of the nmr timescale, the system is in the slow exchange regime, whereas if the lifetime is substantially less than the nmr timescale, the fast exchange regime results. Nmr observations in these two extremes are governed by simple considerations;

1. slow exchange spectra are the superposition of sub-spectra due to each species present.

2. in the fast exchange regime the observed spectrum may be considered as due to a single species whose nmr parameters (chemical shifts and coupling constants) are the relevant averages of those for the individual species (suitably weighted to take account of differing populations).

Rapid exchange leads to sharp averaged lines. If an exchange process occurs during the period T_2, (i.e. during the spin-spin relaxation time of the nucleus) the frequency of the free induced decay (FID) changes. If such an event occurs in a time which is short compared with the difference between the two frequencies, the FID will be indistinguishable from that given by a system with the average frequency i.e. a sharp line results.

When the rate of magnetic site exchange increases from the slow exchange regime so as to begin to affect the nmr spectrum, the situation can be treated by invoking the Uncertainty Principle. If the lifetime of a nucleus in environment A is τ_A, then the uncertainty in the energy is $U = \hbar \tau_A^{-1}$. This will influence the widths of the relevant nmr line, giving a broadening contribution at half-height of;

$$\Delta \nu_{\frac{1}{2}} = (\tau_A \pi)^{-1} \qquad \text{equation 1}$$

The effect of the exchange will only be noticeable if $\tau_A \lesssim T_2$. For two site exchange, $A \rightleftharpoons X$, with unequal populations, the site with the smaller population will have the shorter lifetime and hence the broader line.

The above observations are clearly defined criteria for the effect of kinetic averaging on the nmr spectrum and so the experimental results will be discussed in these terms.

The presence of two doublets which are non-averaged but with averaged chemical shifts implies, that the chair-chair equilibrium must be faster than the difference in the chemical shifts for the axial and equatorial hydroxyls, this must be so since the chemical shift is averaged.

Consider cis cyclohexan-1,2-diol, trans cyclohexan-1,3-diol and cis cyclohexan-1,4-diol. Each isomer possesses an axial hydroxyl group and an equatorial hydroxyl group that coexist. During a cyclohexyl ring inversion the axial hydroxyl moves to the equatorial position and the equatorial hydroxyl moves to the axial position. Compare this ring inversion with that of cyclohexanol itself. During this ring inversion the equatorial hydroxyl moves to the axial position without a simultaneous movement of an axial hydroxyl to an equatorial position. This observation is effectively the same as saying that the rate of exchange between the two hydroxyl sites in the above cyclohexandiols is twice as fast as in cyclohexanol if the axial and equatorial hydroxyl sites of cyclohexanol were equally populated. However, the two sites are not equally populated and at any instant in time about 70 % of the cyclohexanol molecules have an equatorial conformation for the hydroxyl group i.e. on average each cyclohexanol molecule spends obout 70 % of its time in the equatorial hydroxyl position and 30 % of its time in the axial hydroxyl position.

When nuclei exchange between two sites A and B, at a rate which is slow compared with the difference in relaxation rates ($T_{2A}^{-1} - T_{2B}^{-1}$) or the difference in chemical shifts ($\omega_A - \omega_b$), the A and B signals are still observed separately at ω_A and ω_B. However, the line widths depend upon τ_A and τ_B.

$$1/T_{2A\ \mathrm{obs}} = 1/T_{2A} + 1/\tau_A \text{ and } 1/T_{2B\ \mathrm{obs}} = 1/T_{2b} + 1/\tau_B \qquad \text{equation 2}$$

Where $1/T_{2a\ \mathrm{obs}}$ is the line width at half-intensiy.

As soon as the exchange becomes rapid with respect to the chemical shift difference and to the difference in relaxation rates the signal is averaged over A and B.

$$1/T_{2A\ \mathrm{obs}} = \sigma_A/T_{2A} + \sigma_B/T_{2B} + \sigma_A\sigma_B\ \tau_A\tau_B\ /\tau_A + \tau_B\ (\omega_A - \omega_B)^2 \qquad \text{equation 3}$$

If the exchange sites are equipopulated as in cis cyclohexan-1,2-diol, trans cyclohexan-1,3-diol and cis cyclohexan-1,4-diol, and if the relaxation rates are identical ($T_{2A}^{-1} = T_{2B}^{-1} = T_2^{-1}$) then the above equation simplifies to;

$$1/_{2\ \mathrm{obs}} = 1/T_2 + \tau/8\ \omega_A - \omega_B\ )^2 \qquad \text{equation 4}$$

However, it has been claimed (2) that this classical theory fails to describe the fast exchange behaviour of averaged multiplets, even in loosely coupled systems. A quantum correction term must, in fact, be added to equation (4) which becomes;

$$1/T_{2\ obs} = 1/T_2 + \tau/8\ J^2\ [\ 1 + 1/1 + \sigma\omega^2\tau^2/4\ ] \qquad \text{equation 5}$$

J represents the coupling constant and ω the chemical shift difference between the coupled nuclei, in rad s^{-1}.

The implication of this modification is that the conditions of kinetic averaging for chemical shifts and for coupling constants need not necessarily be the same. These considerations are part way to explaining the differences in the coupled spectra. For cis cyclohexan-1,3-diol and trans cyclohexan-1,4-diol, the predominance of the diequatorial conformations over the diaxial will result in only one coupling constant being observed irrespective of whether the coupling constant is averaged or not. The ax/eq, eq/ax degenerate conformations all have an effective rate of interconversion that is twice that of cyclohexanol and also that of trans cyclohexan-1,2-diol (dieq-diax). Here lies the important difference and it seems most likely that the explanation depends on this.

In DMSO solution, the conformations for the configurational isomers of the cyclohexandiols can be summarized as below (table XXVII).

TABLE XXVII

CYCLOHEXANDIOL	CONFORMATIONS
trans 1,2	diaxial/diequatorial (comparable amounts)
cis 1,2	axial/equatorial equatorial/axial (degenerate)
trans 1,3	axial/equatorial equatorial/axial (degenerate)
cis 1,3	diequatorial
trans 1,4	diequatorial
cis 1,4	axial/equatorial equatorial/axial (degenerate)

Clearly it can be seen that the effect of DMSO as the solvent is to shift the equilibrium in favour of the equatorial conformations.

^{13}C NMR CHEMICAL SHIFTS OF CYCLOHEXANDIOLS

As discussed under the effects of solvents, the ^{13}C nmr shifts for the conformationally rigid 4-tert.butyl-cyclohexanols can be used to derive a calculated shift for a pure axial and pure equatorial cyclohexanol. However, errors were shown to be present in the calculation. Similarly, shifts can be calculated for the cyclohexandiol system by the addition of the shielding effect of an axial or equatorial hydroxyl group. A similar set of calculations was carried out by Perlin and Koch (29), but the solvents used were inconsistent and so the results are erroneous and cannot be compared.

From the solvent effect study, the calculated shifs for an axial and equatorial cyclohexanol in $CDCl_3$ were shown to be;

TABLE XXVIII

	CHEMICAL SHIFT (ppm)					
	C_1	C_2	C_3	C_4	C_5	C_6
CYCLOHEXANOL (ax OH)	66.09	33.12	20.29	25.81	20.29	33.12
CYCLOHEXANOL (eq OH)	71.43	35.83	25.0	26.66	25.00	35.83

The shielding effects for axial and equatorial hydroxyl groups were shown to be;

TABLE XXIX

	SHIELDING EFFECT (ppm)					
	C_1 (α)	C_2 (β)	C_3 (γ)	C_4 (δ)	C_5 (γ)	C_6 (β)
AXIAL OH SHIELDING	39.09	6.12	-6.71	-1.19	-6.71	6.12
EQUATORIAL OH SHIELDING	44.43	8.83	-2.00	-0.34	-2.00	8.83

CALCULATION OF CYCLOHEXANDIOL SHIFTS

(i) cis cyclohexan-1,2-diol

The conformations are degenerate (ax/eq = eq/ax). Neglecting the internal hydrogen bond, the shifts of each carbon atom can be calculated;

Shift = axial cyclohexanol shifts + shielding effects of equatorial hydroxyl at C_2 (table XXX).

TABLE XXX

CALCULATED SHIFTS (ppm)

C_1	C_2	C_3	C_4	C_5	C_6
66.09	33.12	20.29	25.81	20.29	33.12
8.83	44.43	8.83	-2.00	-0.34	-2.00
74.92	77.55	29.12	23.81	19.95	31.12

Figure 3.21 shows cis cyclohexan-1,2-diol as a planar molecule, since each alternative chair conformation must be present in 50 % population, then kinetic averaging will occur along the C_2 symmetry axis (note that the symmetry axis is a "pseudo symmetry axis" since it only occurs because the molecule is in a dynamic eqilibrium)

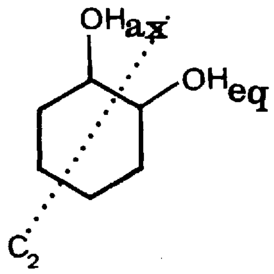


fig.3.21

then, C_1 and C_2 = (74.92 + 77.55)/2 = 76.24 ppm

C_3 and C_6 = (29.12 + 31.12)/2 = 30.12 ppm

C_5 and C_4 = (23.81 + 19.95)/2 = 21.88 ppm

Hence the calculated spectrum for cis cyclohexan-1,2-diol consists of three lines ;

C_2/C_1 = 76.24 ppm

C_6/C_3 = 30.12 ppm

C_4/C_5 = 21.88 ppm

(ii) cis cyclohexan -1,4-diol

Similarly, in this isomer the ax/eq and eq/ax conformations are degenerate. The chemical shifts can be calculated from:

Shift = axial cyclohexanol shifts + shielding effects of equatorial hydroxyl at C_4 (table XXXI).

TABLE XXXI

CALCULATED SHIFTS (ppm)

C_1	C_2	C_3	C_4	C_5	C_6
66.09	33.12	20.29	25.81	20.29	33.12
-0.34	-2.00	8.83	44.43	8.83	-2.00
65.75	31.12	29.12	70.24	29.12	31.12

The chemical shift averaging will occur along the pseudo C_2 rotation axis (fig. 3.22).

$C_1 = C_4 = (65.75 + 70.24)/2 = 68.00$ ppm

$C_2 = C_3 = (31.12 + 29.12)/2 = 30.12$ ppm

$C_5 = C_6 = (29.12 + 31.12)/2 = 30.12$ ppm

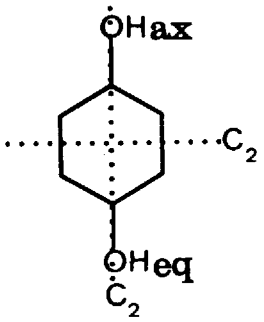


fig.3.22

Hence, $C_2/C_3 = C_5/C_6$, and the spectrum consists of only two lines; at 68.00 ppm and 30.12 ppm.

(iii) trans cyclohexan-1,3-diol

The conformations are degenerate and the chemical shifts are given by;

Shift = axial cyclohexanol shifts + shielding effects of equatorial hydroxyl at C_3 (table XXII).

TABLE XXXII

CALCULATED SHIFTS (ppm)

C_1	C_2	C_3	C_4	C_5	C_6
66.09	33.12	20.29	25.81	20.29	33.12
-2.00	8.83	44.43	8.83	-2.00	-0.34
64.09	41.95	64.72	34.64	18.29	32.78

Figure 3.23 shows the position of the pseudo C_2 rotation axis, about which the shifts will be averaged.

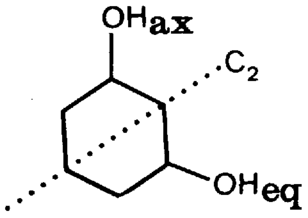


fig.3.23

$C_1 = C_3 = (64.09 + 64.72)/2 = 64.41$ ppm

$C_6 = C_4 = (34.64 + 32.78)/2 = 33.71$ ppm

$C_5 = 18.29$ ppm

$C_2 = 41.95$ ppm

The calculated spectrum of trans cyclohexan-1,3-diol therefore possesses four lines at the above chemical shifts.

(iv) trans cyclohexan-1,4-diol

The conformation may be either diequatorial or diaxial with respect to the hydroxyl groups.

DIEQUATORIAL CONFORMATION

The diequatorial conformation chemical shifts may be calculated from:

Shift = equatorial cyclohexanol shifts + shielding effects of an equatorial hydroxyl at C_4 (table XXXIII).

TABLE XXIII

CALCULATED SHIFTS (ppm)

C_1	C_2	C_3	C_4	C_5	C_6
71.43	35.83	25.00	26.66	25.00	35.83
-0.34	-2.00	8.83	44.43	8.83	-2.00
71.09	33.83	33.83	71.09	33.83	33.83

By symmetry, the conformer possesses two C_2 axes at right angles (fig. 3.24).

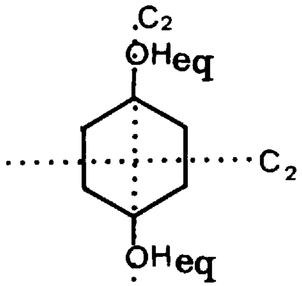


fig.3.24

therefore; $C_1 = C_4 = 71.09$ ppm

$C_2 = C_3 = C_5 = C_6 = 33.83$ ppm

The spectrum therefore consists of two lines at the above chemical shifts.

DIAXIAL CONFORMATION

Shift = shifts of axial cyclohexanol + shielding effects of axial hydroxyl at C_4 (table XXXIV).

TABLE XXXIV

CALCULATED SHIFTS (ppm)

C_1	C_2	C_3	C_4	C_5	C_6
66.09	33.12	20.29	25.81	20.29	33.12
-1.19	-6.71	6.12	39.09	26.41	26.41
64.90	26.41	26.41	64.90	26.41	26.41

Similarly, by symmetry, the calculated spectrum has two lines:

$C_1 = C_4 = 64.90$ ppm

$C_2 = C_3 = C_5 = C_6 = 26.41$ ppm

(v) cis cyclohexan-1,3-diol

The conformations may be either diequatorial or diaxial with respect to the hydroxyl group.

DIEQUATORIAL CONFORMATION

Shift = shifts of equatorial cyclohexanol + shielding effects of equatorial hydroxyl at C_3 (fig.XXXV).

TABLE XXXV

CALCULATED SHIFTS (ppm)

C_1	C_2	C_3	C_4	C_5	C_6
71.43	35.83	25.00	26.66	25.00	35.83
-2.00	8.83	44.43	8.83	-2.00	-0.34
69.43	44.66	69.43	35.49	23.00	35.49

By symmetry, the conformer possesses a C_2 rotation axis (fig.3.25).

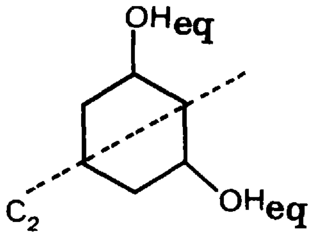


fig. 3.25

therefore; $C_1 = C_3$

$C_4 = C_6$

The calculated spectrum therefore has four lines:

$C_1 = C_3 = 69.43$ ppm

$C_2 = 44.66$ ppm

$C_4 = C_6 = 35.49$ ppm

$C_5 = 23.00$ ppm

DIAXIAL CONFORMATION

Shift = shifts of axial cyclohexanol + shielding effects of axial hydroxyl at C_3 (table XXVI).

TABLE XXVI

CALCULATED SHIFTS (ppm)

C_1	C_2	C_3	C_4	C_5	C_6
66.09	33.12	20.29	25.81	20.29	33.12
-6.71	-6.12	39.09	6.12	-6.71	-1.19
59.38	39.24	59.38	31.93	13.58	31.93

Similarly, by symmetry, $C_1 = C_3$ and $C_4 = C_6$.

The calculated spectrum therefore has four lines:

$C_1 = C_3 = 59.38$ ppm

$C_2 = 39.24$ ppm

$C_4 = C_6 = 31.93$ ppm

$C_5 = 13.58$ ppm

(vi) trans cyclohexan-1,2-diol

The conformation can be either diequatorial or diaxial with respect to the hydroxyl group.

DIEQUATORIAL

Shift = equatorial cyclohexanol shifts + shielding effects of an equatorial hydroxyl at C_2 (table XXXVII).

TABLE XXXVII

CALCULATED SHIFTS (ppm)

C_1	C_2	C_3	C_4	C_5	C_6
71.43	35.83	25.00	26.66	25.00	35.83
8.83	44.43	8.83	-2.00	-0.34	-2.00
80.26	80.26	33.83	24.66	24.66	33.83

The conformer possesses a C_2 symmetry axis (fig.3.26).

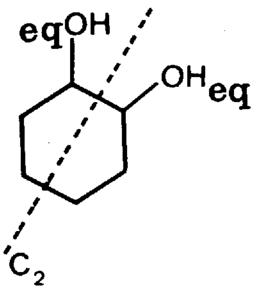


fig.3.26

therefore; $C_1 = C_2 = 80.26$ ppm

$C_3 = C_6 = 33.83$ ppm

$C_4 = C_5 = 24.66$ ppm

DIAXIAL CONFORMATION

Shift = axial cyclohexanol shifts + effects of shielding of an axial hydroxyl at C_2 (table XXXVIII).

TABLE XXXVIII

CALCULATED SHIFTS (ppm)

C_1	C_2	C_3	C_4	C_5	C_6
66.09	33.12	20.29	25.81	20.29	33.12
6.12	39.09	6.12	-6.71	-1.19	-6.71
72.21	72.21	26.41	19.10	19.10	26.41

Similarly, by symmetry,

$C_1 = C_2 = 72.21$ ppm

$C_3 = C_6 = 26.41$ ppm

$C_4 = C_5 = 19.10$

The calculated shifts for all the cyclohexandiols are tabulated below (Table XXXIX).

As a possible means of conformational analysis, the decoupled ^{13}C nmr spectra of the cyclohexandiols were measured in $CDCl_3$ solution at 0.2 M concentration. The conditions of study were maintained as in the solvent effect study. The ^{13}C nmr shifts were assigned to their respective carbon atoms by reference to the literature (32) or in cases of doubt by off- resonance spectra. Table XL lists the measured ^{13}C nmr shifts for the cyclohexandiols.

TABLE XXXIX

CALCULATED SHIFTS (ppm)

CYCLOHEXANDIOL		C_1	C_2	C_3	C_4	C_5	C_6
trans 1,2	(diax)	72.21	72.21	26.41	19.10	19.10	26.41
	(dieq)	80.26	80.26	33.83	24.66	24.66	33.83
cis 1,2		76.24	76.24	30.12	21.88	21.88	30.12
trans 1,3		64.41	41.95	64.41	33.71	18.29	33.71
cis 1,3	(diax)	59.38	39.24	59.38	31.93	13.58	31.93
	(dieq)	69.43	44.66	69.43	35.49	23.00	35.49
trans 1,4	(diax)	64.90	26.41	26.41	64.90	26.41	26.41
	(dieq)	71.09	33.83	33.83	71.09	33.83	33.83
cis 1,4		68.00	30.12	30.12	68.00	30.12	30.12

TABLE XL

CYCLOHEXANDIOL	C1	C2	C3	C4	C5	C6
	OBSERVED SHIFTS (ppm)					
trans 1,2	75.89	75.89	32.98	24.44	24.44	32.98
cis 1,2	70.71	70.71	29.96	21.49	21.49	29.96
trans 1,3	67.01	42.09	67.01	34.00	18.95	34.00
cis 1,3	68.57*	41.95*	68.47*	33.96	18.15	33.96
trans 1,4	69.71	32.91	32.91	69.71	32.91	32.91
cis 1,4	67.66	30.12	30.12	67.66	30.12	30.12

* The signals occur as doublets of unequal intensity, but with a very small difference in chemical shift.

Comparison of the observed shifts and the calculated shifts for the various conformational possibilities shows that serious discrepancies do occur. In cyclohexanol itself, it was shown that only the alpha carbon can be used for conformational analysis. In the case of the cyclohexandiols, the alpha carbon is probably the least accurate.

1. cis cyclohexan-1,4-diol

The best correlation between observed and calculated results occurs for cis cyclohexan-1,4-diol. For the C_1/C_4 shifts the difference between observed and calculated results is 0.29 ppm, but is not within the range of experimental error (estimated experimental error is 0.02 ppm). However, for $C_2/C_3/C_5/C_6$, the observed result is identical with the calculated result (30.12 ppm). The cis and trans isomers of cyclohexan-1,4-diol have the hydroxyl groups furthest removed, ie. they are delta to each other and obviously it is in these configurational isomers that the hydroxyl groups would be expected to have minimum effect on each other. The observed to calculated correlation does however show that the ax/eq and eq/ax conformations are degenerate and that the method of averaging the chemical shifts is valid.

2. trans cyclohexan-1,4-diol

In trans cyclohexan-1,4-diol, (expected to be > 98 % diequatorial), the difference in observed and calculated results is 0.92 ppm. The errors therefore even in the 1,4 configurational isomers are significant and presumably arise due to the reasons outlined for cyclohexanol (above). Although a quantitative conformational analysis of these compounds is probably not valid, qualitatively, trans cyclohexan-1,4-diol corresponds well to a conformation which is almost exclusively diequatorial. If the diaxial conformer were to be present in any significant population, there would be an upfield shift toward the calculated diaxial shifts which does not occur.

3. trans cyclohexan-1,3-diol

Trans cyclohexan-1,3-diol must have the axial/equatorial degenerate conformations. Comparison of observed and calculated results for C_1/C_3 chemical shifts (i.e. the alpha carbons) shows that there is an appreciable difference of 2.60 ppm. The observed chemical shift is shifted upfield from the calculated result, which is suggestive of an enhanced diaxial interaction (fig 3.27).

fig. 3.27

The 1-3 diaxial interaction in cyclohexanol bearing an axial hydroxyl group is simply between the hydroxyl group and an axial hydrogen on a carbon which bears no other substituents apart from hydrogen. In trans cyclohexan-1,3-diol, the axial hydrogen on C_3 is attached to a carbon which also bears an equatorial hydroxyl group. Consequently, this hydrogen experiences deshielding. This effect is considerable and can be seen from the chemical shift of the alpha protons of all the above alchols (see ^1H nmr spectra). The change in electron density around the axial proton must cause conformational changes in the rotamer equilibria of the axial hydroxyl group (fig.3.28).

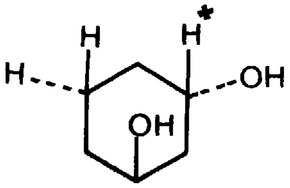


fig.3.28

The steric effect of the 1-3 diaxial interactions is therefore changed from that in an axial cyclohexanol. The Van der Waal repulsions of the proton on C_5 cannot be expected to be the same as that on C_3 since the hydrogens (H and H^*) are non-equivalent and consequently a change in rotamer population is to be expected. It is difficult to say whether or not this effect will be the sole cause of the observed difference in chemical shifts of the alpha carbons of trans cyclohexan-1,3-diol but it is probably part of the explanation.

The beta carbon (C_2) of trans cyclohexan-1,3-diol has a difference between calculated and observed chemical shift of only 0.14 ppm, which in this case is downfield from the calculated results. The difference is not inconsistent with the above explanation since for C_3 the steric effect would be minimal. For the C_4/C_6 chemical shifts the difference between observed and calculated results is small (0.39 ppm) and again downfield from the calculated shift. Consequently, it could be argued that the additivity principle cannot take into account the changes of steric effects which occur on changing from the cyclohexanol system to the cyclohexandiol system. For trans cyclohexan-1,3-diol, these effects are at a mamaximum for C_1 and C_3.

4. cis cyclohexan-1,3-diol

The cis cyclohexan-1,3-diol is extremely difficult to analyze because of the uncertainty of the preferred conformation. The infrared matrix spectra show that there is an appreciable contribution from the diaxial conformation which possesses an internal hydrogen bond. Any diaxial contribution would, on the basis of the above argument, cause considerable additional steric effects between the alpha and gamma carbons which cannot be quantitatively allowed for. Hence, the C_1/C_3 chemical shifts are of little value even in a qualitative analysis of the conformations. In trans cyclohexan-1,3-diol, the beta carbon showed a good correlation with the calculated chemical shift and so, in principle, the same should hold for cis cyclohexan-1,3-diol. The difference in chemical shifts between the calculated diaxial conformation and the observed for C_2 is 2.71 ppm and that between the observed and the calculated diequatorial chemical shifts is 2.71ppm. Quantitatively, from the Eliel equation, this gives K = 1. Similarly, for C_4, K = 1.3 and for C_5, K = 1.1. Although the errors must be very large, and cannot take into account the effect of the internal hydrogen bond, the equilibrium constant probably lies within the limits of 1.0 and 1.3, representing a contribution from the diequatorial population of between 50 % and 56 %.

The most interesting feature of the spectrum of cis cyclohexan-1,3-diol is the appearance of doublets for the resonances of C_1/C_3 and C_2. For C_1/C_3, the doublet components are separated by a chemical shift of

0.2 ppm and for C_2 by 0.1 ppm. Presumably, the other two resonances are unresolved doublets.

