CONFORMATIONAL STUDIES ON ALICYCLIC ALCOHOLS

by

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I N D E X

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ABSTRACT

It is well known that intermolecular hydrogen-bonding is concentration dependent. It is also known that the ^1H chemical shift of an hydroxyl proton is dependent upon concentration. ^1H NMR spectroscopy has therefore been used to study hydrogen-bonding in solution.

It was found previously by Becker, Liddel and Shoolery that at very high dilution in CCl_4, the chemical shift of the hydroxyl group in ethanol is directly proportional to concentration. This was also found by Ouellette et al, for cyclopentanol and cyclohexanol in CCl_4. The present author has extended this work to these two compounds and other alicyclic alcohol systems in both CCl_4 and d-chloroform, and that a chemical shift at infinite dilution can be used as a test of the presence of intramolecular hydrogen-bonding.

Infra red and NMR methods are compared in the study of hydrogen-bonding in a series of alicyclic diols and from the results obtained, predictions are made on their preferred conformations.

The conformational preference of the hydroxyl group in cyclohexanol is determined by the concentration vs. chemical shift method and compared with other standard NMR methods, namely: peak area measurement at low temperature; chemical shift of the α-proton and a lanthanide shift method (in which it is suggested that the complexation does not affect the equilibrium). The chemical shift vs. concentration method quoted above is then used to establish the conformational preferences of the phenyl and ethyl groups in phenyl- and ethylcyclohexane.

The lanthanide shift method is also presented for 1-ethylcyclohexanol and these results cast some doubt on the validity of the original postulation of the equilibrium not being affected.

These experiments rely on a determination of the equilibrium constant between axial and equatorial conformers and a treatment of the accuracy of the method is presented.

Chemical shift at infinite dilution is also used to study intermolecular hydrogen-bonding and as the basis for analysis of mixtures of alcohols.

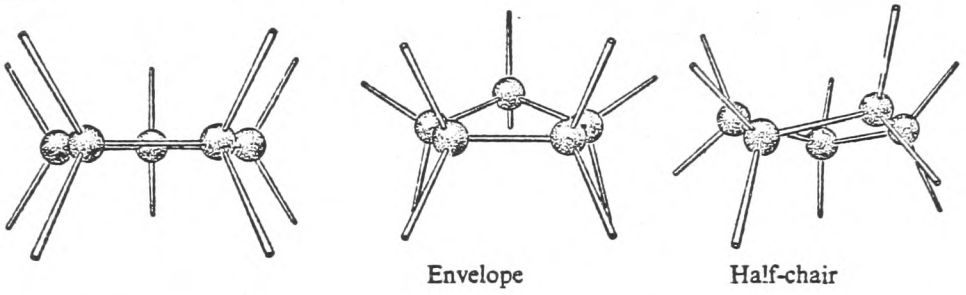
This technique can therefore be used in the quantitative and qualitative study of hydrogen-bonding and conformation in alicyclic systems.

INTRODUCTION

The five-membered ring system

In the planar form cyclopentane has very little angle strain (the internal angle in a regular pentagon being 108^{o}, which is very close to the tetrahedral angle of $109^{o}28'$). However there is substantial eclipsing strain between adjacent hydrogen atoms, and hence it turns out that, by puckering the cyclopentane ring more energy is lost through staggering the hydrogen atoms than is gained by the consequent increase in the angle strain in the molecule. As a result, cyclopentane has the puckered forms shown in Fig.1, rather than the planar form shown.

Fig.1.



(*A*) Planar (*B*) Puckered

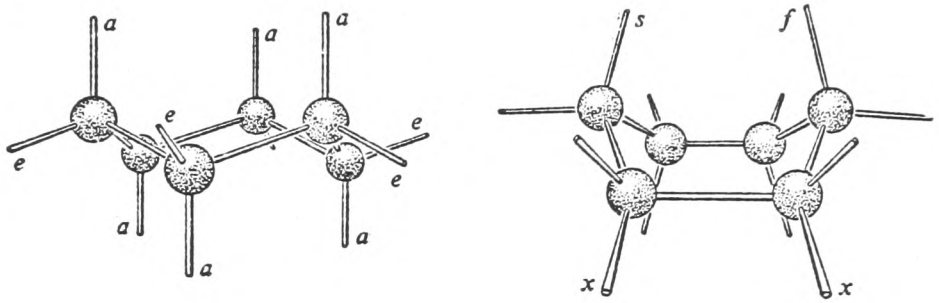
Cyclopentane.

The shape of the ring is not fixed; the individual carbon atoms move up and down at right angles to the average plane of the ring in such a manner as to cause the irregularity or puckering to move around the ring in what has been termed[1] by Pitzer as a "pseudorotation". Although in substituted cyclopentanes, one or the other, of the puckered forms may have greater stability, the conformational energy changes in the cyclohexane system are far more extreme, as will be shown later, i.e. compared to the six-membered system the cyclopentane system is fairly rigid.

The six-membered ring system

It was pointed out by Sachse[2] in 1890 and later revived by Mohr[3] in 1918, that two puckered, i.e. non-planar, models of cyclohexane could be constructed in which the valence bonds of all the carbons were at the tetrahedral angle ($109^{o}28'$) to each other and which were therefore free of angle strain. These are a rigid or chair form (Fig.2-C) and a mobile form which can readily be distorted into a variety of shapes, some of which resemble a boat (Fig.2-B).

Fig.2.



"C" Chair

a Axial bonds
e Equatorial bonds

"B" Boat

s-f Bowsprit-flagpole interaction
x-x Pair of eclipsed bonds