The presence of the doublets shows that two carbons are present in a slightly different chemical environment. The shift differences between the carbons are very small, too small to be due to a conformational difference between an axial form and an equatorial form, where a large chemical shift difference is expected c.a. 10 ppm.

Figure 3.29 shows the diaxial conformations of cis cyclohexan-1,3-diol.

fig.3.29

The presence of the internal hydrogen bond causes C_1 and C_3 to become non-equivalent. However, it is usually the case that an equilibrium exists between (a) and (b) above, so that the hydrogen bond roles are alternating. The ^1H nmr spectrum of the coupling constants for the alkanediols (above) clearly show that this equilibrium is slow (fast equilibrium would result in loss of spin-spin coupling), so that the presence of an intramolecular hydrogen bond should always be detectable by a small shift difference of the alpha carbon atom. The inequality is also relayed throughout the cyclohexyl ring or the alkyl chain, but the effect diminishes the further away the carbons are from the intramolecular hydrogen bond. However, in the alkanediols, the doublets are not observed, but the lack of observation may be due to limited resolution of the nmr spectrometer. In cis cyclohexan-1,3-diol, the conformational equilibrium still exists between the diaxial and diequatorial conformations. This is evident from the fact that the carbon resonances are all averaged signals for the diaxial and diequatorial conformations. Therefore, the rate of breaking of the intramolecular hydrogen bond is dependent upon the rate of inversion of the cyclohexyl ring. Conversely, the rate of inversion of the cyclohexyl ring must be affected by the rate of breaking of the internal hydrogen bond (fig.3.30).

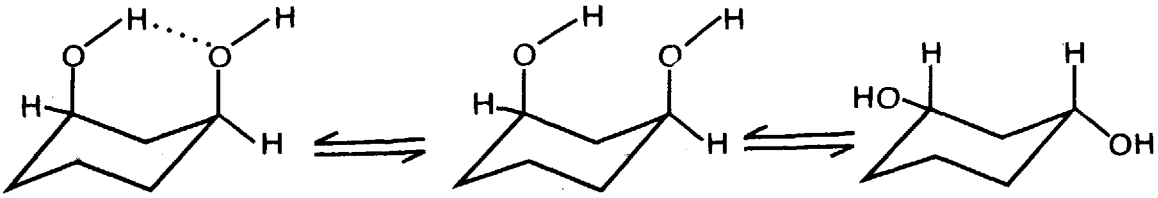


fig.3.30

This leads to the conclusion that although the internal hydrogen bond may be breaking at a rate identical to that of the rate of inversion of the cyclohexyl ring, the roles of the two hydroxyl protons cannot be interchanging as this would result in the doublet averaging to the

fig.3.31

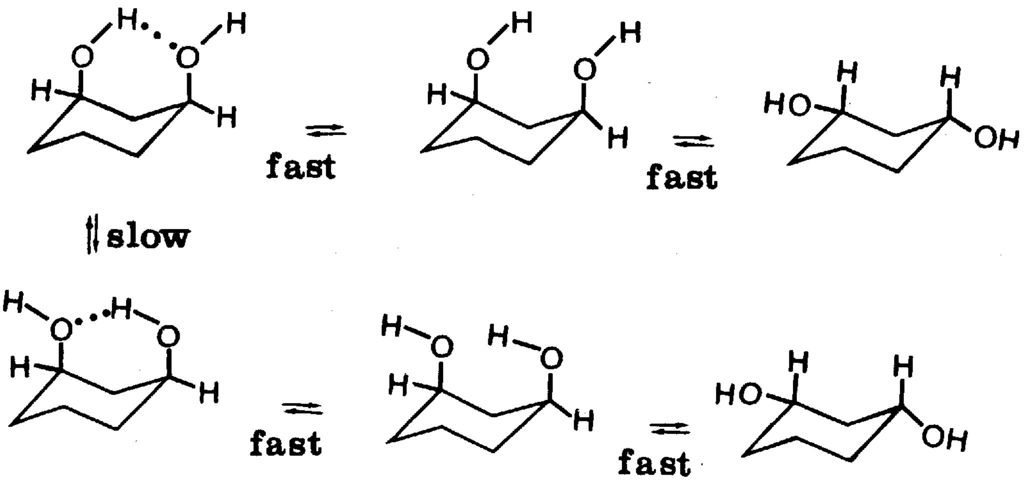
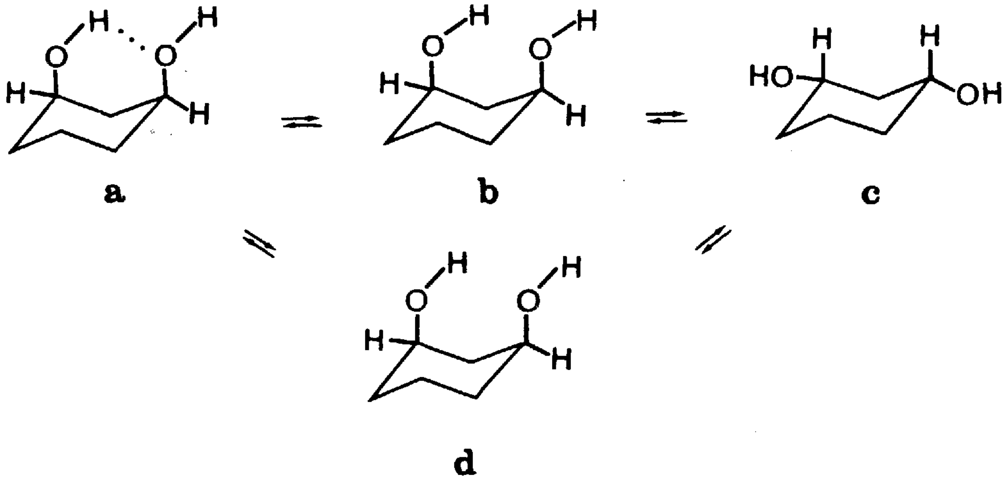


fig.3.32



singlet (fig.3.31).

In order for the doublet to be observed, the cycle from the diaxial intramolecularly hydrogen bonded conformer, to the diequatorial conformer and back to the diaxial conformer would have to occur with retention of conformation of the hydroxyl rotamers (fig.3.32).

Clearly, this is not possible, since the rotamer orientations in the equatorial conformation are substantially different from those in the internally hydrogen bonded axial conformer. It is inconceivable that any retention of rotamer orientation would occur. Consequently, hydrogen bond roles must be exchanging at a rate equal to or greater than the rate of inversion of the ring. Therefore the above conformations cannot describe the observed result and cannot be wholly correct.

Infrared solution and matrix spectra give substantial evidence that two types of internal hydrogen bonding occur in cis cyclohexan-1,3-diol, a single hydrogen bond type and a double hydrogen bond type. The possible conformations of a double hydrogen bond is shown below (fig.3.33).

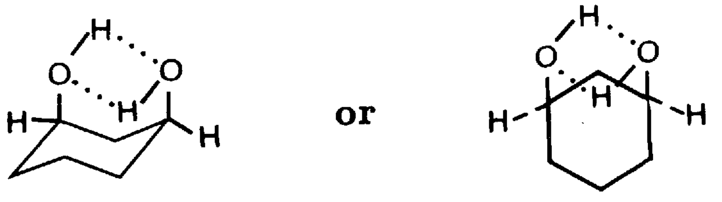


fig.3.33

If this species were in equilibrium with other conformations, then an explanation for the doublet becomes readily available.

If the lifetime of any internal hydrogen bond is dependent upon the rate of inversion of the cyclohexyl ring, then the following equilibria must be present (fig 3.34).

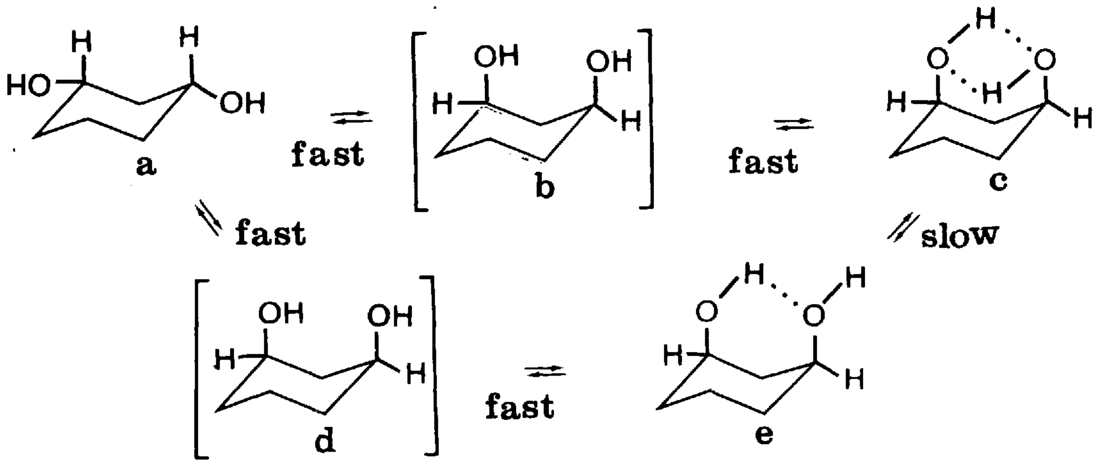


fig.3.34

The double internally hydrogen bonded species is in equilibrium with the non bonded diaxial form. The ring inversion to the diequatorial conformation and back to the diaxial conformation can result in the internal hydrogen bond forming in two ways, either doubly (and hence identical to (**c**)) or singly, to create a new conformation (**e**). The probability of reforming either type of associate will of course depend upon the relative energies of the double and single internal hydrogen bonds. If (**c**) is reformed, then no apparent change has occurred during the lifetime of the ring inversion. If (**e**) is formed, then a change has occurred during the lifetime of the ring inversion. A change that occurs during this lifetime is subject to kinetic averaging. If (**c**) is reformed the two environments are the same. However, the cyclohexyl ring may invert many times during the nmr timescale and so kinetic averaging will still occur, since the probability of reforming (**c**) on each subsequent inversion during the nmr timescale is very low. Consequently, although each signal will be averaged, the weighted average of each form (**c** and **e**) will not be the same, and will give rise to a chemical shift difference.

If the above is true, then the doublet represents the chemical shift averaging of a double hydrogen bonded diaxial conformation with the diequatorial conformation, and the singly hydrogen bonded diaxial conformation with the diequatorial conformation. Hence, on the nmr timescale (and infrared timescale) the equilibrium (if any) between (**c**) and (**e**) does not occur directly i.e. the conformational change from one type of internally hydrogen bonded conformer to the other occurs via the diequatorial form.

This explanation is entirely consistent with the observed infrared spectra in Argon matrix and in solution, and may also apply to trans cyclohexan-1,2-diol.

5. trans cyclohexan-1,2-diol

The configurational isomers of cyclohexan-1,2-diol pose rather special problems for conformational analysis. The thermodynamic considerations above show that for trans cyclohexan-1,2-diol the diequatorial conformation should be greatly preferred. However, the thermodynamic calculations do not allow for the large steric repulsions that must occur between the two equatorial hydroxyls groups. This repulsive force must in principle be greatly relieved by the formation of an intra molecular hydrogen bond (fig 3.35).

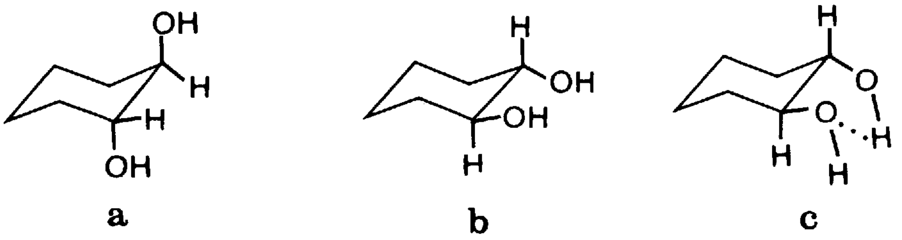


fig.3.35

For solutions in DMSO this is not possible and so the conformational equilibrium is much simplified, being solely an equilibrium between the diaxial conformation (a) and the diequatorial conformation (b) (fig.3.35). The effect of the diequatorial interaction can also be inferred from the DMSO coupling constants of trans cyclohexan-1,2-diol, from which it was noted that the coupling constant for the hydroxyl protons was considerably reduced from that of an equatorial hydroxyl in cyclohexanol. The result is quite well explained by a change in dihedral angle resulting from re-orientation of the hydroxyl groups.

The above considerations indicate that in $CDCl_3$ solution the internally hydrogen bonded diequatorial conformation should have a significant population. $CDCl_3$ causes a reduction in the total hydrogen bonding of the system, however, it appears from the infrared solution measurments that intermolecular and intramolecular hydrogen bonding are affected to different extents. Nevertheless, it would be expected that the diaxial/diequatorial equilibrium should be displaced towards the diequatorial conformation on changing from DMSO to $CDCl_3$ as the solvent.

Comparison of the observed ^{13}C nmr chemical shifts of trans cyclohexan-1,2-diol with the calculated shifts for the diaxial and diequatorial conformations shows that the observed shifts lie between the two conformations. For the two alpha carbon atoms (C_1 and C_2), large errors are likely to be present due to the steric and dipole interactions which are not allowed for in the calculations (as with the thermodynamic calculations). Therefore, the calculated shifts of these carbons are far too unreliable to be used for a conformational analysis. The carbons most likely to be of value should be the ones furthest away from the hydroxyl groups, i.e. C_4 and C_5. Applying the Eliel euation to these shifts:

$$K = (24.4 - 19.10)/(24.66 - 24.44) = 24 \ (96\ \%\ \text{diequatorial})$$

The calculation based on C_3/C_6 gives:

$$K = (32.98 - 26.41)/(33.83 - 32.98) = 8 \ (88\ \%\ \text{diequatorial})$$

The values calculated on C_3/C_6 are rather dubious due to the involvement of the 1 - 3 diaxial interaction experienced by both hydroxyls in the diaxial conformation (fig.3.36).

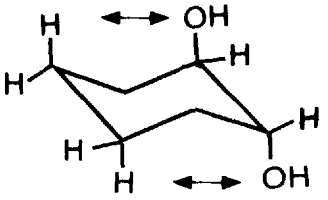


fig.3.36

The results do however indicate that the diequaorial conformation is greatly preferred, in contrast with the results in DMSO solution.

6. cis cyclohexan-1,2-diol

Like trans cyclohexan-1,2-diol, dipole and steric repulsions are expected between the axial and equatorial hydroxyls. The chair conformations are of course degenerate. However, the infrared data shows that an intramolecular hydrogen bond exists. With a similar argument to that pertaining to trans cyclohexan-1,2-diol, the shifts of C_1 and C_2 (the alpha carbon atoms) are unreliable. This is readily seen by comparison of the observed and calculated results, where almost a 6 ppm difference occurs. Similarly, the most reliable results should occur for

C_4/C_5, and here the observed and calculated results differ by only 0.39 ppm and for C_6/C_3 the difference is only 0.16 ppm. In light of these results it can be concluded that the equilibrium constants calculated for trans cyclohexan-1,2-diol are realistic and probably better correlate to the C_3/C_5 equilibrium constant (88 % diequatorial) than to C_4/C_5 (96 % diequatorial). Table XLI lists the inferred conformations as deduced from the above measurments in $CDCl_3$.

TABLE XLI

CYCLOHEXANDIOL	PREFERRED CONFORMATIONS
trans 1,2	diaxial / diequatorial (88 %)
cis 1,2	axial / equatorial (degenerate)
trans 1,3	axial / equatorial (degenerate)
cis 1,3	diaxial (two internal H bonds) / diequatorial
trans 1,4	diequatorial
cis 1,4	axial / equatorial (degenerate)

The qualitative preferences deduced from the ^{13}C nmr chemical shifts give at least a qualitative analysis, although large errors may be present, particularly when 1-3 diaxial interactions are involved. The results show that the thermodynamic criteria hold well provided no additional forces are present. Trans cyclohexan-1,4-diol is a good example of a system where no additional forces are present and the preferred conformation in $CDCl_3$ is in accordance with the expected greater than 98 % diequatorial conformation.

The ax/eq and ex/aq conformations of cis cyclohexan-1,4-diol, trans cyclohexan-1,3-diol and cis cyclohexan-1,2-diol are obviously the most easy to analyze, since their conformations are fixed and it is probably true to say that the best assessment of the accuracy of this method comes from the experimental work on these compounds. Trans cyclohexan-1,2-diol and cis cyclohexan-1,3-diol are the most interesting from the conformational point of view, since the stability of the internal hydrogen bond is the dominating factor in determining the position of equilibrium. Since the conformation of these compounds is expected to show a great dependency upon the solvent, as a comparison, the above measurments were carried out in DMSO solution for cis cyclohexan-1,3-diol. Table XLII lists the measured ^{13}C nmr shifts for the above compound under the same conditions detailed above.

TABLE XLII

CALCULATED CHEMICAL SHIFTS IN DMSO (ppm)

CYCLOHEXANOL	C_1	C_2	C_3	C_4	C_5	C_6
equatorial cyclohexanol	69.30	35.57	24.51	25.51	24.51	35.57
axial cyclohexanol	63.45	32.82	19.85	26.20	19.85	32.82

TABLE XLIII

SHIELDING EFFECTS OF HYDROXYL GROUP IN DMSO (ppm)

	α	β	γ	δ
equatorial hydroxyl	43.00	9.27	-1.79	-0.79
axial hydroxyl	37.15	6.52	-6.45	-0.10

cis cyclohexan-1,3-diol

The chemical shifts of cis cyclohexan-1,3-diol were calculated as for the solutions in $CDCl_3$. The calculated shifts in DMSO are tabulated below (table XLIV).

TABLE XLIV

CALCULATED CHEMICAL SHIFTS IN DMSO (ppm)

CYCLOHEXANDIOL	C_1	C_2	C_3	C_4	C_5	C_6
cis 1,3 (dieq)	67.51	44.84	67.51	34.78	22.72	34.78
(diax)	57.00	39.34	57.00	32.72	13.40	32.72

TABLE XLV

OBSERVED CHEMICAL SHIFTS (ppm)

CYCLOHEXANDIOL	C_1	C_2	C_3	C_4	C_5	C_6
cis 1,3	67.39	45.43	67.39	34.77	20.54	34.77

As with the chemical shift correlations in $CDCl_3$, the C_1/C_3 chemical shifts are expected to be the least accurate. The C_4/C_6 shifts correlate well with the calculated diequatorial conformation (0.01 ppm difference), whilst C_5 shows a 2.18 ppm difference with the diequatorial calculated shifts and C_2 0.59 ppm difference. The correlation with the diaxial conformation gives much larger differences (C_4/C_6 = 2.05 ppm, C_5 = 7.14 ppm, C_2 = 6.09 ppm).

Equilibrium constants (from the Eliel Equation) based on these nuclei show the diequatorial conformation to be in excess of 90 %. Contrasted with the results in $CDCl_3$, this shows the extreme effect of the change of solvent. In cyclohexanol, both $CDCl_3$ and DMSO give a similar conformational preference to the equatorial conformation, whilst in cis cyclohexan-1,3-diol, $CDCl_3$ gives a conformational preference to the diaxial conformation (or the shift to equatorial conformations is substantially reduced from that in DMSO). The difference arises from the fact that the internal hydrogen bond in cis cyclohexan-1,3-diol is little affected in $CDCl_3$, whilst in DMSO the internal hydrogen bond does not exist. The study highlights the dramatic effect that the change of solvent properties can have on the cyclohexandiol equilibria.

ALPHA HYDROGEN CHEMICAL SHIFTS

The alpha hydrogen chemical shifts were used for the determination of the solvent effect for cyclohexanol. Under the same experimental conditions, the alpha hydrogen chemical shift can be used for the conformational analysis of the cyclohexandiols. For this study, a comparison was made between the two solvent extremes i.e. DMSO and $CDCl_3$.

The chemical shifts of the alpha carbon atoms are tabulated below (table XLVI).

TABLE XLVI

CYCLOHEXANDIOL	α HYDROGEN CHEMICAL SHIFT (ppm)	
	$CDCl_3$	DMSO
trans 1,2	3.30	3.08
cis 1,2	3.75	3.42
trans 1,3	4.10	3.80
cis 1,3	3.84	3.32
trans 1,4	3.65	3.34
cis 1,4	3.77	3.46

1.DMSO SOLUTIONS

The study is analogous to that of the measurment of DMSO solution coupling constants, in that the ax/eq conformations of cis cyclohexan-1,4-diol and trans cyclohexan-1,3-diol can be taken as representing mole fractions of 0.5 for an axial hydroxyl and 0.5 for an equatorial hydroxyl. The trans cyclohexan-1,4-diol must essentially be diequatorial so that the alpha hydrogen chemical shift will represent the shift for an equatorial hydroxyl. Notice that the chemical shift of cis cyclohexan-1,3-diol is very similar to that of trans cyclohexan-1,4-diol (0.02 ppm difference). This is additional evidence for the conclusion that cis cyclohexan-1,3-diol is almost exclusively diequatorial in DMSO. In trans cyclohexan-1,3-diol, there is a deviation of 0.34ppm from the ax/eq shift of cis cyclohexan-1,4-diol. This corresponds to the difference in chemical shift between the calculated and observed C_1/C_3 ^{13}C chemical shifts trans cyclohexan-1,3-diol, which were attributed to the 1 - 3 diaxial interactions. Surpisingly however, the coupling constant of this compound in DMSO did not deviate from the expected ax/eq average (see DMSO coupling constants), which implies that the interaction does not affect the dihedral angle.

Cis cyclohexan-1,2-diol is expected to deviate greatly from the ax/eq average chemical shift, due to the dipole and steric effects between the vicinal hydroxyls. However, the shift difference between cis cyclohexan-1,2-diol and cis cyclohexan-1,4-diol is only 0.04 ppm. It appears therefore, that perturbation of the alpha chemical shift is more sensitive to the 1 -3 diaxial interaction than the vicinal interaction.

On a tentative basis, the Gutowsky averaging technique, used for the DMSO coupling constants, can be used to determine the conformational equilibrium in trans cyclohexan-1,2-diol, by determining the chemical shift for the axial hydroxyl conformation.

From the measurments of the diequatorial trans cyclohexan-1,4-diol, the chemical shift for the equatorial conformation = 3.34 ppm.

From the cis cyclohexan-1,4-diol, the averaged ax/eq chemical shift = 3.46 ppm.

$$\sigma_{obs} = \chi_{eq} \ \sigma_{eq} + \chi_{ax} \ \sigma_{ax}$$

$$3.46 = 0.5(3.34) + 0.5(\sigma_{ax})$$

$$\sigma_{ax} = 3.58 \text{ ppm}$$

Reference to the observed chemical shift for trans cyclohexan-1,2-diol, shows that the equation cannot be applied since both the equatorial chemical shift and the diaxial chemical shift are greater than the observed shift.

2. $CDCl_3$ SOLUTIONS

The comparable study in $CDCl_3$ shows a similar pattern of results to that in DMSO solution, the ax/eq conformations of cis cyclohexan-1,4-diol and cis cyclohexan-1,2-diol have very similar chemical shifts (difference = 0.02 ppm). As in the DMSO solution, trans cyclohexan-1,3-diol does not show the "expected" ax/eq average (difference = 0.33 ppm).

In contrast to DMSO solutions, the chemical shift for cis cyclohexan-1,3-diol differs considerably from that in the diequatorial trans cyclohexan-1,4-diol. In DMSO the shift difference is 0.02 ppm whilst in $CDCl_3$ the difference is 0.19 ppm. This result is a good indication that the diequatorial conformation is not the only conformation present i.e. there is probably a significant contribution from the diaxial conformation.

Similarly, as in DMSO, the conformational analysis of trans cyclohexan-1,2-diol is unsatisfactory, due to the proximity of the vicinal hydroxyl groups, and the method involving Gutowsky averaging is not applicable.

The conformational information gained from this study is tabulated below (table XLVII).

TABLE XLVII

CYCOHEXANDIOL	PREFERRED CONFORMATION	
	$CDCl_3$	DMSO
trans 1,2	*	*
cis 1,2	ax/eq	ax/eq
trans 1,3	ax/eq	ax/eq
cis 1,3	dieq/diax	dieq
trans 1,4	dieq	dieq
cis 1,4	ax/eq	ax/eq

* The conformation cannot be determined from this study.

The alpha chemical shift study is probably the least useful of all the investigatory methods undertaken. However, notably for cis cyclohexan-1,3-diol the method does identify indirectly the presence of the diaxial internal hydrogen bond.

INFRARED STUDIES OF THE HYDROXYL STRETCH BANDS

CCl_4 SOLUTION SPECTRA

In some respects the infrared solution spectra are simpler compared with the nmr spectra, in that infrared is essentially a "faster" technique. The rate of change of the dipole moment is in excess of 10^9 S^{-1} and consequently, there are very few kinetic processes which occur at a rate faster than this. For the hydroxyl stretch spectra, this means that the association phenomena, whether intermolecular or intramolecular are characterized by an observable shift in wavenumber of the hydroxyl stretch band. It is therefore possible to observe all three species, i.e. monomer, intermolecularly hydrogen bonded species and intramolecularly bonded species simultaneously.

In conformational analysis however, there are severe drawbacks. The main drawback is the fact that although there is a difference in wavenumber between an axial and equatorial substituent, the shift differences are usually too small to be resolved in solution spectra. Direct conformational analysis of a composite hydroxyl stretch band therefore usually requires band splitting techniques (28).

The infrared stretch bands of hydroxyl groups do however provide substantial information which may be used for conformational analysis. In the case of cyclic diols, the presence of an intramolecular hydrogen bond can be directly observed, in contrast with nmr techniques where its presence is usually inferred. The infrared spectra can therefore be used in conjunction with the nmr methods and the combination prove a powerful tool for conformational analysis.

The infrared spectra of the cyclohexandiols were measured in dilute

FIG.3.37

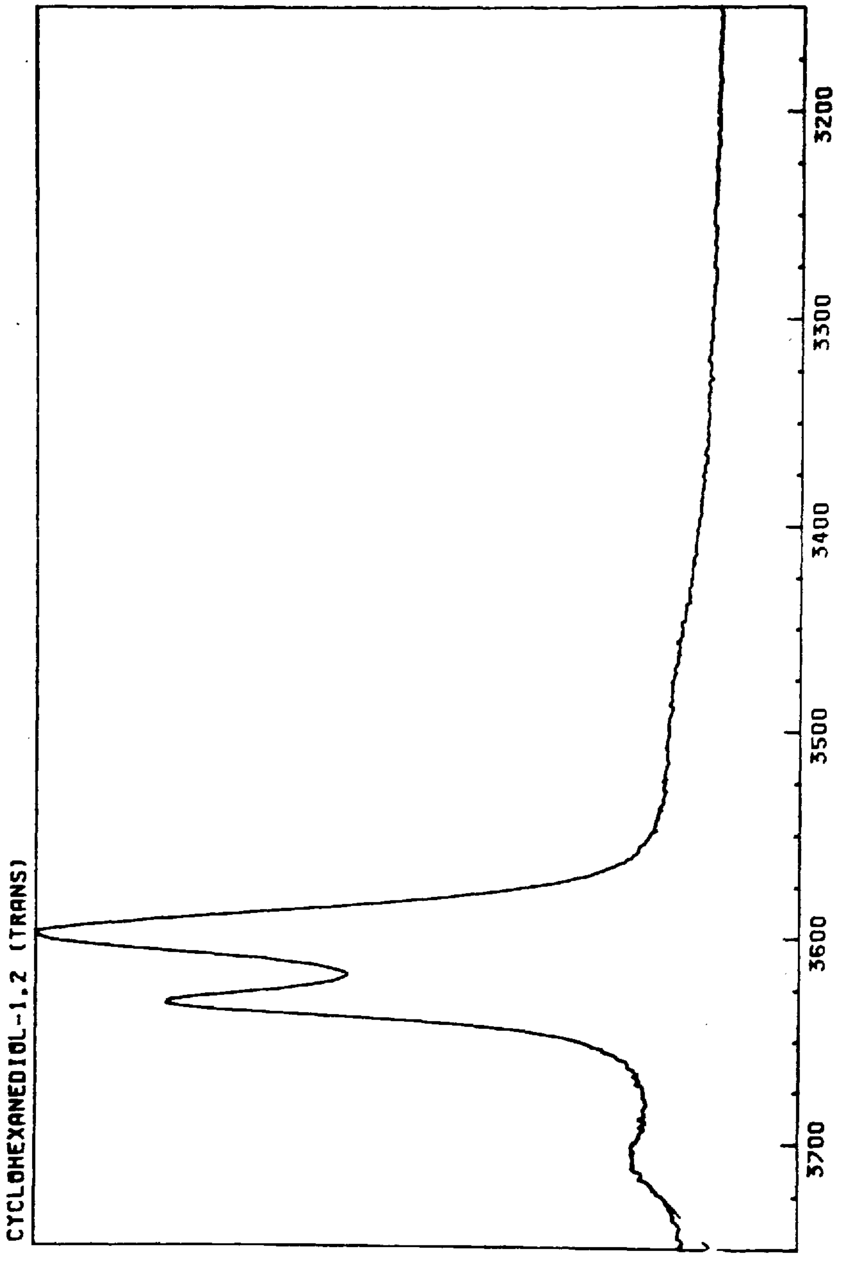


FIG. 3.38

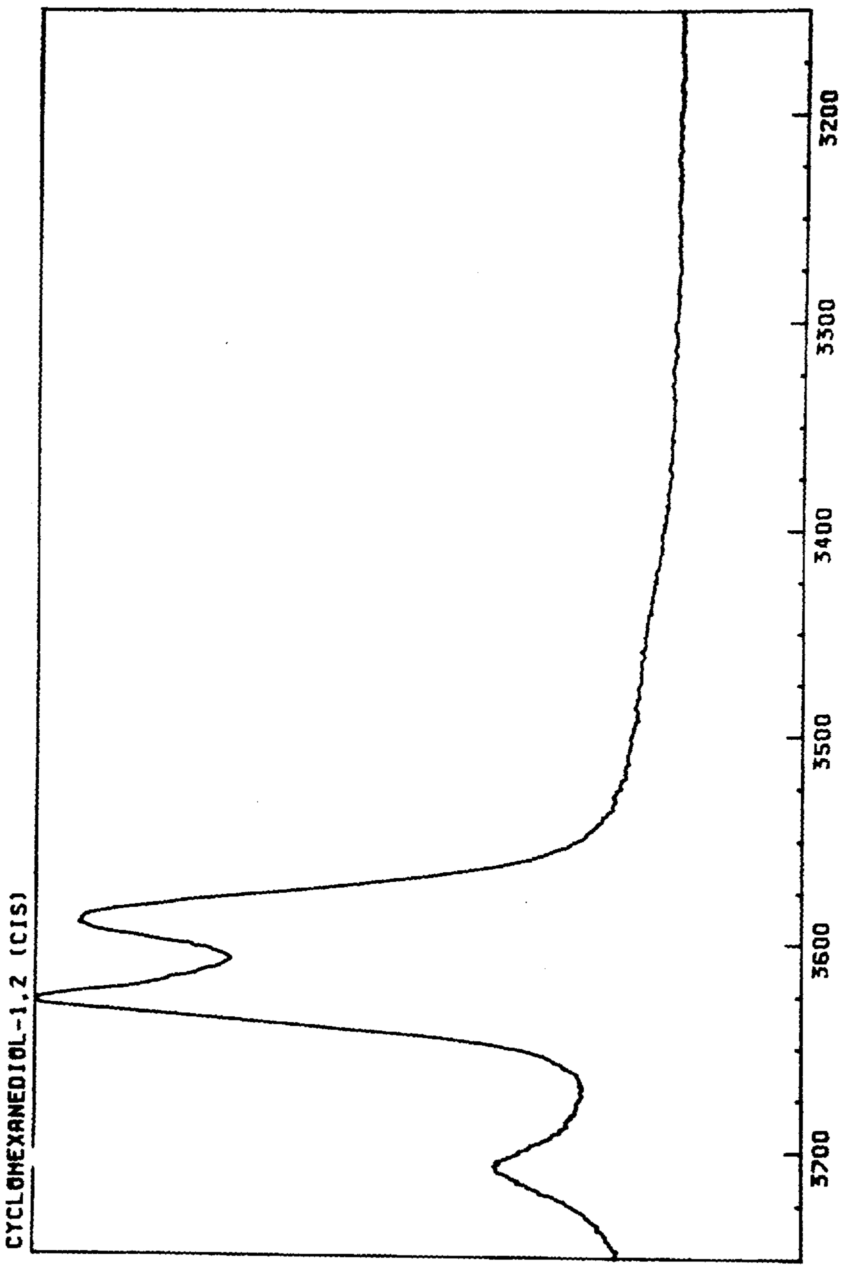


FIG.3.39

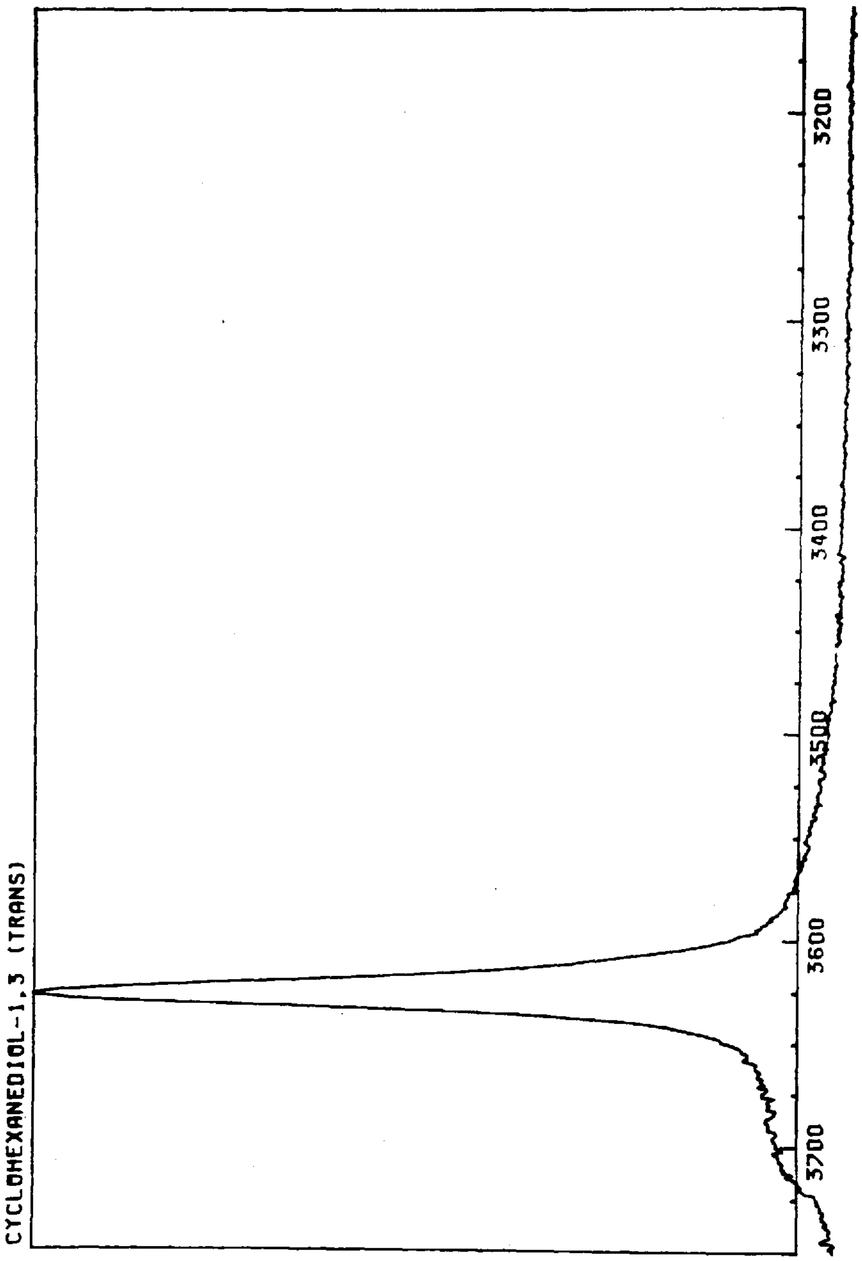


FIG.3.40

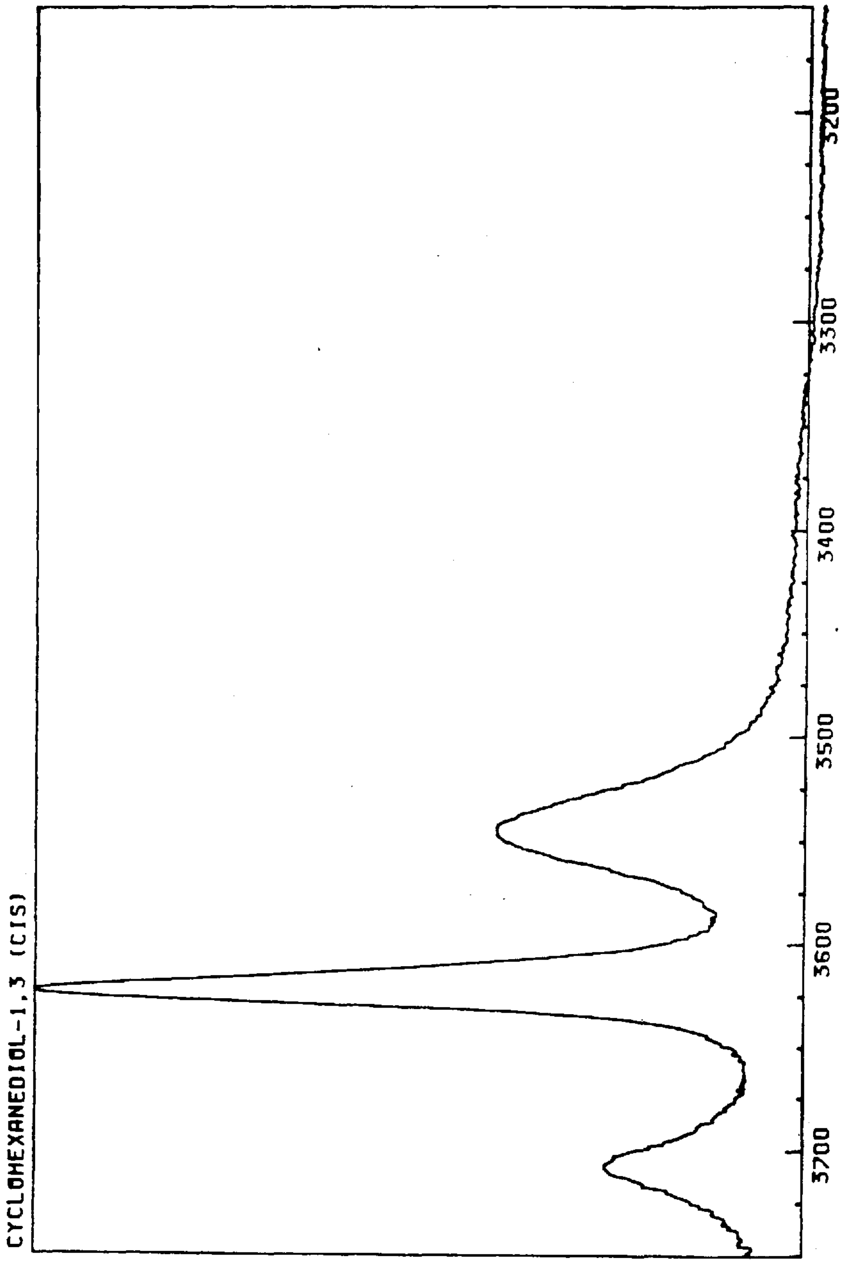
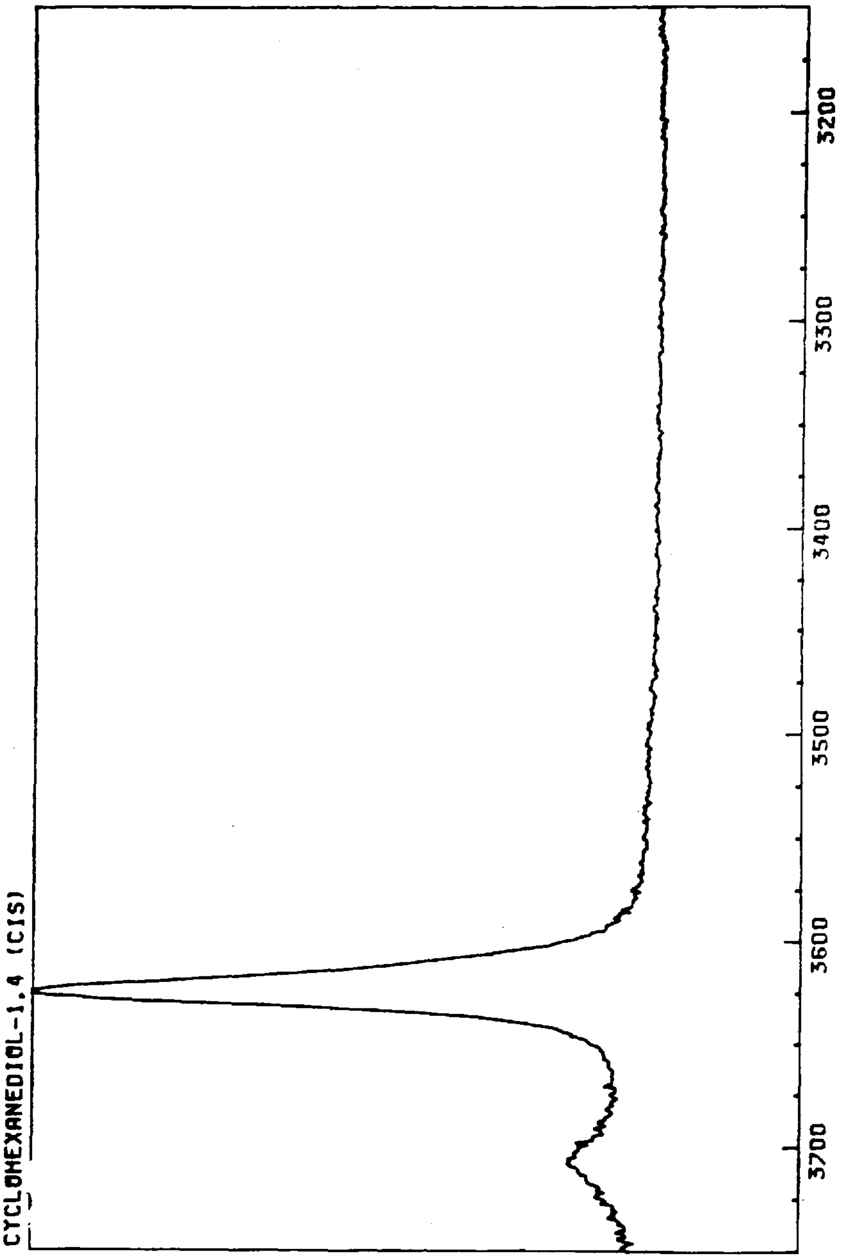


FIG. 3.41



carbontetrachloride solution at a maximum concentration of 0.004M for the configurational isomers of cyclohexan-1,2-diol. The configurational isomers of the 1,3 and 1,4 compounds are substantially less soluble in carbontetrachloride and in these cases saturated solutions were used. The spectra were measured 1) On a Perkin Elmer PE 1800 F.T. infrared spectrometer at maximum resolution of 2cm^{-1}. 2) On a Perkin Elmer PE 580 infrared spectrometer at various resolutions, corresponding to scan modes 4B, 6B and 7B (table XLVIII). All solution spectra were measured in "Infrasil" quartz 1 cm path length cells at ambient temperature. The solvents were previously dried over molecular sieves 3A (Aldrich).

TABLE XLVIII

SCAN MODE	MAXIMUM RESOLUTION cm^{-1}	RELATIVE NOISE
4B	1.7	0.8
6B	1.0	1.5
7B	0.8	3.0

The low resolution F.T. spectra are shown below (figs 3.37 to 3.41) and the wavenumbers of the hydroxyl stretch bands are tabulated in table XLIX.

Fig.3.42

trans–1,2–diol

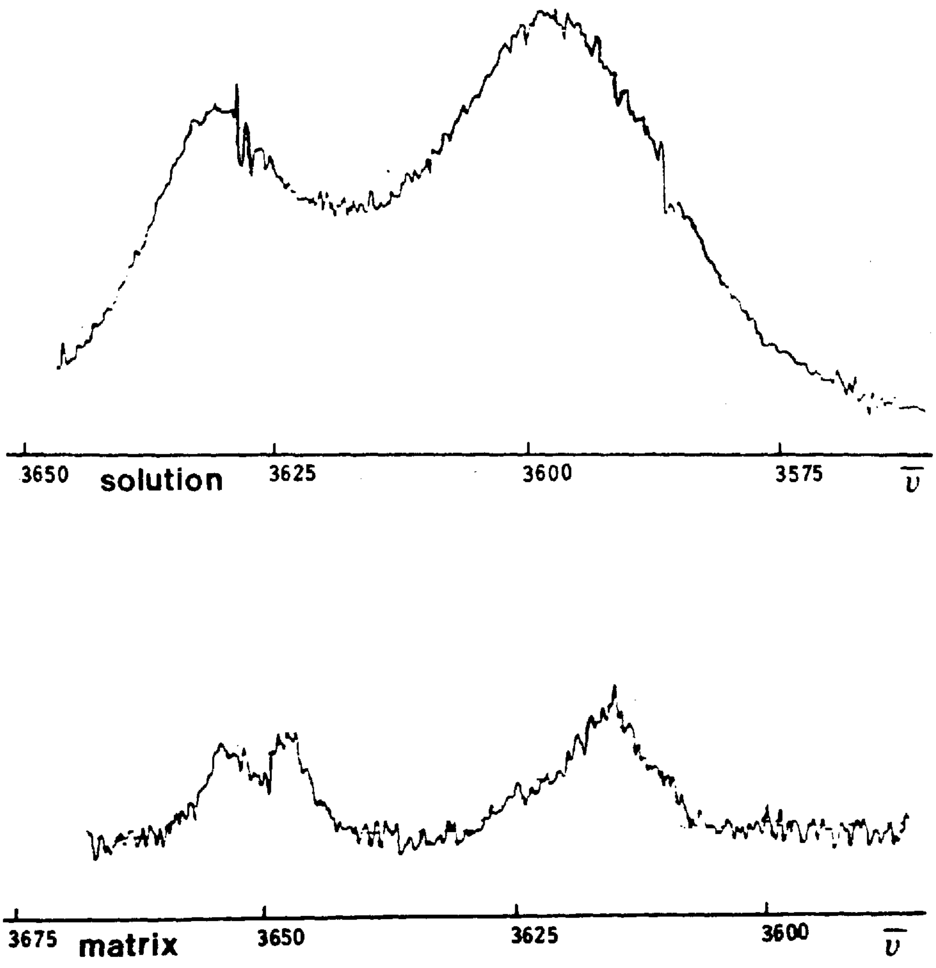


Fig.3.43

cis–1,2–diol

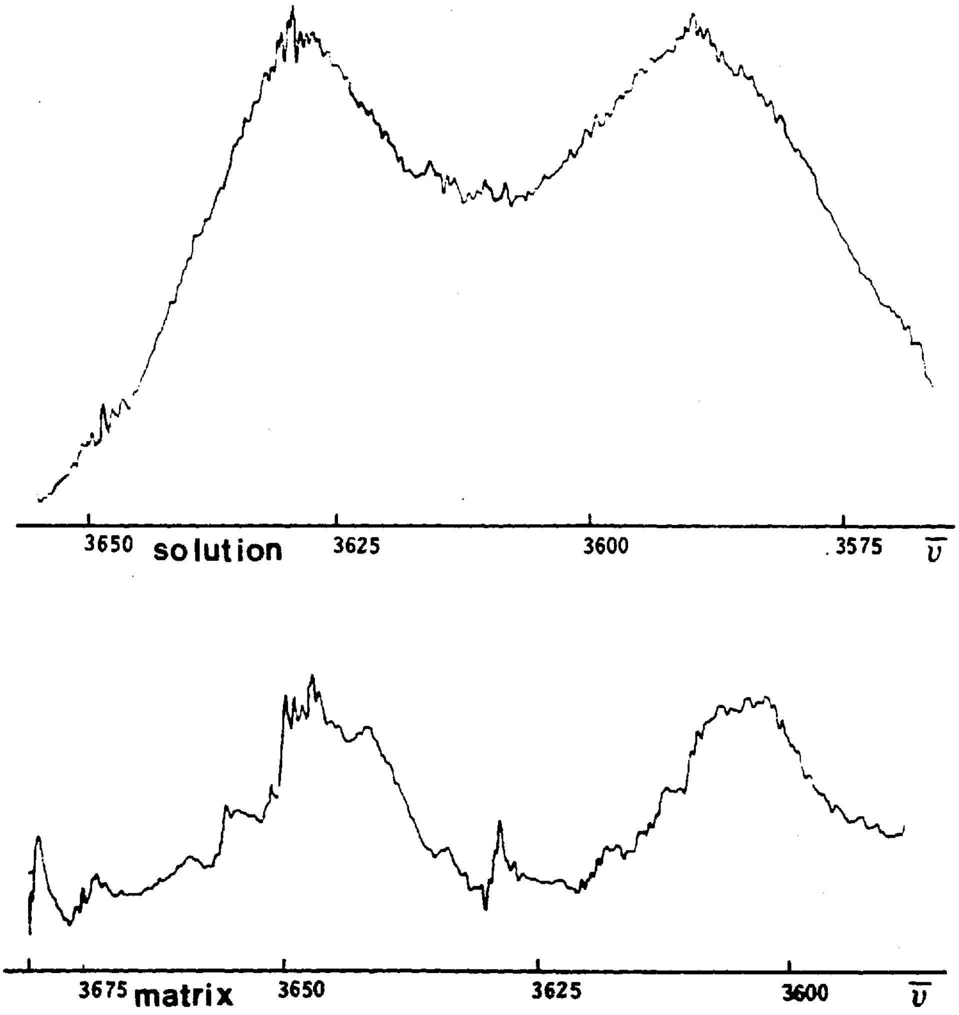


Fig.3.44

trans–1,3- diol

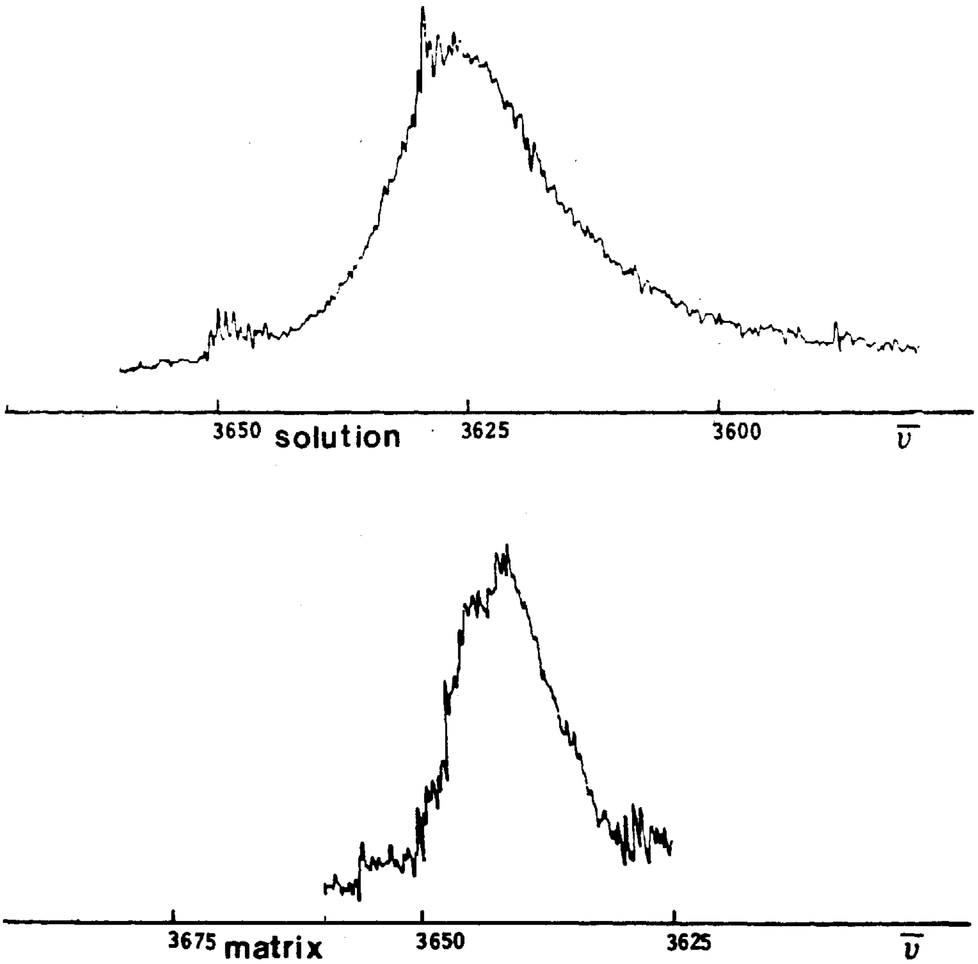


Fig.3.45

cis-1,3-diol

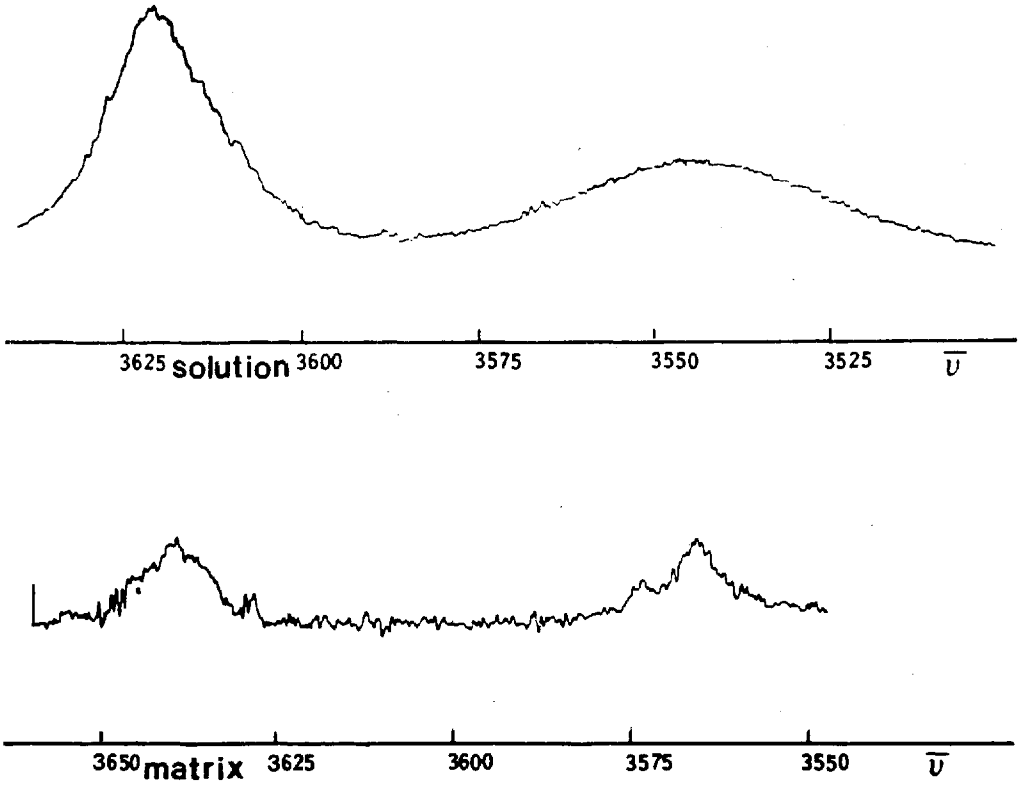


Fig.3.46

trans-1,4-diol

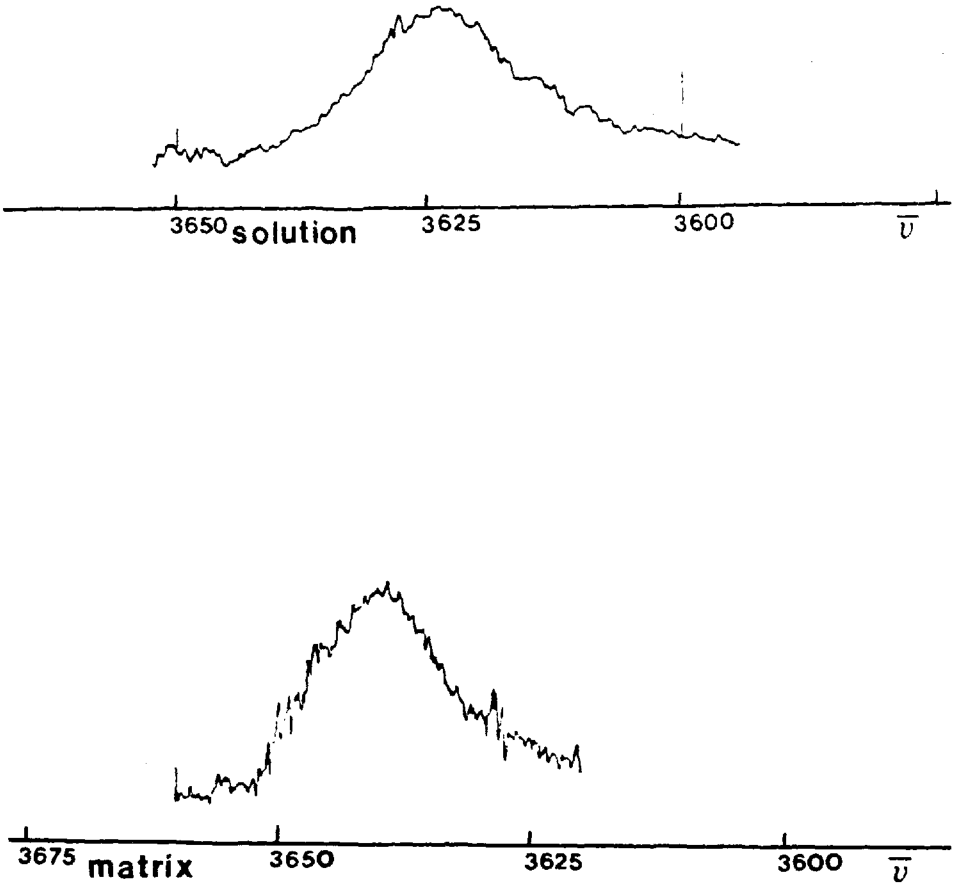


Fig.3.47

cis–1,4–diol

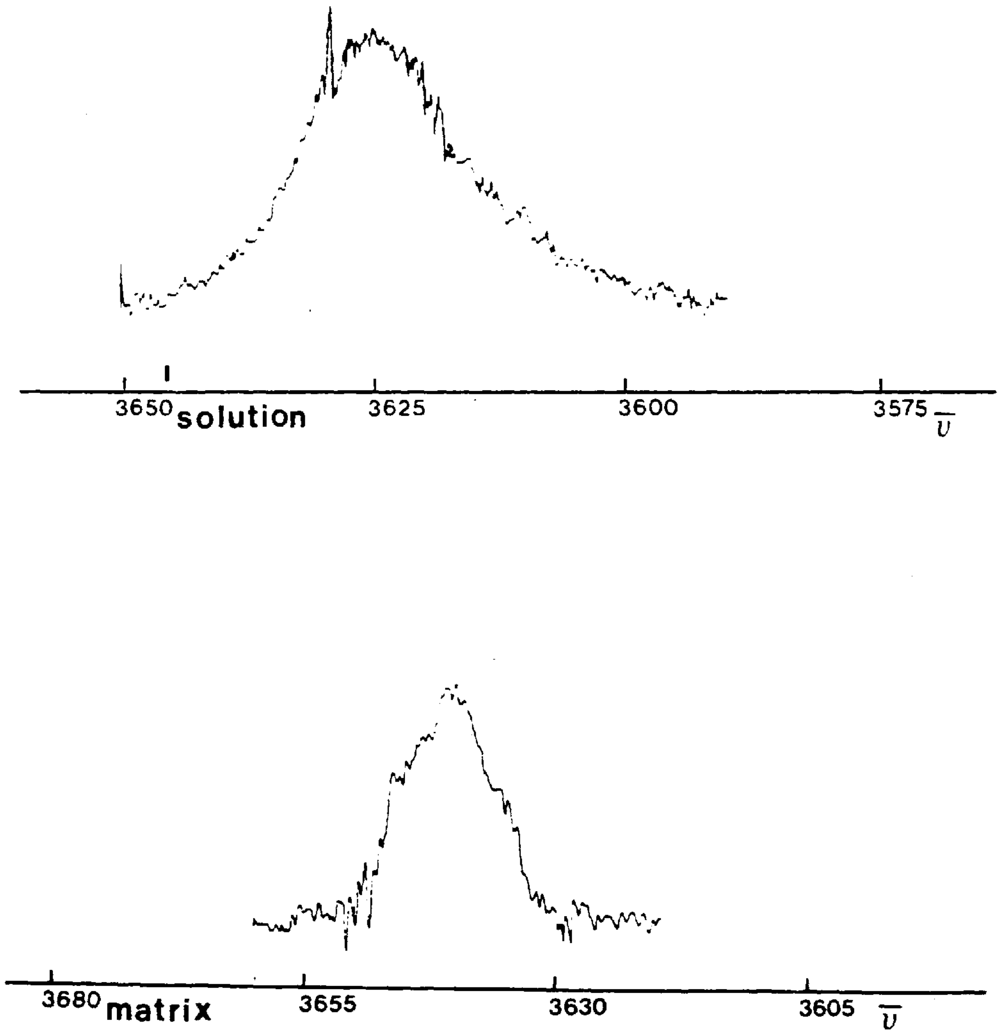


TABLE XLIX

CYCLOHEXANDIOL	FREE OH cm^{-1}	INTRA OH cm^{-1}	$\Delta\upsilon$ cm^{-1}
trans 1,2	3632	3598	34
cis 1,2	3628	3590	38
trans 1,3	3626		
cis 1,3	3623	3545	77
trans 1,4	*		
cis 1,4	3625		

Where $\Delta\upsilon$ is the difference in wavenumber of the free and intramolecular bands.

* The trans 1,4 isomer was unavailable at the time of measurment at Utrecht University, Holland.

The high resolution PE 580 spectra are shown below (figs 3.42 to 3.47) and the wavenumbers are tabulated in table L.

TABLE L

CYCLOHEXANDIOL	FREE OH cm^{-1}	INTRA OH cm^{-1}	$\Delta \nu$ cm^{-1}
trans 1,2	3631	3598	33
cis 1,2	3628	3589	39
trans 1,3	3626[1]		
cis 1,3	3622	3545	77
trans 1,4	3624		
cis 1,4	3625		

[1] Shoulder to higher wavenumber side.

The trans 1,2, cis 1,2 and cis 1,3 isomers all possess an intramolecular hydrogen bond in accordance with the above assumptions. The difference between the free OH wavenumber and the intramolecular OH wavenumber is usually taken as a measure of the strength of the intramolecular hydrogen bond (7) i.e. it is related to the enthalpy of the intramolecular hydrogen bond. Correspondingly, the cis 1,2 compound ($\Delta \nu$= 38cm^{-1}) possesses a stronger intramolecular hydrogen bond than the trans 1,2 isomer ($\Delta \nu$= 34cm^{-1}).

Conformationally, the formation of an intramolecular hydrogen bond in the trans 1,2 isomer must occur in the diequatorial conformation (fig. 3.48).

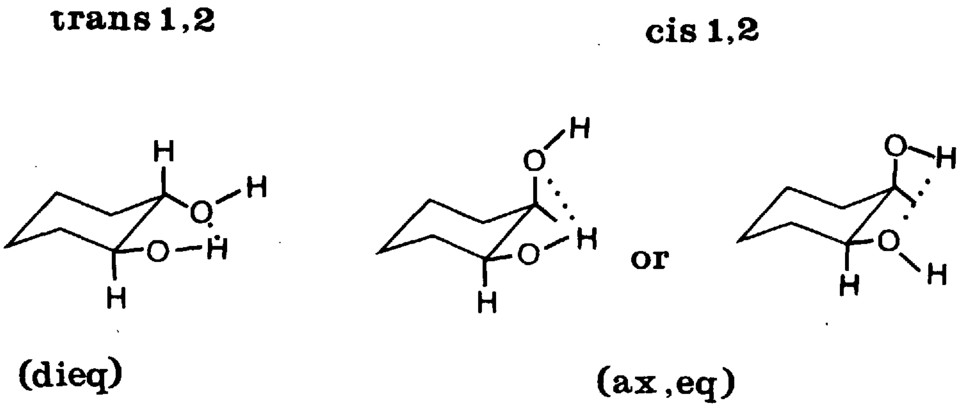


fig.3.48

In the cis 1,2 isomer, the conformation is either ax/eq or eq/ax (degenerate) (fig 3.48). Hence, in accordance with the conclusions of other workers the ax/eq or eq/ax intramolecular hydrogen bond is stronger than a diequatorial intramolecular hydrogen bond (36).

The "free" hydroxyl stretch bands of diols possessing intramolecular hydrogen bonds are a combination of the free hydroxyl bands of the non-associated forms and the "free" hydroxyl groups of the intramolecular hydrogen bond. For example, in the trans 1,2 isomer the free hydroxyl OH stretch band is probably a combination of the diaxial hydroxyls in the diaxial conformation, the equatorial hydroxyls of the non-associated diequatorial conformation and the "free" hydroxyl of the intramolecular hydrogen bond (fig. 3.49).

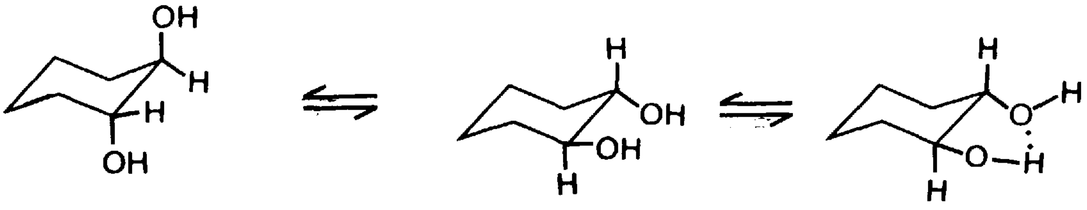
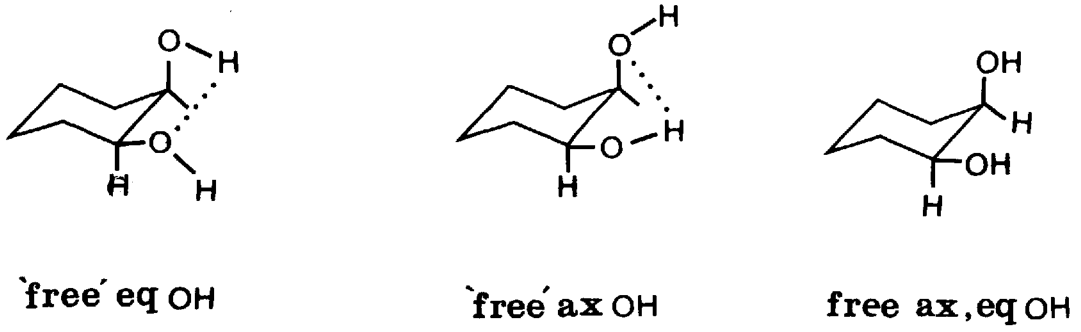


fig.3.49

Unlike the formation of the intramolecular hydrogen bond in cis cyclohexan-1,3-diol, in the diaxial conformation the non-bonded diequatorial conformation of trans cyclohexan-1,2-diol is expected to be more stable (although subject to severe steric and dipole repulsions). Hence it can be considered as being present at a significant population at equilibrium.

In cis cyclohexan-1,2-diol, the free hydroxyl band will be due to a combination of the axial and equatorial hydroxyls of the non-bonded form and either a "free" axial hydroxyl from an internal hydrogen bond and/or, a "free" equatorial hydroxyl from an internal hydrogen bond (fig. 3.50).



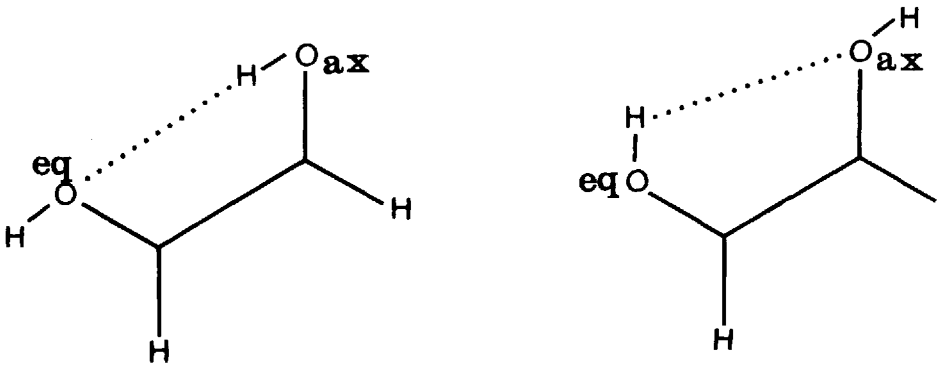
'free' eq OH

'free' ax OH

free ax,eq OH

fig.3.50

Considering the orientation of the hydroxyl groups that is required to form an internal hydrogen bond in cis cyclohexan-1,2-diol (fig 3.51);



a

b

fig.3.51

In case a, the hydrogen of the axial hydroxyl is directed toward the lone pair of electrons on the oxygen of the equatorial hydroxyl. In case b, the hydrogen of the equatorial hydroxyl is directed toward the lone pair of the axial hydroxyl. The Newman projections for the corresponding rotamers of a and b are shown below (fig.3.52).

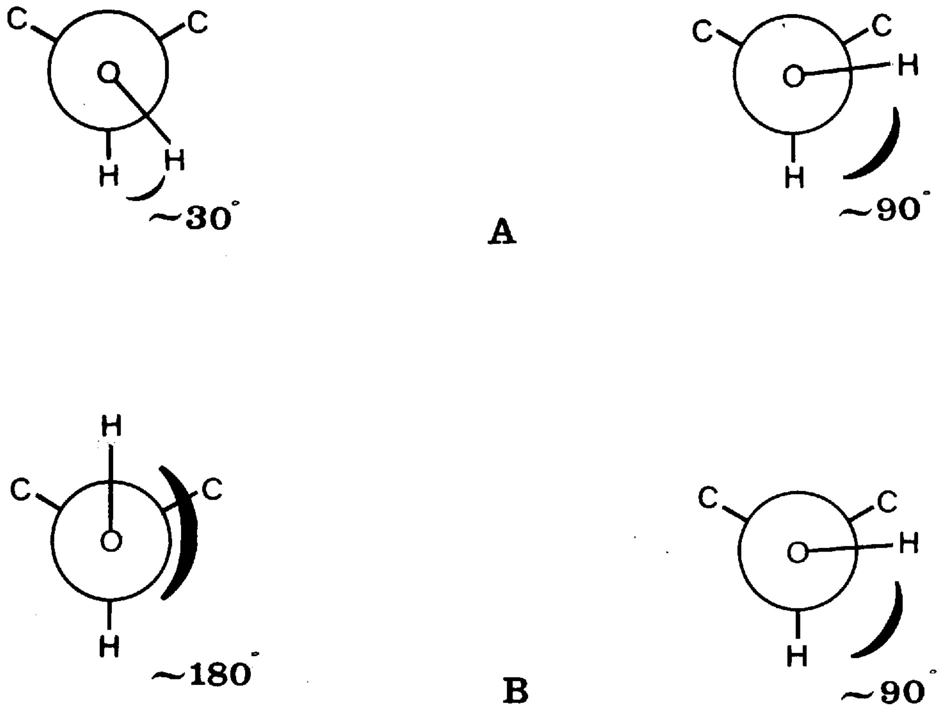


fig.3.52

In cyclohexanol, the preferred rotamer populations of the free hydroxyl groups were shown to be gauche for an axial hydroxyl and gauche/anti for an equatorial hydroxyl. In the above, B has an anti rotamer conformation for the equatorial hydroxyl and an approximate 90 degree dihedral angle for the axial hydroxyl i.e. the axial rotamer requires only a 30 degree change in the dihedral angle to form the hydrogen bond. In A, neither the dihedral angle of the axial hydroxyl group or the equatorial hydroxyl group corresponds to that of a free axial hydroxyl cyclohexanol. The axial rotamer requires a change in dihedral angle of about 30 degrees to acquire the gauche conformation, whilst the equatorial rotamer also requires a similar change. The absolute potential energies of the conformations are not known, so that the supposed relationships are highly approximate. Nevertheless, it can be argued that B is energetically more favoured, resulting in a "free" axial hydroxyl group from the internal hydrogen bond. If this were the case, then the free hydroxyl stretch band should be a composition of free axial and free equatorial hydroxyls and a contribution from the mainly axial "free" hydroxyl from the internal hydrogen bond. However, the computer graphic study gives an exactly opposite result. The high resolution solution spectrum in CCl_4 is unresolved and few conclusions regarding its composition can be drawn (fig.3.43). The Argon matrix spectra is however far more informative.

In the case of trans cyclohexan-1,2-diol, the diequatorial internally hydrogen bonded form must always have a " free" equatorial hydroxyl resulting from the internal hydrogen bond . The rotamer conformations of the hydroxyls involved in this internal hydrogen bond are shown below (fig.3.53).

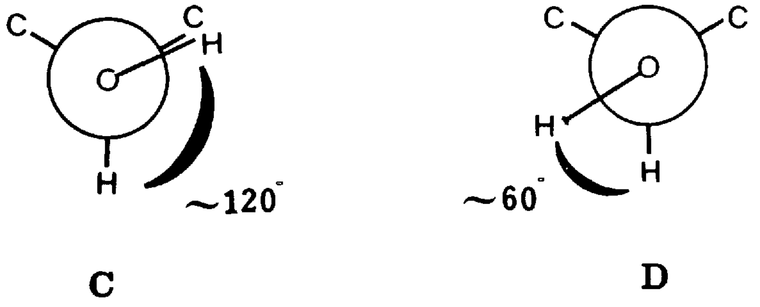


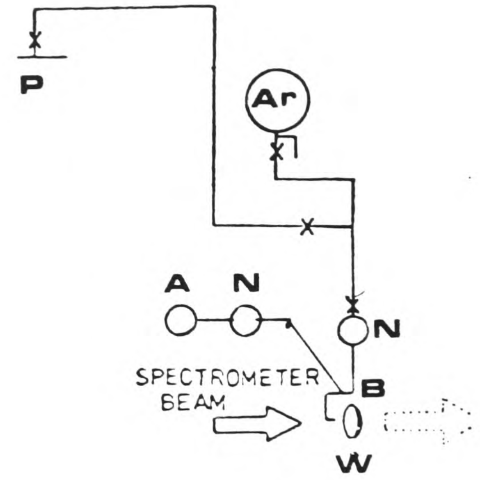
fig.3.53

Conformation D is highly favoured, as it corresponds to the preferred gauche rotamer of an equatorial cyclohexanol, whilst conformation C lies in a potential energy maximum (**P155** graphic simulation). Consequently, the bond strengths can be understood from these considerations.

Although the ax/eq internal hydrogen bond is stronger than the eq/eq hydrogen bond, the absorbance and band areas of the hydroxyl stretch bands of the free hydroxyl and intramolecularly hydrogen bonded hydroxyl for the cis and trans compounds, clearly show that the ratio of intra to free hydroxyl in trans cyclohexan-1,2-diol is much greater than in cis cyclohexan-1,2-diol. Apparently, the trans compound possesses a much greater population of internally hydrogen bonded species than does the cis compound (figs.3.42 $ 3.43). However, the matrix studies may offer an alternative explanation of this result.

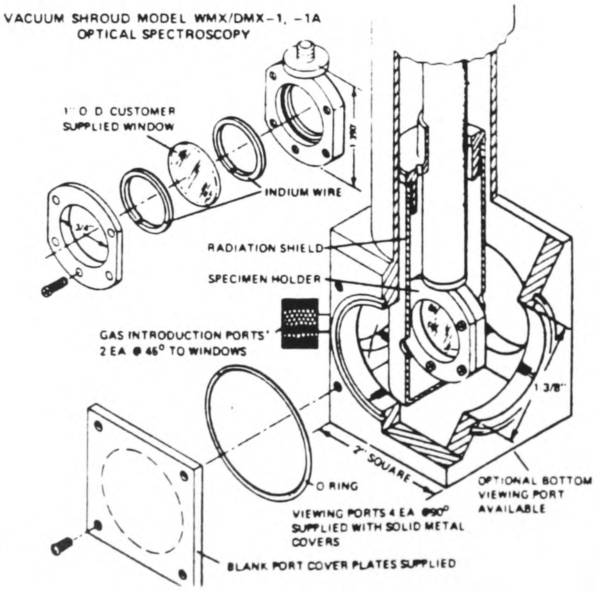
The CCl_4 solution spectra of the remaining isomers are totally unresolved. However, in conjunction with the matrix spectra they become

Fig. 3.54 SCHEMATIC DIAGRAM
MATRIX TECHNIQUE



P, pumping station
Ar, argon source
N, needle valves
A, sample port
W, CsI window
B, gas entry point

WINDOW AND SHROUD



rather more informative.

ARGON MATRIX ISOLATED SPECTRA

The configurational isomers of cyclohexandiol were isolated in an Argon matrix at a temperature of 7K. The method of isolation varies somewhat from the usual procedures due to the non-volatile nature of the compounds. Figure 3.54 diagramatically shows the matrix isolation apparatus. Essentially, the sample is vapourized at a point A, which is closer to the matrix than when a volatile sample is used. The sample vapour mixes with the Argon at point B and then passes into the cryogenic cooling system. In the case of trans cyclohexan-1,3-diol and cis and trans cyclohexan-1,4-diol, the samples required heating for up to 5 minutes in a hot air stream directed toward the tube at A. In most cases an approximate Argon:sample ratio of 1000:1 was achieved and the matrix deposition was complete within three hours.

The matrix spectra were measured at various resolutions corresponding to the same conditions used for the measurments in CCl_4 solution. Figures 3.42 to 3.47 show the hydroxyl stretch region of the matrix isolated compounds compared with the CCl_4 solution spectra. The wavenumbers of the bands are tabulated below (table LI) and are considered accurate to 0.5 cm^{-1}.

TABLE LI

CYCLOHEXANDIOL	FREE OH BAND (cm^{-1})		INTRAMOLECULAR OH BAND (cm^{-1})	
trans 1,2	3659.5	3648.0	3618.5	3615.5
cis 1,2	3647.5	3643.0 *	*	
trans 1,3	3643.5	3640.5		
cis 1,3	3647.0	3640.0	3573.5	3566.0
trans 1,4	3640.5			
cis 1,4	3643.5	3640.5		

* See text

The matrix spectra differ in wavenumber from the CCl_4 solution spectra, the differences which are tabulated below (table LII) and are based on the low resolution spectra. In theory, the matrix isolated compounds are subject to a much lower degree of "solvent" interaction compared with the CCl_4 solutions. In practice, the matrix isolated compounds are also subject to Van der Waals forces (albeit much reduced) and the perturbation is analogous to a "solvent" shift of the wavenumbers. Of particular interest is the fact that cis cyclohexan-1,3-diol and trans cyclohexan-1,2-diol show a significantly greater solvent shift than the other isomers. This could possibly be related to the significant contribution of the diaxial conformation which only these two isomers possess.

TABLE LII

CYCLOHEXANDIOL	Δ FREE OH (cm^{-1})	Δ INTRA OH (cm^{-1})
trans 1,2	23	19
cis 1,2	17	18
trans 1,3	16	
cis 1,3	22	25
trans 1,4	17	
cis 1,4	17	

Where Δ free OH is the difference in wavenumbers between the free hydroxyl stretch band measured in the matrix spectra and the free hydroxy stretch band measured in CCl_4 solution. Similarly, Δ intra is the difference in wavenumber between the intra molecular hydrogen bond band measured in the matrix spectra and the CCl_4 solution spectra. (Difference calculated from low resolution spectra and are meant as a approximate guide only.)

Analysis of the high resolution matrix spectra shows that the compounds can be correlated in two groups. The first group includes the trans configurational isomer of cyclohexan-1,3-diol and cyclohexan-1,4-diol. In this group, the interaction between the hydroxyl groups does not appear to influence the wavenumbers of the free hydroxyl groups. The second group comprises the cis and trans isomers of cyclohexan-1,2-diol and the cis cyclohexan-1,3-diol, all of which possess an internal hydrogen bond.

GROUP 1

trans cyclohexan-1,3-diol

The high resolution spectrum shows that the free hydroxyl stretch band is composed of two bands, which are only partially resolved. However, their maxima can be measured as 3643.5 cm^{-1} and 3640.5 cm^{-1}.

The conformational forms of this isomer are degenerate, and both the axial and equatorial free hydroxyls must be present. On the tentative basis that the axial hydroxyl stretch band occurs at a higher wavenumber than the equatorial band, the band at 3643.5 cm^{-1} can be assigned to the axial hydroxyl and that at 3640.5 cm^{-1} to the equatorial hydroxyl (fig 3.54).

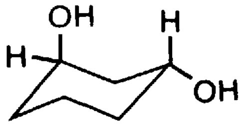


fig.3.54

In the CCl_4 solution spectrum, the band is far less resolved, however, a slight shoulder can be observed at the higher wavenumber side.

cis cyclohexan-1,4-diol

The conformational equilibrium of the cis 1,4 compound is analogous to that in trans 1,3 in that the ax/eq and eq/ax conformations are degenerate. The resultant spectrum therefore must be a composition of the axial hydroxyl stretch band and the equatorial hydroxyl stretch band (fig 3.55).

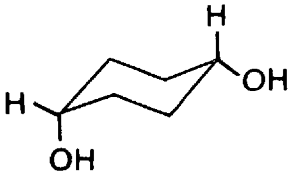


fig.3.55

Significantly, the solution spectrum appears to be somewhat more resolved than the matrix spectrum and this is rather difficult to explain. However, the matrix spectrum reveals a band at 3640.5 cm^{-1} with a shoulder at 3643.5 cm^{-1}. These bands correspond exactly to the bands in the trans 1,3 compound and so can be correlated to the equatorial free hydroxyl stretch and the axial hydroxyl stretch respectively.

trans cyclohexan-1,4-diol

The conformational equilibrium allows the diequatorial and diaxial conformations to coexist. However, the thermodynamic calculations show that the diaxial conformation must be present at a very low population (fig 3.56).

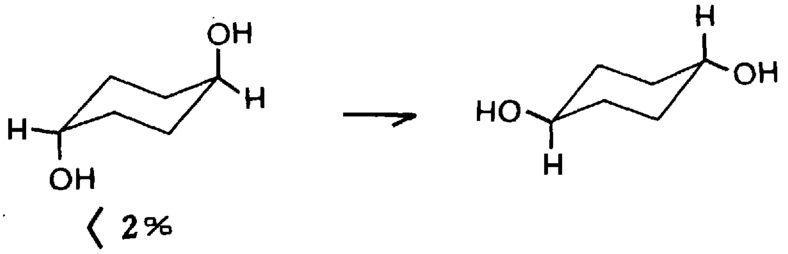


fig.3.56

In accordance with this consideration, the observed free hydroxyl stretch band in the matrix spectrum occurs at 3640.0 cm^{-1}. This measurement can therefore be correlated to that of the free hydroxyl stretch band as in the above isomers.

GROUP 2

cis cyclohexan-1,3-diol

The conformational equilibrium between the diequatorial form and the diaxial form is shown in figure 3.57.

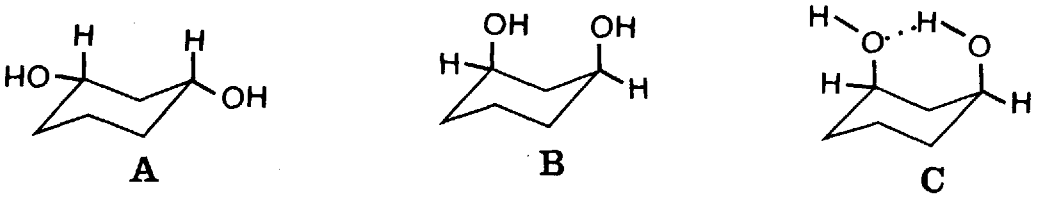


fig.3.57

On the basis of the thermodynamic calculations, the diequatorial conformation should dominate the equilibrium (> 98 %). However, in accordance with the observations of other infrared studies, the low resolution spectrum of the CCl_4 solution and the matrix spectrum both show the presence of an intramolecular hydrogen bond (24). Hence, the diaxial conformation exists at a significant population. Further, the difference in wavenumber between the free hydroxyl stretch band and the intramolecular hydrogen bond band is large ($77cm^{-1}$ in CCl_4), more than double the same difference for the configurational isomers of cyclohexan-1,2-diol, suggesting that the internal hydrogen bond in this compound is much stronger than in the 1,2 isomers.

The high resolution spectrum clearly show that the intramolecular hydrogen bond band is actually composed of two bands centred at 3573.5 cm^{-1} and 3566cm^{-1}. A possible way in which this can be explained is that two types of internal hydrogen bonds are present. This can only be achieved if one association involves a single hydrogen bond and the other a double hydrogen bond (double chelation) (fig 3.58).

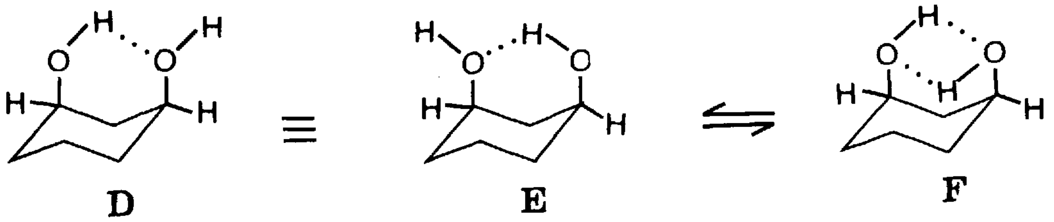


fig.3.58

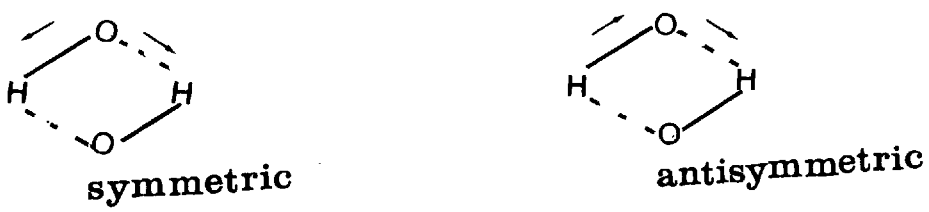
D and **E** are equivalent, and can only give rise to one hydroxyl stretch band, whilst **F** is different and results in a shift of wavenumber.

This result is in complete agreement with the ^{13}C nmr spectrum of cis cyclohexan-1,3-diol, where the presence of two types of internal hydrogen bonds results in separate signals for the two conformationally distinct forms **D**/**E** and **F**.

Since the non-bonded diaxial form is present at a very low population, the free hydroxyl band is not expected to possess a contribution from **B** (fig 3.57). Contributions will however arise from

D/E and **A**. **F** possesses no free hydroxyl groups and hence will not contribute. The free hydroxyl band should therefore comprise two bands, the free equatorial from **A** and the "free" axial from **D/E**. The partially resolved matrix spectra show two maxima at 3640.0 cm^{-1} and 3647.0 cm^{-1}. The band at 3640.0 cm^{-1} can be assigned to the free diequatorial hydroxyls of **A**, whilst the band at 3647.0 cm^{-1} must be assigned to the "free" axial of **D/E**. Consequently it can be seen that the "free" axial hydroxyl of the internal hydrogen bond in **D/E** has a wavenumber shift of 3.5cm^{-1} compared with the "totally free" axial hydroxyl of the trans 1,3 ond cis 1,4 isomers.

Another possible explanation for the observation of two bands for the internal hydrogen can be obtained on the premise that only the double internal hydrogen bond is present. It could be argued that the cyclic internal hydrogen bond structure could give rise to two stretching modes, the antisymmetric stretch and the symmetric stretch (fig 3.59).



symmetric **antisymmetric**

fig.3.59

These vibrational modes can be compared with the same stretching modes observed in the infrared spectrum of water. However, the observed free hydroxyl stretch bands do not agree with this interpretation, since a "free" axial hydroxyl is certainly present. Also, the presence of only one type of internal hydrogen bond is not consistent with the nmr results. Nevertheless, there is no reason why two bands should not occur for the double cyclic structure, only that the difference in wavenumber is unresolved.

trans cyclohexan-1,2-diol

Both the cis and trans configurational isomers of cyclohexan-1,2-diol possess vicinal hydroxyl groups. In the nmr studies, the observed spectra of these compounds were always perturbed from the calculated chemical shifts. Likewise, the vicinal arrangement of the hydroxyl groups must have electronic effects within the O - H bond and so a change in the force constant is understandable. However, on the premiss that the effect of a change in the force constant will be of similar magnitude for both the cis and trans configurations, the two sets of spectra show a good correlation.

The diequatorial conformation of trans cyclohexan-1,2-diol posesses an intramolecular hydrogen bond. This is clearly revealed by the presence of the band at 3598 cm^{-1} in the CCl_4 solution spectrum. In the matrix spectra however, the band shows two maxima at 3615.5 cm^{-1} and 3618.5 cm^{-1}. As for cis cyclohexan-1,3-diol, the explanation must be that both the single and double intra molecular hydrogen bonded forms are present (fig 3.60).

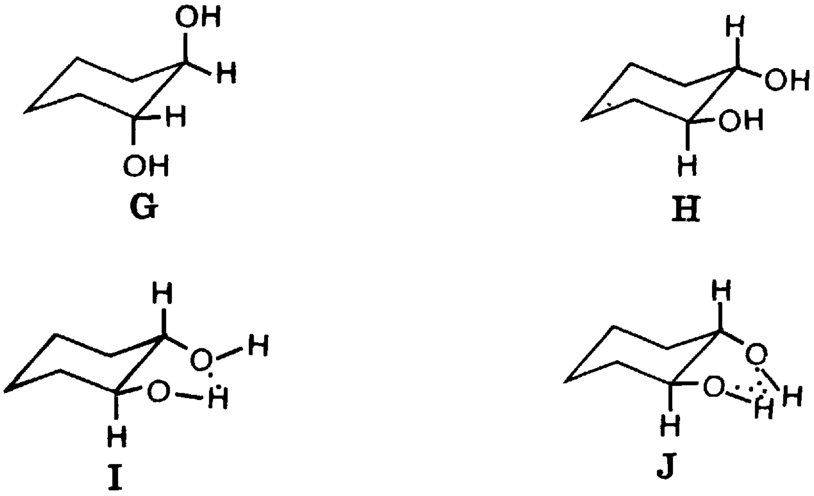

G **H** **I** **J**

fig.3.60

The diequatorial conformation **I**, possesses a single internal hydrogen bond and a "free" equatorial hydroxyl, whilst **J** possesses the double internal hydrogen bond and no "free" hydroxyls.

The free hydroxyl stretch band of trans cyclohexan-1,2-diol can therefore be composed of ;

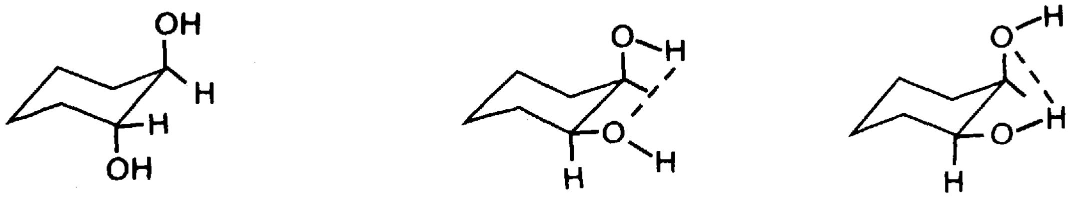
1. A free axial hydroxyl stretch band from **G**.
2. A free equatorial hydroxyl stretch band from **H**.
3. A "free" equatorial hydroxyl stretch band from **I**.

In the matrix spectra, the free hydroxyl stretch band is resolved to show two well separated bands at 3659.5 cm^{-1} and 3648.0 cm^{-1}, with a possible shoulder on the higher wavenumber side of the band at 3648.0 cm^{-1}. The two bands can be assigned to the axial and equatorial free hydroxyls, the band at 3659.5 cm^{-1} can be correlated to the diaxial free hydroxyls of **G**, whilst the band at 3648.0 cm^{-1} is ambiguous. Considering the high degree of internal hyrogen bonding that occurs, in this compound it can be assumed that a large proportion of the total population is internally hydrogen bonded, either **I** or **J** . Either conformation will lead to a considerable reduction of the population of conformation **H**. This is is not suprising in view of the fact that the internal hydrogen bond(s) must reduce the dipole repulsions between the equatorial hydroxyl groups. It can therefore be concluded that the band at 3648.0 is due to the "free" equatorial hydroxyl of **I**.

The internal hydrogen bond band has two maxima of unequal intensity, the maximum at 3615 cm^{-1} being far more intense than the higher wavenumber maximum . On the basis of the above argument, the "free" equatorial band of **I** predominates the total free equatorial band and likewise, the band at 3615.5 cm^{-1} must be due to the single internal hydrogen bond band of **I**. The shoulder between the two free hydroxl stretch bands must therefore be due to the non-hydrogen bonded diequatorial conformation **H**, and the smaller internal hydrogen bond band at the higher wavenumber must be due to the double internal hydrogen bond conformer **J**.

cis cyclohexan-1,2-diol

This isomer possesses bands for the internal hydrogen bond and the free hydroxyls, which are highly complex and are obviously due to contributions from a number of species. In principle, three conformations at least can be present (fig 3.61).



K **L** **M**

fig.3.61

The ax/eq and eq/ax degenerate forms of **K** can be in equilibrium with **L** and **M**. Conformation **L** possesses an intra molecular hydrogen bond which results from the interaction of the axial hydroxyl hydrogen with the equatorial hydroxyl oxygen. Conformation **M**, results from the interaction of the equatorial hydroxyl hydrogen with the axial hydroxyl oxygen. Conformation **L** will result in an equatorial "free" hydroxyl group, whilst conformation **M** will result in an axial "free" hydroxyl. Without considering the possibility of a double internal hydrogen bond conformation, the resultant free hydroxyl stretch band should be composed of the following;

1. A free axial hydroxyl stretch band from **K**.
2. A free equatorial hydroxyl stretch band from **K**.
3. A "free" equatorial hydroxyl stretch band from **L**.
4. A "free" axial hydroxyl stretch band from **M**.

Similarly, the internal hydrogen bond band will be composed of;

1. The internal hydrogen bond band from **L**.
2. The internal hydrogen bond band from **M**.

The above considerations explain the complexity of the free hydroxyl band. Although there is considerable overlap of bands, certain maxima can be identified at 3641.0 cm^{-1}, 3647.0 cm^{-1} and 3659 cm^{-1}. If the cis and trans isomers of cyclohexan-1,2-diol can be related in the same manner as the other configurational isomers, then the band at 3641.0 cm^{-1} can be correlated to the "free" equatorial of conformation **L** (corresponding to conformation of trans 1,2). The band at 3659.0 cm^{-1} can then be correlated to the free axial hydroxyl of conformation **K** (corresponding to the free axial of conformation of trans 1,2). The most intense band at 3647.0 cm^{-1} must therefore now be assigned to the "free" axial hydroxyl of conformation **M**. The equatorial hydroxyl corresponding to conformation **K** (corresponding to the free axial of conformation **G** in trans 1,2). The more intense band at 3647.0 cm^{-1} must therefore now be assigned to the "free" axial hydroxyl of conformation **M**. The equatorial hydroxyl corresponding to the free equatorial of **K** cannot be located. Obviously, its intensity must be of the same order of magnitude as that of the axial hydroxyl, and so it must be present but unresolved due to the overlap.

The band structure, although highly complex, does show that the internally hydrogen bonded forms are the most highly populated conformations.

The infrared studies show an excellent correlation with the nmr experiments, in particular, the presence of the double hydrogen bond in cis cyclohexan-1,3-diol. In the ^{13}C nmr experiments, the presence of the double hydrogen bond is easily detected in cis cyclohexan-1,3-diol, whilst in trans cyclohexan-1,2-diol it cannot be detected. This can be explained by;

1.Insufficient resolution to observe the smaller energy difference.
2.The relative population of the double hydrogen bond conformation in the trans cyclohexan-1,2-diol. The matrix spectra shows its intensity to be considerably less than the singly hydrogen bonded form. Consequently, the sensitivity of ^{13}C nmr may be insufficient to detect the relatively small population.

The most likely explanation is that a combination of both the above factors are responsible.

Fig. 3.62

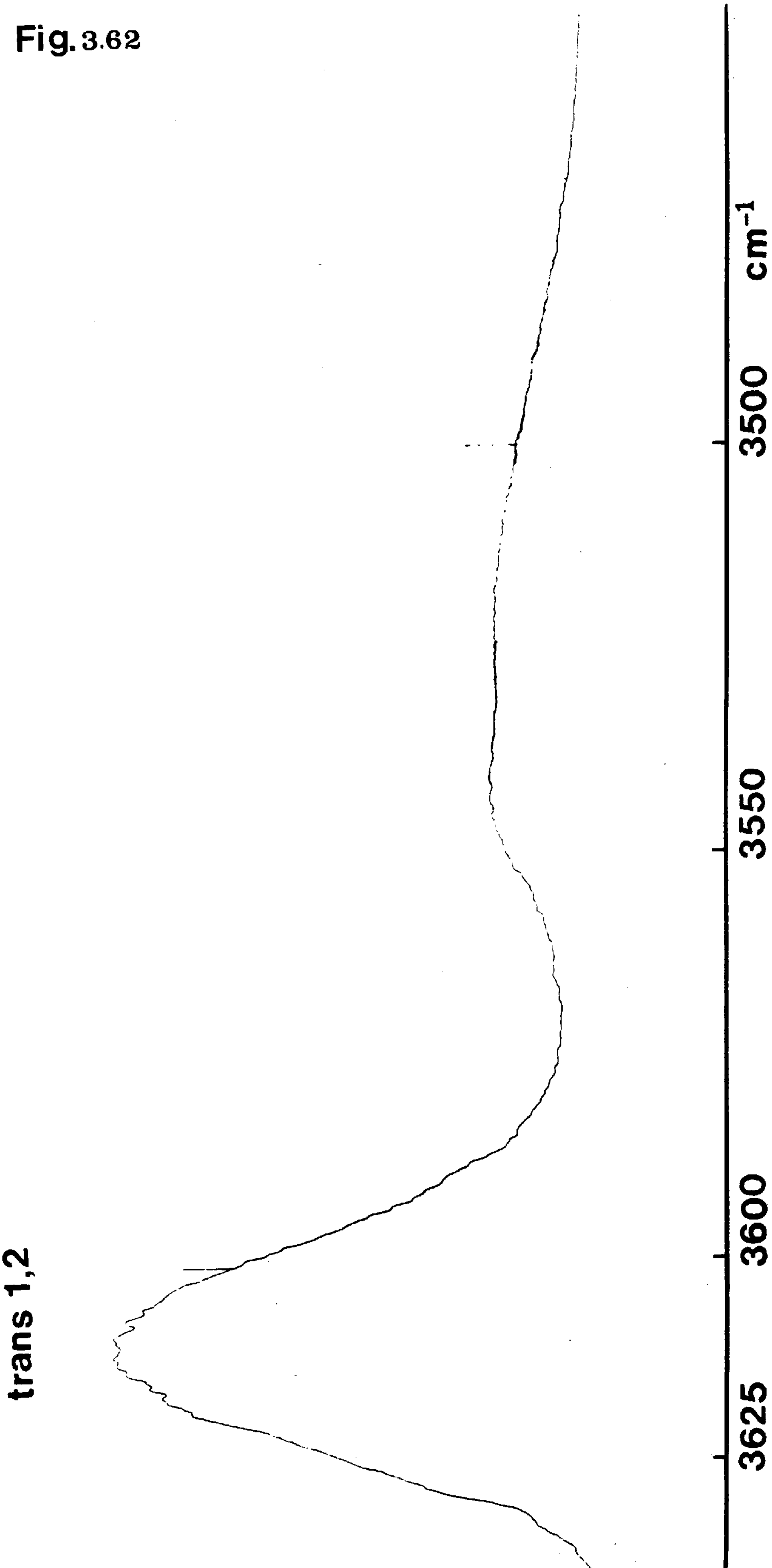


Fig.3.63

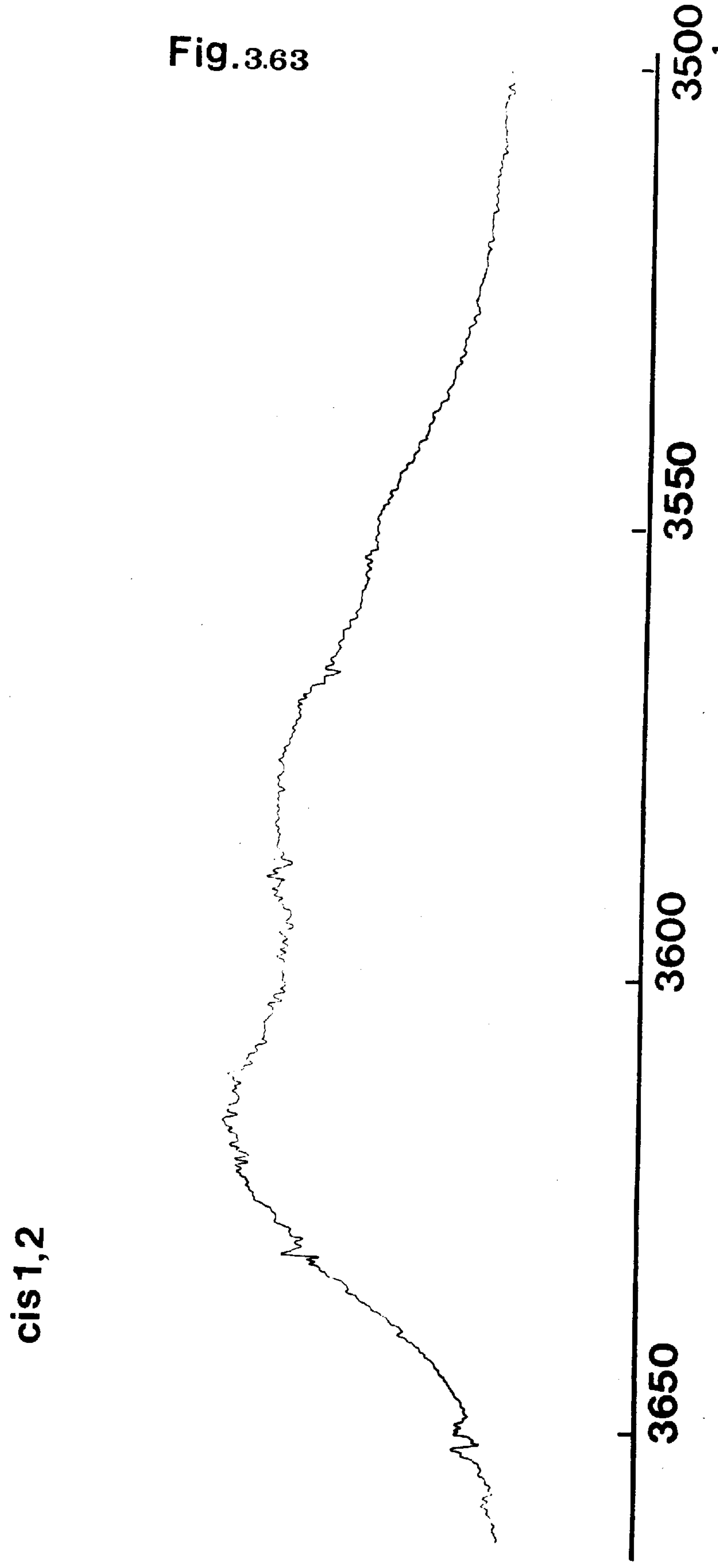


fig.3.64

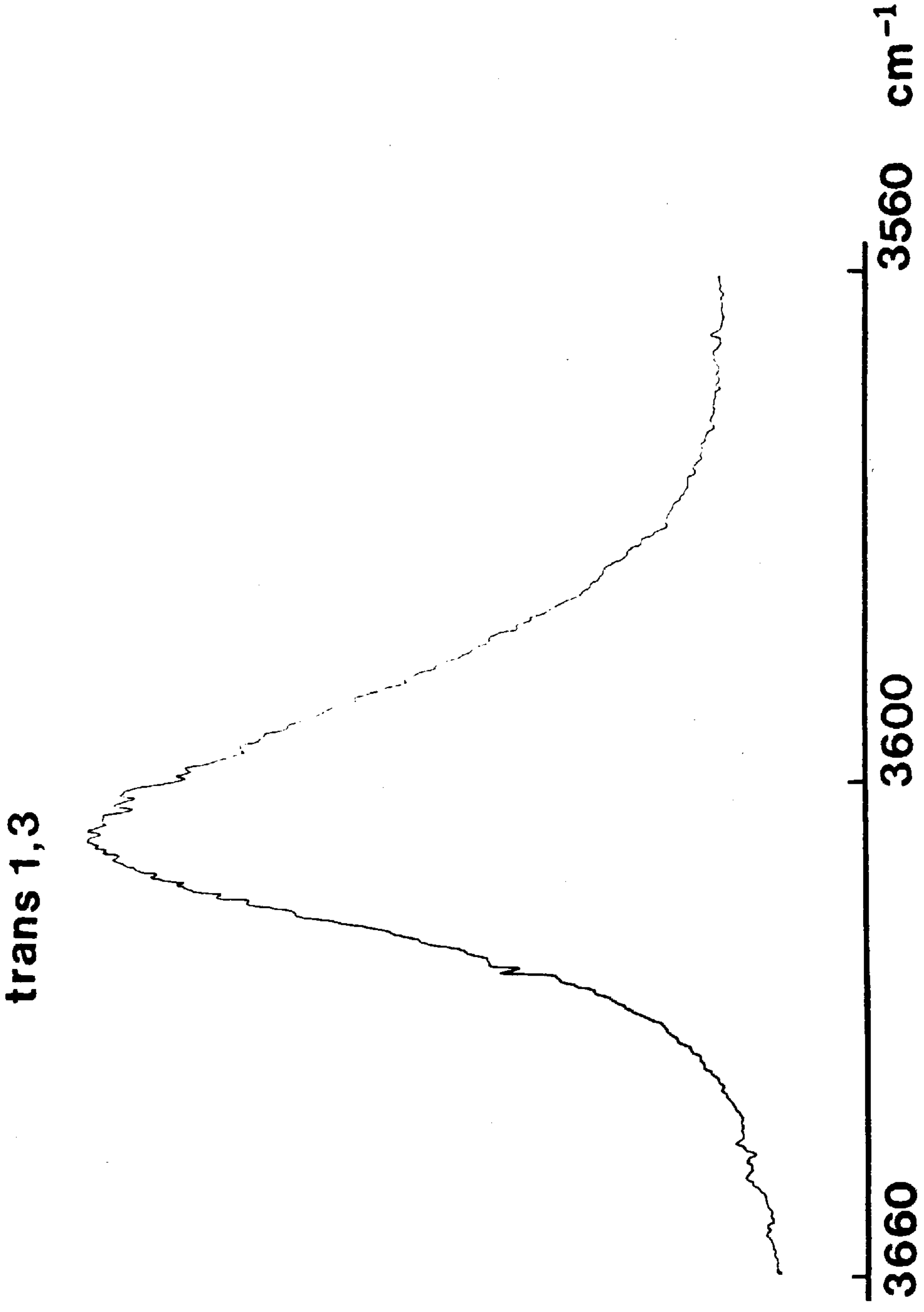


fig.3.65

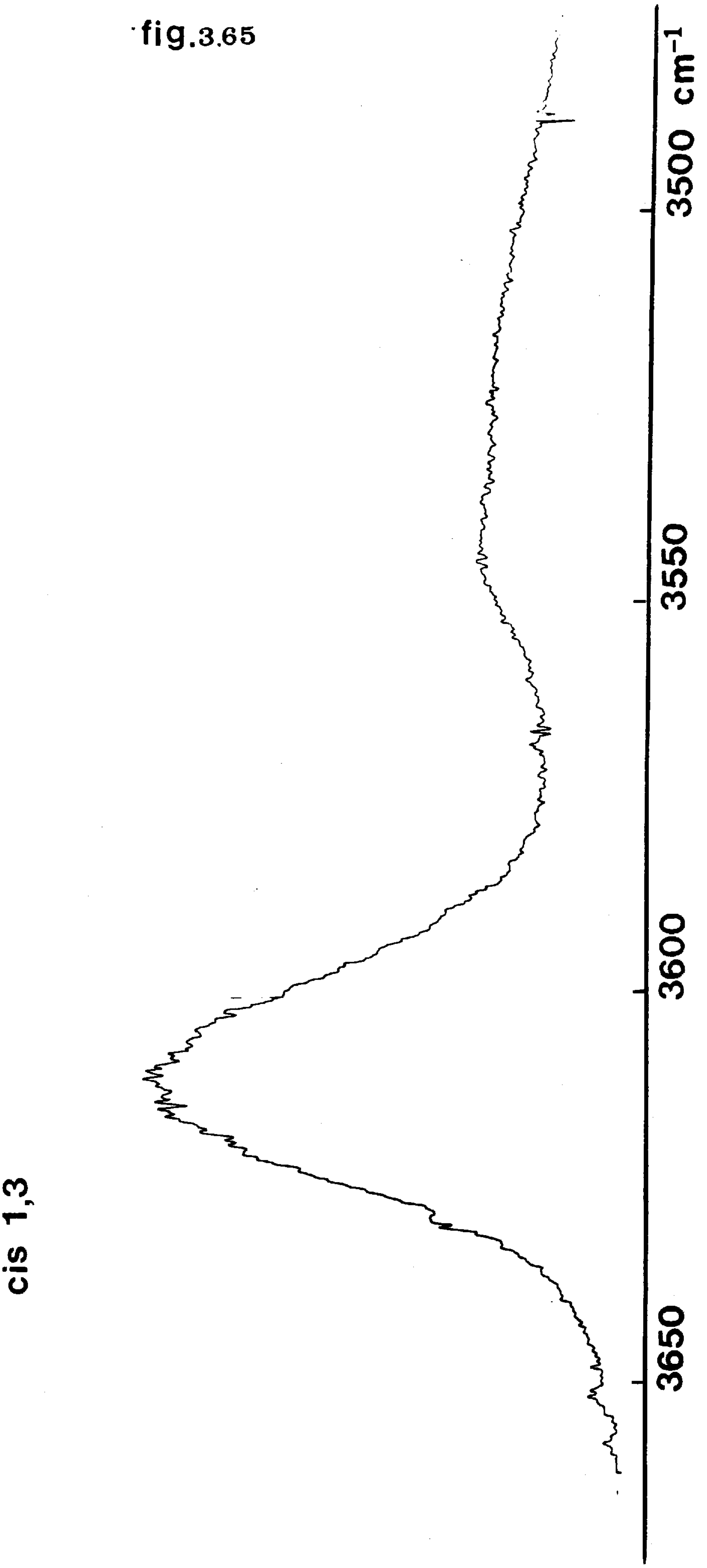


fig.3.66

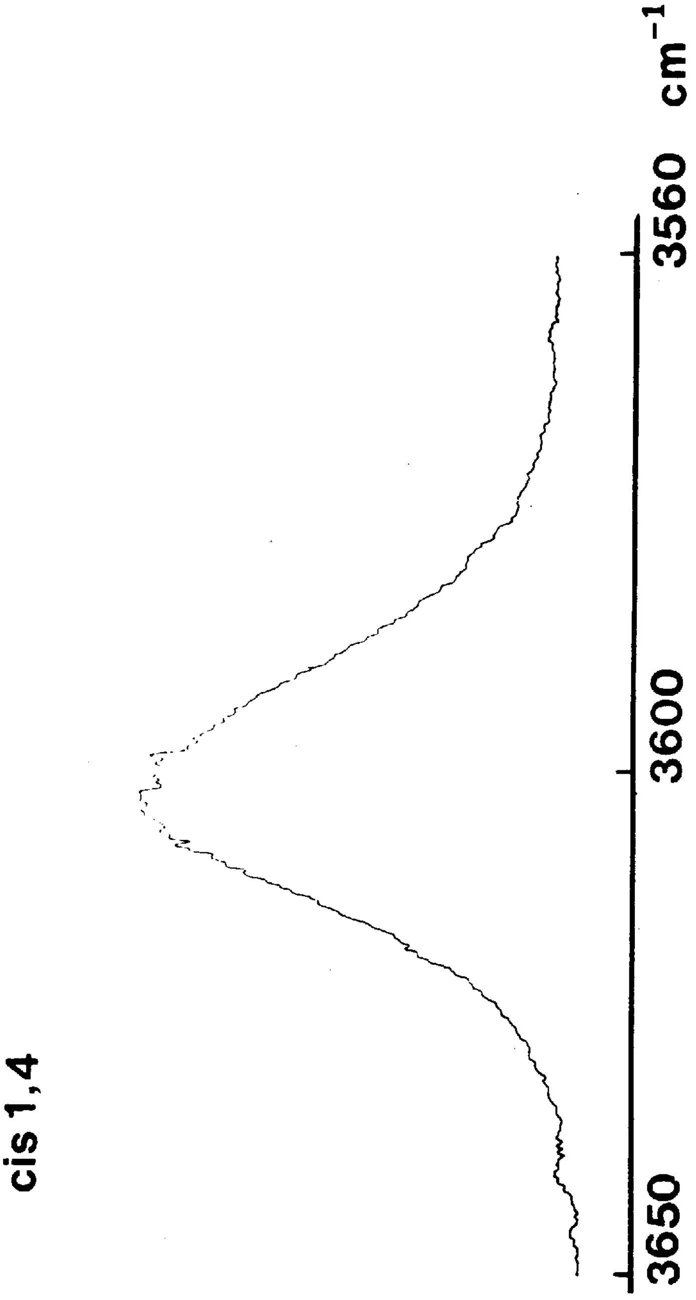
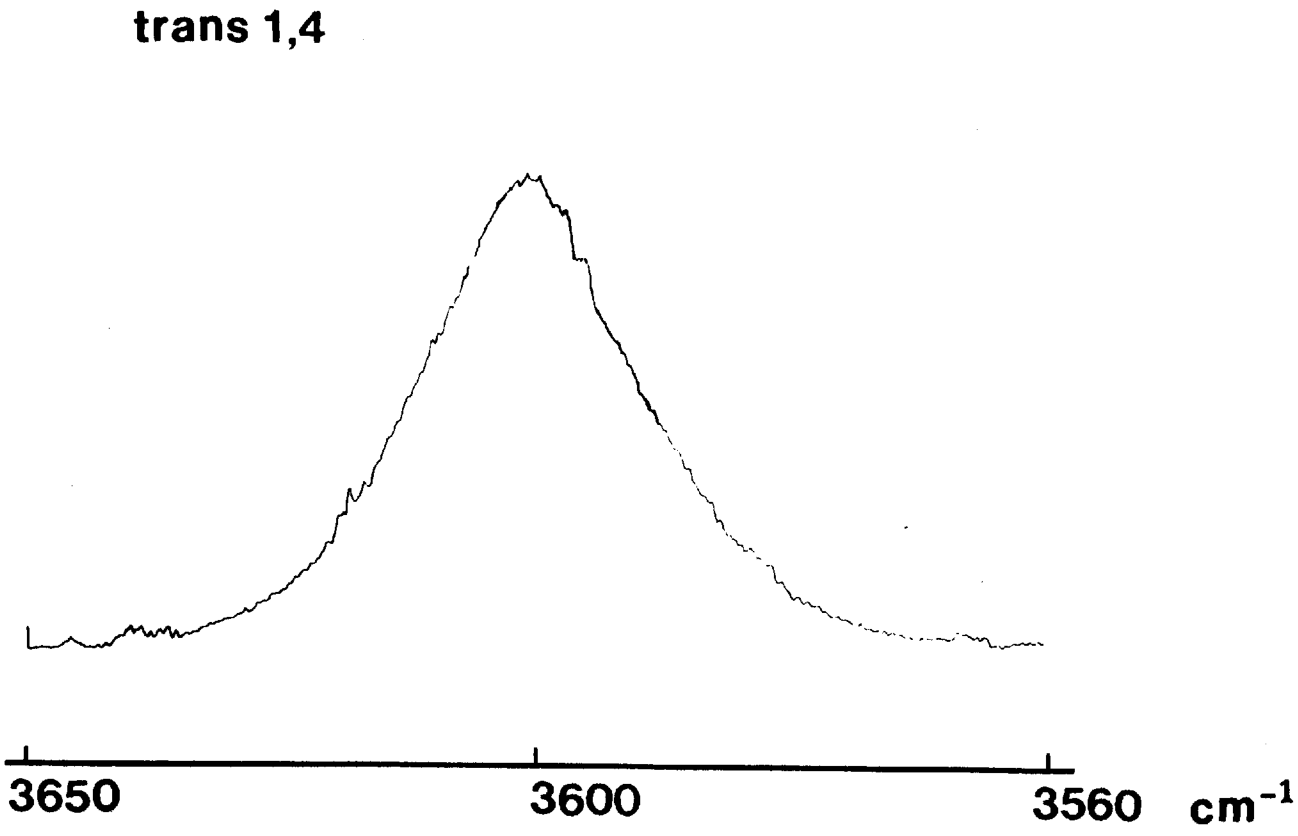


fig.3.67



INFRARED STUDIES IN $CDCL_3$ SOLUTION

The nmr experiments have shown that $CDCl_3$ as a solvent has a considerable non-bonded effect upon the hydroxyl group. The infrared studies, performed in conjunction with the nmr experiments have shown that the net effect of $CDCl_3$ compared with that of CCl_4 as the solvent is to considerably reduce hydrogen bonding associations. Intermolecular hydrogen bonding appears to be affected more than intramolecular hydrogen bonding, presumably because the internal hydrogen bond tends to be stronger than the intermolecular hydrogen bond. The infrared solution study of the cyclohexandiols in $CDCl_3$ solution gives considerably more information regarding the solvent effect on the intranolecular hydrogen bond and the nature of the association.

The infrared solution spectra of the cyclohexandiols were measured under the same conditions as used for the CCl_4 solutions. The high resolution spectra are shown below (figs 3.62 to 3.67), and the wavenumbers of the hydroxyl stretch bands are tabulated in table LIII.

TABLE LII

CYCLOHEXANDIOL	FREE OH BAND (cm^{-1})	INTRA OH BAND (cm^{-1})
trans 1,2	3609.0 [1]	3545.0 [1]
cis 1,2	3614.0	3579.0, 3549.0
trans 1,3	3614.0, 3628.0	
cis 1,3	3611.5 3628.0	3546.0 [1]
trans 1,4	3614.0	
cis 1,4	3613.0 3628.0	

[1] Poorly resolved shoulders, wavenumber difficult to determine due to overlaps.

As with the matrix spectra, a similar pattern of results is observed, although resolution of the bands is far less complete. Nevertheless, the band maxima are very useful aids in the conformational assignment. In particular, the axial and equatorial bands of cis cyclohexan-1,4-diol and trans cyclohexan-1,3-diol show good agreement, the axial band maximum occuring at 3628.5 cm^{-1} and the equatorial band maximum 3613.0 cm^{-1}. These bands are shifted from the corresponding bands in the Argon matrix by 15 cm^{-1} and 27 cm^{-1} respectively. Similarly, trans cyclohexan-1,4-diol has an equatorial band centred at 3614.0 cm^{-1}, which shows good agreement with the free equatorial bands of trans cyclohexan-1,3-diol and cis cyclohexan-1,4-diol.

The $CDCl_3$ solution spectrum of cis cyclohexan-1,3-diol is rather unusual, like the matrix spectra it shows two maxima for the internal hydrogen bond band, which results in a very broad band. The higher wavenumber maximum occurs at 3645.0 cm^{-1} and is the more intense. The second maxima cannot be resolved sufficiently to record the wavenumber, but it results in a highly assymetric "tail" to the band. The free hydroxyl band occurs at 3628.0 cm^{-1}, which corresponds to the diequatorial conformation. The second band occurs at 3612.0 cm^{-1}. This band is very close to the free axial wavenumbers found in the isomers above (although somewhat lower in wavenumber). In the matrix spectra , this band was correlated to the "free" axial hydroxyl of the internal hydrogen bond. Therefore, it would be expected that the "free" axial of the internal hydrogen bond would be shifted to a higher wavenumber than the free axial hydroxyl. A possible explanatunexpected wavenumber of this band in $CDCl_3$ arises from the fact that the solvent effectively increases the steric bulk of the axial hydroxyl group, thus reorientation of the rotamer must occur to minimise the steric repulsions (fig 3.68).

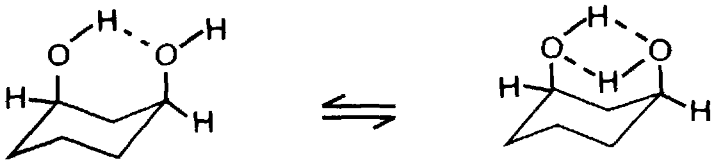


fig.3.68

This steric effect, due to the solvent, gains further support from the fact that the higher wavenumber internal hydrogen bond maximum has a much higher intensity than the lower wavenumber.

Cis cyclohexan-1,2-diol has two maxima for the intramolecular hydrogen bond band, centred at 3579.0 cm^{-1} and 3549.0 cm^{-1}, showing that at least two types of internal hydrogen bonds are present. Which is in accordance with the matrix spectra. The free hydroxyl stretch band is poorly resolved, with a maximum centred at 3614 cm^{-1}.

Similarly, in trans cyclohexan-1,2-diol, the intramolecular hydrogen bond band suggests that two maxima are present, although only the maximum at 3545.0 cm^{-1} can be measured. The free hydroxyl band occurs at 3609.0 cm^{-1} with a shoulder on the high wavenumber side, presumably due to the free hydroxyls of the diaxial conformation.

CONFORMATIONAL SUMMARY

The infrared studies provide an abundance of information regarding the conformational equilibria of the cyclohexandiols. In particular, the Argon matrix isolated spectra show conclusively that the resolution of axial and equatorial hydroxyl groups is possible under matrix conditions. The most important conclusion is that the diaxial conformation of cis cyclohexan-1,3-diol possesses two types of internal hydrogen bonds and further that the nature of the solvent may influence the relative populations of the two types of internal hydrogen bonds. The evidence also strongly suggests that trans cyclohexan-1,2-diol possesses two types of internal hydrogen bonds, together with an unassociated diequatorial conformation and a diaxial conformation. Cis cyclohexan-1,2-diol exists in at least three non-degenerate conformations, the unassociated ax/eq, eq/ax and two types of internally hydrogen bonded conformations. The conformational summary is tabulated below (table LIV).

TABLE LIV

CYCLOHEXANDIOL	CONFORMATIONS
trans 1,2	1.diaxial
	2.diequatorial
	3.diequatorial with single internal hydrogen bond.
	4.diequatorial with double internal hydrogen bond.
cis 1,2	1.axial/equatorial, equatorial/axial.
	2.ax/eq, eq/ax internal H bond O - H_{eq}----O_{ax} - H.
	3.ax/eq, eq/ax internal H bond O - H_{ax}----O_{eq} - H.
trans 1,3	1.axial/equatorial, equatorial/axial
cis 1,3	1.diequatorial
	2.diaxial with single internal hydrogen bond.
	3.diaxial with double internal hydrogen bond.
trans 1,4	diequatorial
cis 1,4	1.axial/equatorial, equatorial/axial

COMPUTER GRAPHIC SIMULATION STUDIES

The "CHEMX" Chemical Design graphics system supported on a VAX 8650 computer has been utilized in this investigation of conformation. Although a number of modes of thermodynamic studies are possible on the CHEMX system, for practical reasons, the Van der Waals (VDW) repulsion energy has been predominantly used in this study.

The CHEMX system is capable of generating conformations by change of intermolecular distance, bond angles and torsion angles. In the case of cyclohexanol, the system is able to generate all possible rotamers of the hydroxyl group and identify the maximum and minimum energies (fig.3.69)

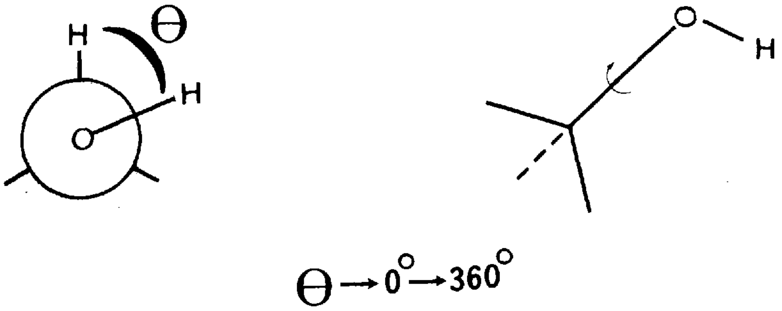


fig.3.69

As a compromise between accuracy and computer time, limits are set upon the number of conformations that are generated. Thus for cyclohexanol, 360 rotamer conformations are generated (one rotamer per one degree). This limit allows a plot of the VDW energy against the dihedral angles to be constructed. Other suitable parameters may be used, such as bond lengths or bond angles. For the cyclohexandiols, there are severe limitations regarding such an energy study. If 360 conformations are generated for each hydroxyl group, the total number of conformations generated by simultaneous rotation of both hydroxyl groups is 360^2 (129,600 conformations). Obviously, an energy plot involving this number of data points is unacceptable and of no practical use. Consequently, no energy plots of the cyclohexandiols are displayed. However, the minimum energy conformations are shown and their geometrical parameters displayed.

The calculation of the VDW repulsion energy is performed by the Chemx system itself, the method of calculation is detailed in the Appendix.

1. STUDY OF AXIAL AND EQUATORIAL CYCLOHEXANOLS

a) cyclohexanol with an equatorial hydroxy group (fig.3.70).

fig.3.70

fig.3.71

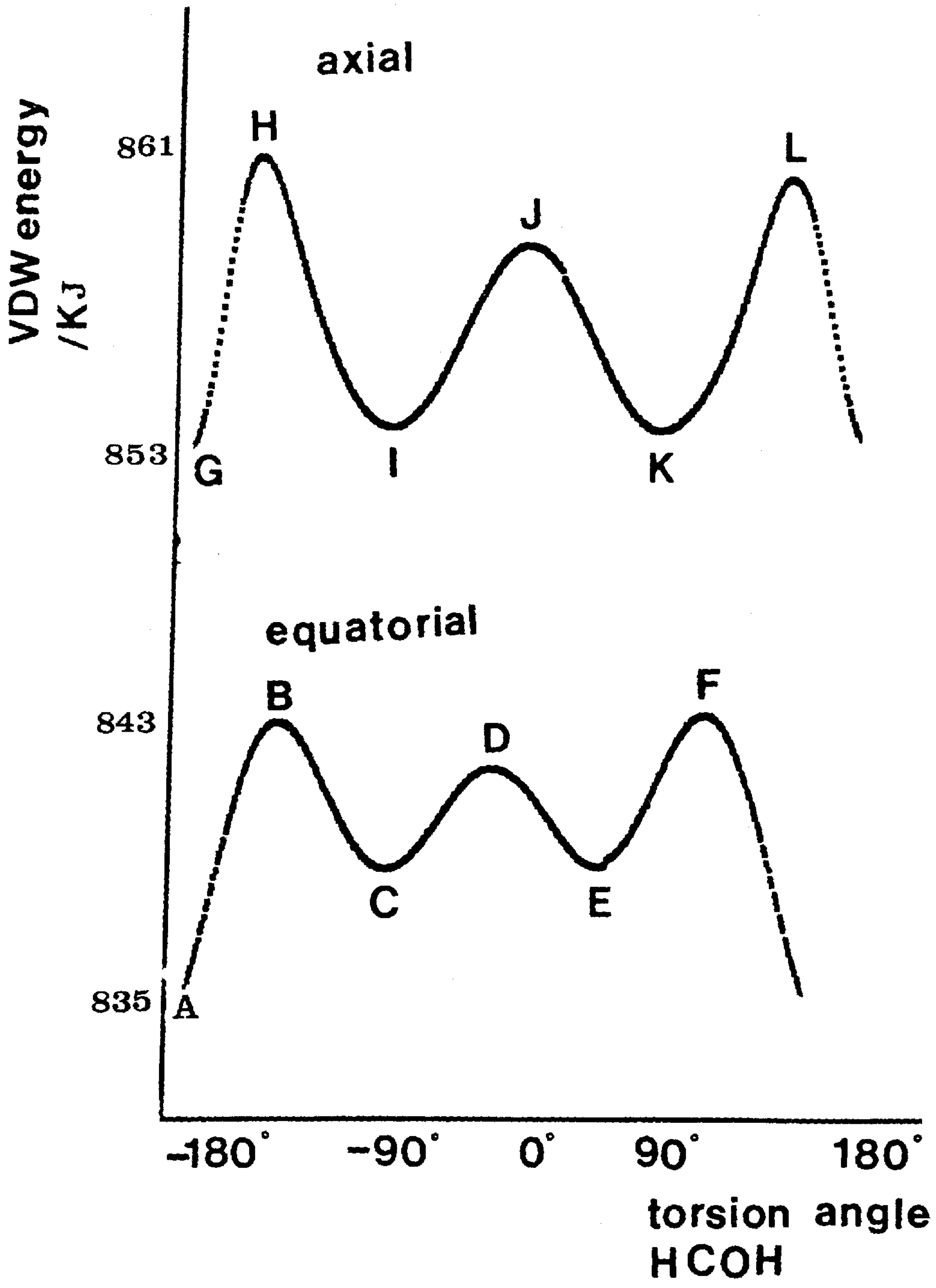
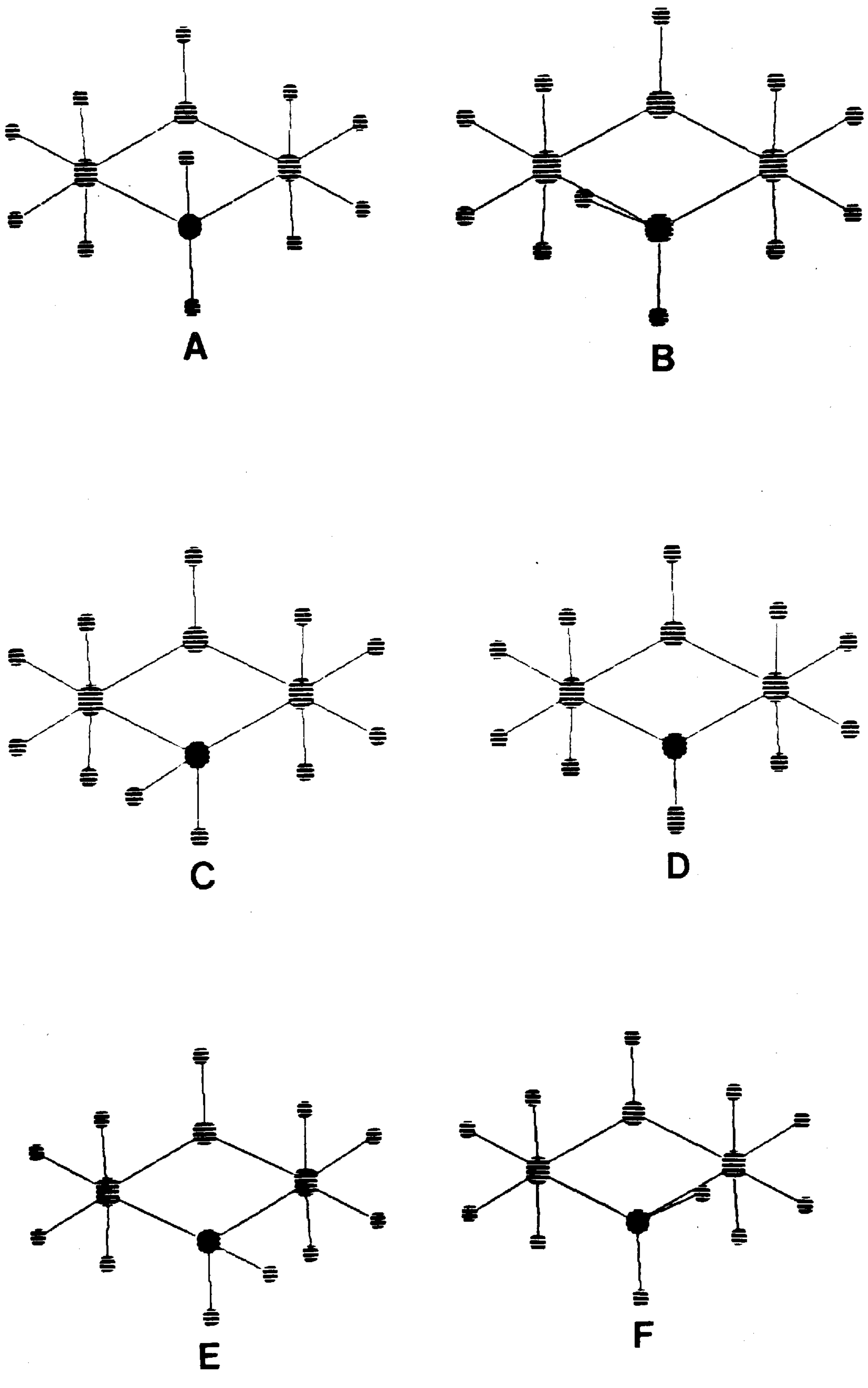

VDW energy /KJ
axial
861
853
H
J
L
G
I
K
equatorial
843
835
B
D
F
C
E
A
-180°
-90°
0°
90°
180°
torsion angle HCOH

fig.3.72



By rotation of the O - C bond, using 360 data points, the possible rotamers of an equatorial cyclohexanol are generated. Figure 3.71 shows the plot of the dihedral angle HCOH against the VDW repulsion energy.

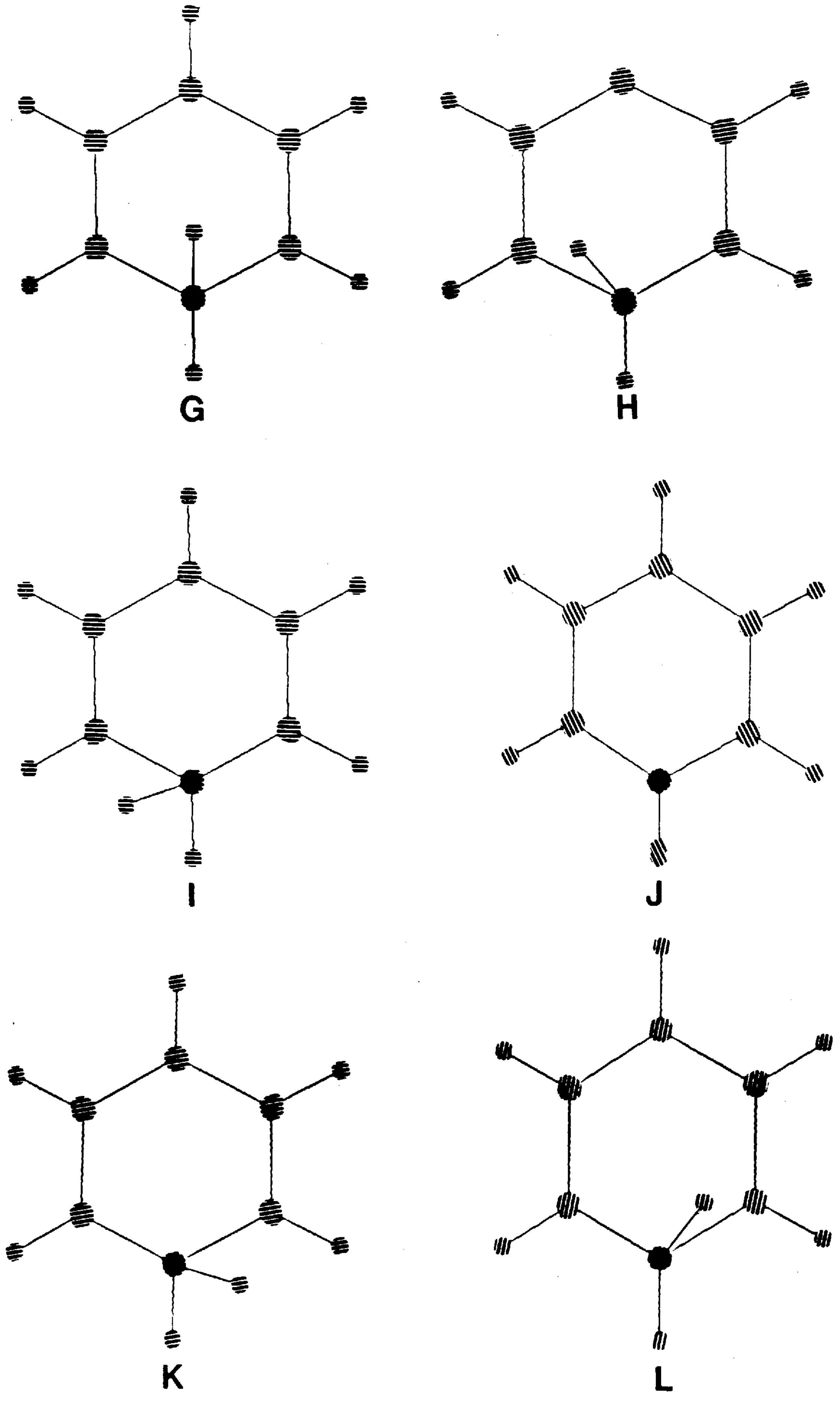
The maximum and minimum energy conformations are summarized below in table LIV.

TABLE LIV

CONFORMATION	DIHEDRAL ANGLE (degrees)	VDW REPULSION ENERGY (KJ/mol)
A	180	835.258
B	114	843.812
C	57	839.927
D	0	842.539
E	57	839.927
F	114	843.812

The rotamer conformations corresponding to conformations **A** to **F** are plotted below (fig 3.72).

fig.3.73



G H I J K L

b) cyclohexanol with an axial hydroxyl group (table LVI)

TABLE LVI

CONFORMATION	DIHEDRAL ANGLE (degrees)	VDW REPULSION ENERGY (KJ/mol)
G	180	853.404
H	141	861.070
I	71	853.831
J	0	858.642
K	71	853.634
L	140	860.312

The rotamer conformations corresponding to conformations G to L are plotted below (fig 3.73).

The energy plots show the VDW maxima and minima for an axial and an equatorial cyclohexanol. The energy distribution between the rotamers can be used to obtain the Boltzman distribution.

1) cyclohexanol with an equatorial hydroxyl group

The minimum energy rotamers, as given by the VDW energy plot, occur for the anti rotamer and the gauche rotamer. Significantly, the gauche rotamer does not have a dihedral angle of 60 degrees but of 56 degrees.

The cause of this reduction can be attributed to the slight repulsion the hydroxyl hydrogen experiences from the vicinal hydrogens (see below).

The energy minima occur at: θ = 180 degrees and 56 degrees. Hovever, there are two forms of the gauche rotamer, so that an entropy effect is present.

$$N_i/N_j = g_i/g_j \; . \; e^{-\,H/RT}$$

Where N_i and N_j are the populations of states i and j,

g_i and g_j are the degeneracies of states i and j

Assuming that the difference in VDW repulsion energy between the rotamer conformations is equivalent to the enthalpy difference, then:

$$N_{anti}/N_{gauche} = 1/2 \; . \; e^{-(\;(835258\;-\;839927)/8.314\;.\;298\;)}$$
$$= 3.29$$

and $K = N_{anti}/N_{gauche} = 3.29 = 76\ \%$ anti conformation.

2) cyclohexanol with an axial hydroxyl group

Similarly for the axial conformation, the rotamer minima occur for the anti conformation and the gauche conformation. However, the gauche dihedral angle is 71 degrees instead of 60 degrees, thus this can again be attributed to vicinal hydrogen repulsions.

The Boltzman distribution gives:

$$N_{anti}/N_{gauche} = 1/2 \; . \; e^{-} \left\{ (85340-853831)/8.314.298 \right\}$$

$$K = N_{anti}/N_{gauche} = 0.594 = 37 \; \% \; anti$$

CYCLOHEXANOL (EQUATORIAL HYDROXYL GROUP)

The Van der Waal repulsion energy minima of the anti and gauche rotamers correspond to dihedral angles of 180 degrees and 56 degrees. The Newman projections of these conformations are shown below (fig.3.74).

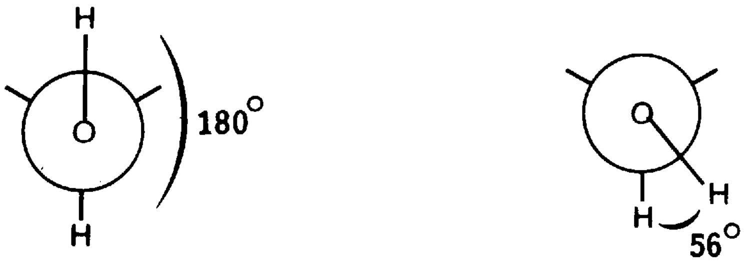


fig.3.74

The 180 degree dihedral angle is consistent with previous assumptions. However, the gauche dihedral angle is not 60 degrees but 56 degrees. This can be rationalized in terms of the steric repulsion from the alpha hydrogen and the beta axial hydrogen (fig 3.75).

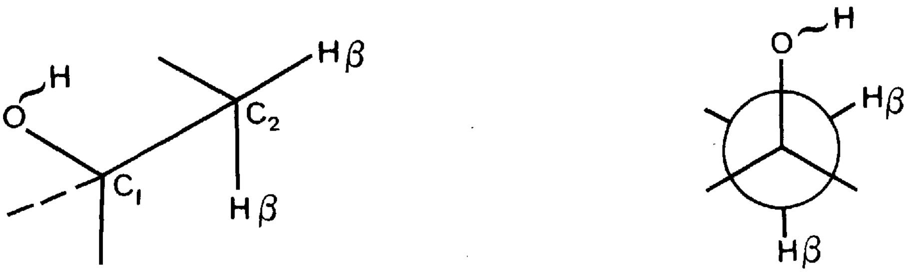


fig.3.75

If the beta equatorial hydrogen were absent then the dihedral angle would be 60 degrees.

Since the populations of the two preferred rotamers are known, the average dihedral angle for the equatorial conformation can be calculated:

Average coupling constant = 76/100 . 180 + 24/100 . 56 = 150 degrees

CYCLOHEXANOL (AXIAL HYDROXYL GROUP)

The Van der Waals repulsion energy minima occur for the anti rotamer and the gauche rotamer, the anti rotamer is 180 degrees, whilst the gauche rotamer is 71 degrees. The average coupling constant is therefore calculated as:

average coupling constant = 37/100 . 180 + 63/100 . 71 = 111 degrees

These calculated rotamer populations apply to the pure axial and equatorial hydroxyl conformations in the absence of any solvent or Van der Waal interactions. In the axial conformation, the percentage of anti rotamers was calculated to be 37 %. This equilibrium population should hold well for very dilute solutions in "inert" solvents. However, on increasing the concentration, self-association will occur and the equilibrium rotamer population will change. The most important change that will occur will be a destabalization of the anti rotamer. Similarly, in an associating solvent, there must be a destabalization of the anti rotamer. The anti-rotamer is by far the most "vulnerable" conformation in that it is subject to the 1,3 diaxial repulsions any increase of the steric bulk of the anti hydroxyl will result in the gauche rotamers being favoured or, if the system is in a conformational equilibrium between axial and equatorial forms (chair-chair equilibrium), a transition to the equatorial form may be favoured. Such a steric bulk increase of the hydroxyl group will result either through self-association or through solvent association. Consequently, the solutions of the conformationally rigid cis 4-tert.butylcyclohexanol and trans 4-tert.butylcyclohexanol in e.g. CCl_4, $CDCl_3$ and DMSO cannot be expected to have the same equilibrium population of rotamers as calculated above.

The equilibrium populations of the rotamers in the axial conformation has been the subject of previous discussion (31). In contrast with other authors, Joris, Scleyer and Osawa interpreted infrared data with the conclusion that the anti population is significantly populated (20). The most important factor in this case seems to be that the anti population depends upon the solvent and upon the concentration. Following this argument, the gas phase studies of axial cyclohexanols should have a significant anti population. Similarly, a very dilute solution of the axial hydroxyl compound in a solvent such as CCl_4 should exhibit a significant anti population. Noticeably, the evidence in favour of the anti population was from infrared measurments in CCl_4, whilst the evidence against the anti population was mainly conducted in $CDCl_3$ solution.

Rader (31) concluded that the anti rotamer in DMSO solution is absent, and the molecule is almost exclusively in the gauche rotamer conformation. The gauche rotamer was calculated to be 71 degrees for the axial hydroxyl conformation, however, it would be naive to assume that this dihedral angle is not affected by the associating solvent. Although a DMSO associated molecule can be represented in the graphic simulation, the exact nature of the association is not known. A 1:1 complex is also assumed but this may be an erroneous asumption. Therefore, it was considered unreasonable to attempt to calculate a rotamer with a Van der Waal repulsion minimum in an associating solvent.

The above argument also holds for the equatorial hydroxyl because the dihedral angles of the rotamers are subject to changes in an associating solvent. Therefore, the correlation of coupling constants measured in DMSO solution with the calculated diheral angles cannot be made on a quantitative basis. Nevertheless, the calculations show that the equatorial conformation possesses a larger average dihedral angle (150 degrees) than the axial hydroxyl conformation (71 degrees), assuming that the anti population is absent in DMSO. This is then entirely consistent with the observed coupling constant of the equatorial hydroxyl being larger than that of the axial hydroxyl.

THE INTERNAL HYDROGEN BONDS IN CYCLOHEXANDIOLS

THE DOUBLE INTERNAL HYDROGEN BOND

In cyclohexan-1,3-diol there is an abundance of evidence, from both nmr and infrared matrix and solution, to show that two types of internal hydrogen bonding occur. For trans cyclohexan-1,2-diol the evidence comes from the infrared studies alone, any difference in the ^{13}C nmr spectrum is unresolved.

The subject of double internal hydrogen bonds has appeared in the literature for about twenty years. The appearance of two bands in the internal hydroben bond band region of the infrared spectra of ethan-1,2-diol at -3^{o}C was concluded by Krueger and Mettee (23), to be due to two forms of internal hydrogen bonding, one involving the single hydrogen bond and the other the double hydrogen bond (fig.3.76), which they claimed was more stable. These authors were however reluctant to extend the double chelation phenomenon to 1,3 and 1,4 diols in light of conflicting evidence from Bue and Neel (6).

fig.3.76

A quantitative study of the strengths of alpha, omega internal hydrogen bonds by Busfield (7) did not consider the possibility of double chelation, but showed that the cyclization process occured for ; n = 2 to n = 6 (fig.3.77).

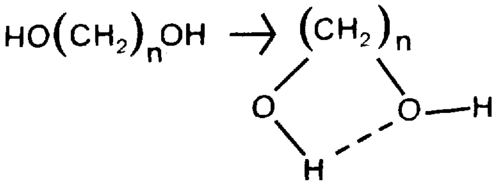
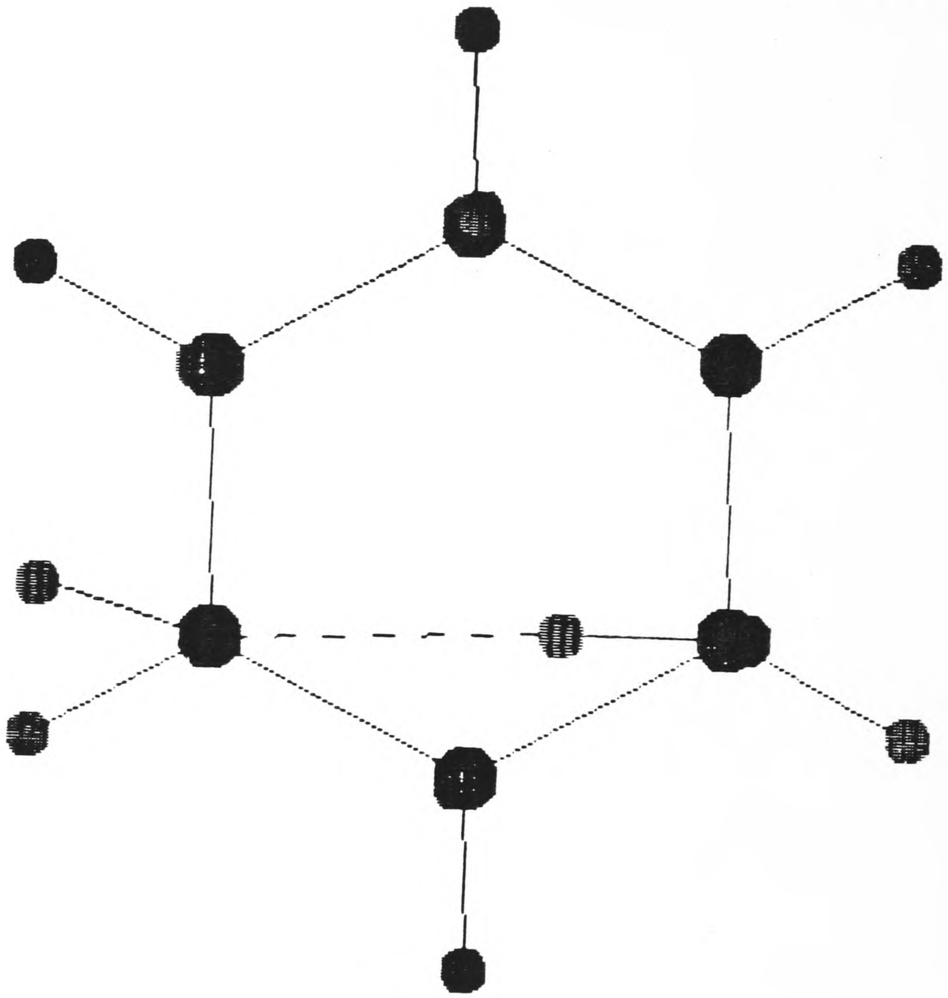


fig.3.77

fig.3.79



They concluded that - G for the above process decreased as n increased. However, the strongest internal hydrogen bond occured when n = 4, i.e. butan-1,4-diol. Examination of the spectrum of this compound reveals that the internal hydrogen bond band is much broader than for the other diols (fig.3.74). This strongly suggests that more than one type of internal hydrogen bond is present. Interestingly, the same effect is seen with cyclohexan-1,3-diol.

The computer graphic simulation has been used to compare the relative Van der Waal repulsion energies and torsion angles involved in the formation of single and double internal hydrogen bonds.

cis cyclohexan-1,3-diol

The diaxial conformation of cis cycohexan-1,3-diol was generated;

(a) with a single hydrogen bond

(b) with a double hydrogen bond.

The hydroxyl groups were then rotated simultaneously about the C-O bond to generate 360^2 conformations. The minimum energy conformation for (a) and (b) above was then calculated by the computer as were the geometry variables and the Van der Waals repulsion energy.

a) Single hydrogen bond

The minimum energy conformation as calculated by the computer is shown below (fig.3.79) and the VDW repulsion energy and geometry variables tabulated (table LVII). The Newman projections for C_1 and C_3

are shown in figure 3.80.

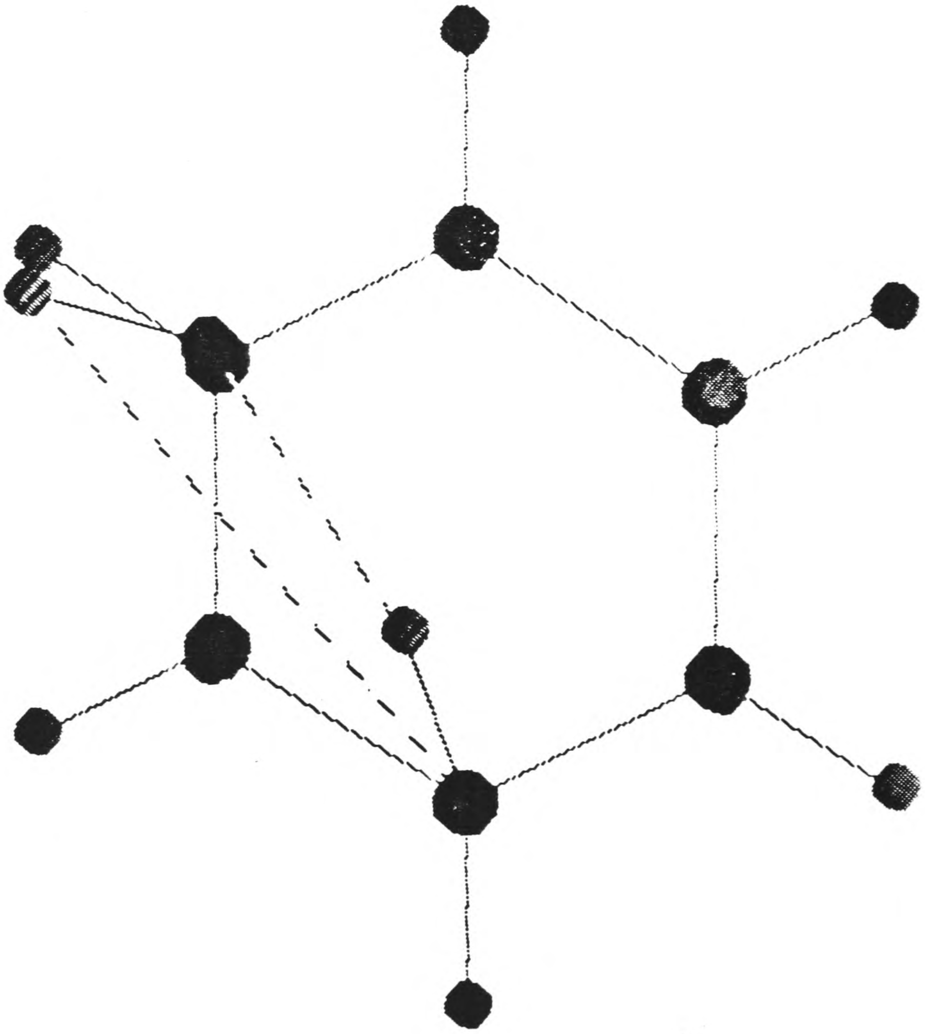
TABLE LVII

VDW ENERGY (KJ/mol)	DIHEDRAL ANGLES (DEGREES)
1131.345	152, 49

fig.3.80

The effect of the 1 - 3 diaxial interaction is clearly seen. The dihedral angle of the hydroxyl group which donates the hydrogen to the hydrogen bond is calculated as 152 degrees. This is substantially less than the "ideal" dihedral angle of 180 degres which would give the closest distance of approach of the hydroxyl hydrogen to the hydroxyl oxygen on C_3.

fig.3.81



b) Double hydrogen bond

The calculated VDW energy and the geometrical variables for the minimum energy conformation are tabulated below (table LVIII). The minimum energy conformation is shown in figure 3.81 and the Newman projections for C_1 and C_3 are shown in figure 3.82.

TABLE LVI

VDW ENERGY (KJ/mo)	DIHEDRAL ANGLES (DEGREES)
1095.887	160, 180

fig.3.82

The double internal hydrogen bond conforamation as calculated by the computer shows a significant decrease in the VDW repulsion energy

(35.458 KJ/MOL), even though the changes that occur force the dihedral angle of C_1 to increase to 160 degrees from 152 degrees with the single hydrogen bond. This brings the C_1 hydrogen closer to the axial hydrogen and increases the VDW repulsion energy. Similarly, the dihedral angle on C_3 of 18 degrees is far from ideal. However, the contribution of two hydrogen bond interactions clearly offsets the increased VDW repulsions and the net effect is a VDW repulsion energy decrease.

Using the Boltzman distribution law for the populations distributed between the two energy levels (double hydrogen bond and single hydrogen bond) is given by:

$$N_{double}/N_{single} = e^{-}\left\{(1095887-1131345)/8.314 \;.\; 298\right\}$$

$K = 2.7$ (73 % double hydrogen bond)

The Boltzman distribution law gives an equilibrium population of the double hydrogen bonded conformer of approximately 78 %. This being the case, it may now be necessary to re-evaluate the matrix and $CDCl_3$ solution spectra of cis cyclohexan-1,3-diol. During the discussion of the infrared measurments, it was assumed that the higher wavenumber band for the internal hydrogen bond in the matrix spectrum was due to the double hydrogen bond. However, the calculation above suggests that the double hydrogen bonded conformer is of lower energy than the single hydrogen bonded conformer and consequently of higher population. This being the case, then the assignments of the two bands must be reversed. In the $CDCl_3$ solutions, the reverse may be true ,since the higher wavenumber band appears to be of higher intensity and consequently of higher population. The explanation must therefore lie in the fact that the double hydrogen bond is destabilized to a greater extent than the single hydrogen bond by $CDCl_3$. However, since the nature of the interaction is uncertain at present the observation can only be taken as an empirical result.

In conclusion, the computer graphic simulation and calculation of VDW repulsion energies is useful in that it may identify the maxima and minima energy conformations. However, it represents an ideal system, i.e. a system in which there are no external forces operating. Obviously, in practice no system can behave in this manner and consequently the method is best used as a qualitative guide rather than a quantitative analytical tool.

LOW TEMPERATURE NMR STUDIES

Most of the nmr studies detailed above have involved the use of the conformationally rigid 4-tert.butyl cyclohexanols as reference standards for pure axial and equatorial hydroxyl groups. This method of analysis has, quite justifiably been the subject of much critisism (5). In particular, the weakness of the methods are the reliance on the precept that the tert.butyl group does not interact in any way with the hydroxyl group. In practice, the above studies have shown that some sort of interaction must occur, at least when the hydroxyl group is in an axial position.

As a consequence of this tert.butyl group effect, it has been generally suggested that a more accurate method of conformational analysis of the cyclohexane system is the low temperature approach (5). The method involves the lowering of the temperature at which the observations are made until a temperature is reached at which the rate of ring inversion is slower than the nmr timescale, at which point separate signals are observed for the alternative conformations e.g. for bromocyclohexane at approximately -100°C, the ^{13}C and ^{1} H nmr spectra show separate signals for equatorial bromocyclohexane and the axial bromocyclohexane. Integration of the separate signals for either the ^{1}H nmr experiment or a quantitative ^{13}C experiment then yield directly the equilibrium constant at that temperature which may be related to room temperature assuming a linear free energy/temperature relationship.

For bromocyclohexane there are no serious objections to this method. However, for a molecule such as cyclohexanol or any conformationally mobile molecule possesing a functional group capable of self association or non-bonded interaction with a solvent, a simple analysis of the above type cannot be valid. Consider cyclohexanol itself, for example, at a concentration required for a ^{13}C nmr experiment. Typically, the concentration required would be of the order of 0.1M to 0.2M to produce a reasonable signal to noise ratio within a practical duration. At this concentration, for example, in an inert low melting point solvent such as CS_2, self-association will occur so that in solution the monomer will be in an equilibrium with dimers, trimers or other polymeric forms. All these associates may have conformational possibilities in respect of the way the hydrogen bond is formed, e.g. axial OH to equatorial OH or equatorial OH to equatorial OH etc. Therefore, the number of distinct species may be quite large. However, on the simplest possible premiss that there is only one associate formed and that this associate is the dimer, the thermodynamic problem is still great. The self-association of the monomer to form the dimer is governed by thermodynamic parameters, In particular, there is a free energy change associated with the formation of the hydrogen bond. The low temperature study of trans cyclohexan-1,2-diol in $CDCl_3$ solution showed quite clearly that there are large changes in the degree of hydrogen bonding as the temperature is lowered. Therefore, the enthalpy, entropy and consequently the free energy of the associative process changes with temperature. Therefore, if the equilibrium constant for the ring inversion is determined (and consequently the free energy) at the lower temperature, there will be a far greater degree of self-association than at room temperature. Unfortunately, the change in the degree of self association with temperature is non-linear (as seen from the trans cyclohexan-1,2-diol study) and so the free energy detemined at the lower temperature may deviate considerably from that at room temperature.

This problem is not easy to solve, since it involves a knowledge of the effect of self-association on the conformational (chair inversion) equilibrium. This study itself is complex, and only in cases where a linear enthalpy of association against temperature plot can be attained will the problem be simplified (if any such cases exist).

Therefore, in consideration of the above it was felt that any low temperature studies would unjustified and although practically easy would yield values for free energy which could not be correlated to other methods.

CONFORMATIONAL ANALYSIS OF AMINO SUBSTITUTED CYCLOHEXANES

Preliminary investigations into the conformational analysis of cyclohexyl systems containing amino and hydroxyl groups show, as expected, that the conformational equilibria may be far more complex than in the diol systems. There are inherent difficulties in the study of the amino group itself. In ^1H nmr spectroscopy it was shown that it is possible to retard the proton exchange reactions by choosing a suitable solvent. In many cases pyridine proved the most suitable solvent. However, the quadrouple moment of the Nitrogen nucleus produces complex spectra due to coupling with the two amino protons (NH_2) and to the coupling with the alpha hydrogen protons. The resultant multiplet is therefore highly complex and not easy to analyze. The problem may however be circumambulated by the use of a nitrogen frequency decoupler, which can decouple the nitrogen spins from the protons (in a similar manner to the decoupling of protons from ^{13}C nuclei). With the use of this equipment it is envisaged that useful information may be gained from the amino proton coupling constants and the alpha hydrogen coupling constants. ^{13}C nmr studies of these compounds have not been performed, but it is likely that their usefulness would be comparable to that of the diol studies and may provide a suitable analytical tool.

Amines are unstable in halogenated hydrocarbons, and this poses a minor problem for infrared studies. However, other solvents are available together with the matrix isolation technique and undoubtably a combination of methods will give detailed information regarding the conformational eqilibria in these compounds.

CONCLUSIONS

The most important conclusions from the above studies, together with a brief appraisal of the main methods of analysis are given below:

SOLVENT EFFECTS

1)ALPHA HYDROGEN NMR STUDY

At the concentration of study (0.2 M), in an inert solvent such as CCl_4, considerable self-association occurs. The alpha hydrogen chemical shift therefore represents the degree of hydrogen bonding and also the conformation of the hydroxyl group. The change to a polar solvent always results in a shift of equilibrium in favour of the equatorial conformation. This is interpreted in terms of a solvent association to the hydroxyl group, which competes with the self-association process. In a solvent capable of strong hydrogen bonding association with the hydroxyl group, the equilibrium will lie far to the left.

2)HYDROXYL PROTON CHEMICAL SHIFTS

These were shown to be far too unreliable to even be of any qualitative use due to their extreme dependence upon concentration and temperature.

3) ^{13}C NMR CHEMICAL SHIFTS

For cyclohexanol this method was considered accurate only for the alpha carbon nuclei, the tert.butyl effect produced large errors for all the other carbons. Consistent with the alpha hydrogen chemical shift study, the ^{13}C alpha carbon chemical shifts showed that all polar solvents caused a shift of the conformational equilibrium in favour the equatorial conformation.

Two types of solvent behaviour were identified,

a) bulk solvent effect.
An effect which is analogous to the "solvation" of the molecule as a whole, which causes electron drift and a consequential chemical shift changes.

b) local solvent effect.
A direct interaction of the solvent with the hydroxyl group, which may or may not involve bond formation.

Hydrogen bonding solvents such as acetone and DMSO cause deshielding of the alpha carbon nucleus resulting from the higher degree of association in the system. The magnitude of the deshielding can be directly related to the hydrogen bonding strength of the solvent (DMSO > acetone).

$CDCl_3$ causes the unusual effect of shielding of the alpha carbon atom. This is a local effect and can be attributed to the disruption of hydrogen bonds i.e. $CDCl_3$ inhibits the self-association process.

CS_2 is unusual in that it behaves differently towards axial hydroxyls than towards equatorial hydroxyls, a phenomenon that is explained on the basis of the pi bonding nature of CS_2.

3) Infrared solution spectra

Comparison of solution spectra at a constant concentration in the solvents CCl_4, DMSO and $CDCl_3$, show that when the solvent is changed from "inert" CCl_4 to the associating DMSO, a new intermolecular hydrogen bond band for the solvent-alcholol association occurs. Simultaneously, the free hydroxyl band almost disappears. In $CDCl_3$ there is a decrease in intensity of the self-associated intermolecular hydrogen bond band relative to the free hydroxyl band. The observation is consistent with the ^{13}C nmr experiments. The infrared experiments also show that no solvent-alchol hydrogen bond occurs. The interaction which results in disruption of intermolecular hydrogen bonding must therefore be assumed to be a specific non-bonded interaction. This interaction does however cause a streic bulk increase which therefore favours the equatorial conformation.

CYCLOHEXANDIOLS

1) THERMODYNAMIC CRITERIA

The thermodynamic calculations correctly predict the conformations of cyclohexandiols which possess the axial/equatorial and equatorial/axial degenerate forms i.e. trans cyclohexan-1,3-diol and cis cyclohexan-1,4-diol. The thermodynamic calculations cannot however account for conformations in which there are unaccounted for steric interactions (trans cyclohexan-1,2-diol) or where the formation of an internal hydrogen bond stabalizes a particular conformation which may otherwise be unfavourable (cis cyclohexan-1,3-diol).

2)HYDROXYL PROTON CHEMICAL SHIFTS

The hydroxyl proton chemical shifts, although subject to large errors, show qualitatively that alkandiol solutions in $CDCl_3$ may retain spin-spin coupling in the presence of internal hydrogen bonds. In such cases, where an equilibrium exists between the internally hydrogen bonded form and the free diol, neither species contributes to proton exchange. The proton exchange reactions are inhibited by the solvent , probably due to the inhibition of cyclic dimer formation. The inhibition is concentration dependent and increased concentration results in loss of spin-spin coupling of the hydroxylic proton to the alpha hydrogen and the advent of fast proton exchange.

The same process can be applied to the cyclohexandiol system. However, the ring inversion process always results in the breaking of the internal hydrogen bond, which may lead to loss of spin-spin coupling depending upon the rate of ring inversion.

The study in CCl_4 solution is rather uninformative due to the extremely low solubility of the cyclohexandiols in CCl_4.

3) DMSO COUPLING CONSTANTS

The coupling constants for the hydroxylic proton in DMSO solution provide a good accurate method for conformational analysis. However, the solvent effect of DMSO always increases the equatorial population and this effect may be extreme as in cis cyclohexan-1,3-diol. The conformation in DMSO solution is exclusively diequatorial, whilst in CCl_4 and $CDCl_3$ the diaxial internally hydrogen conformation has a comparable population to that of the diequatorial.

4) ^{13}C NMR CHEMICAL SHIFTS

In general, the most reliable measurments come from the carbon nuclei resonances that are furthest removed from the hydroxyl groups. In all cases, an axial hydroxyl group has a perturbing effect on the chemical shifts of all the carbon nuclei. Although a highly approximate analysis, qualitatively the method can distinguish between axial and equatorial conformations. The most notable result is seen in the spectrum of cis cyclohexan-1,3-diol in $CDCl_3$, in which the carbon resonances show a splitting. This observation in conjunction with the matrix infrared measurments, is interpreted in terms of a double and single internal hydrogen bond. In a strongly associating solvent such as DMSO, the diaxial internal hydrogen bond does not occur and the conformation is almost entirely diequatorial.

5) INFRARED SOLUTION AND ARGON MATRIX STUDIES

The solution spectra of the hydroxyl stretch region are unresolved with respect to the conformational differences of the hydroxyl groups. The solution spectra do however, readily identify the presence of an internal hydrogen bond, in contrast to nmr where the timescale does not allow this observation directly.

The Argon matrix spectra are far more resolved and in some cases show complete resolution of axial and equatorial hydroxyl stretch bands (trans cyclohexan-1,2-diol). In the majority of cases however, the spectra consist of asymmetric bands with definite shoulders. Wavenumber assignments have been made to these bands and excellent correlations with conformation have been made. The matrix spectrum of cis cyclohexan-1,3-diol clearly distinguishes two types of internal hydrogen bonds and this correlates well with the ^{13}C nmr measurments.

The solution spectra in $CDCl_3$ are surprisingly better resolved than in CCl_4 solution spectra, and this is discussed in terms of a non-bonded solvent interaction.

6)COMPUTER GRAPHIC SIMULATION STUDY

For the monohydroxy compounds, the computer graphic simulation provides an adequate description of the Van der Waals interactions that predominate in the axial and equatorial hydroxyl conformations. The VDW repulsion energy plots give a graphic explanation for observed coupling constants in axial and equatorial cyclohexanols. This theoretical description is however subject to severe limitations in that no solvent interactions can be accounted for. The actual behaviour of these systems must therefore differ considerably from that described in this study.

The internal hydrogen bond study described in this section may be erroneous. The main difficulty seems to arise from the fact that it is necessary to generate such a large number of conformations for an accurate geometric calculation. It is possible therefore that during the energy minimum scanning process, local minima have been identified. In practice, in a "real" system (one in which the solvent plays its role) such minima may not occur and the conformations may be entirely different.

In conclusion, the factors which may affect the conformational preference of a molecule may be quite varied and individual. The classic example from this study is the effect of $CDCl_3$ as a solvent. In the case of cyclohexanol it favours the equatorial conformation, whilst in the case of cis cyclohexan-1,3-diol it favours the internally hydrogen bonded diaxial conformation. To predict such effects therefore, it is necessary to examine all the possible effects on conformation.

As a result of this study, it must be true to state that it is insufficient to say that a molecule has a particular conformation in solution, the proviso must always be added that a molecule has a particular conformational preference under specific conditions of solvent, temperature and concentration.

SYNTHETIC METHODS

PREPARATION OF ALKANEDIOLS

octan-4,5-diol

Into a 100ml two-necked flask, fitted with a 10ml dropping funnel, 30ml of 88% formic acid (0.6 mol) was added together with 7ml (0.062 mol) of 30% hydrogen peroxide. The mixture was stirred with a magnetic stirrer, and the temperature lowered to 0 - 5°C in an ice bath. To this solution 5g (0.05 mol) of trans oct-4-ene was added slowly over a period of about ten minutes, the temperature of the solution being maintained between 45° and 50°.

The solution was then refluxed for one hour and then cooled to room temperature.

The excess formic acid and the water were then removed on a rotary evaporator, the temperature being kept as low as possible to avoid vacuum sublimation of the hydroxyl formate ester.

The crude hydroxyl formate ester was then cooled to 0°C in an ice - salt bath, and an ice - cold solution of 4g (0.1 mol) of sodium hydroxide in 7.5ml of water was added in small portions, keeping the temperature below 45°C.

The precipitated octan-4,5-diol was then filtered at the pump, washed with cold water and recrystallized from an alcohol / water mixture.

yield = 84 %

melting point = 145 C

octan-1,2-diol

This was commercially available from Aldrich Chemical Company (99%) purity and the sample was stored in a dessicator.

CYCLOHEXANDIOLS

The configurational isomers of the cyclohexandiols were all separated by fractional vacuum sublimation at 2 - 4 mm Hg. The crystalline fractions were allowed to sublimate in a long glass delivery tube, and the two fractions checked for purity using melting point and ^{13}C nmr.

For the 1,2 and 1,3 diols, separation was achieved at 100°C over a period of three hours, using a water bath. For the 1,4 isomers, separation was achieved at 120°C, using an oil bath.

ALKANOLS

These were all commercially available from Aldrich chemical Co., and were all analytical grade. Futher purification was unecessary apart from drying over molecular seives 3A.

BICYCLO(3,3,1)NONANOLS

The bicyclo(3,3,1)nonanols were obtained from Mr. C.Richards, of the Polytechnic of Wales.

NMR AND I.R. SOLVENTS

All solvents were obtained from Aldrich Chemical Co. The solvents were distilled twice and stored over molecular sieves 3A.

APPENDIX

The VDW energy expression used in CHEM-X has the following form and is summed over all non-bonded atom pairs:

$$A.\exp(-B.r) \;/\; r^{D} \;-\; C \;/\; r^{6} \;+\; K.q1.q2 \;/\; r$$

Where: A,B,C,D are constants.

q1,q2 are the atomic charges.

K is a unit conversion constant.

r is the separation of the atom pair.

For small molecules this can be quickly evaluated, but for larger molecules it is faster to evaluate the VDW energy of pairs of entries instead of pairs of atoms.

For each entry, the centroid, the radius R (distance from the centroid to the furthest atom), the total charge Q and the sum of the VDW attractive terms C are calculated and the following expression is used to evaluate the interaction energy of the two distinct entries.

$$K.Q1.Q2 \;/\; r \;-\; C1+C2 \;/\; 2r^{6}$$

Where: Q1 and Q2 are the charges on the entries.

K is a unit conversion constant.

C1 and C2 are the total attraction constants of the entries.

r is the separation of the centroids.

The change over from atom-atom calculation to the entry-entry calculation is controlled as follows (d is usually 1 angstrom):

1. $r > R1 + R2 + d$, the entry-entry expression is used.

2. $r < R1 + R2$, the atom-atom expression is used.

3. $R1 + R2 < r < R1 + R2 + d$, a linear interpolation based on r is used.

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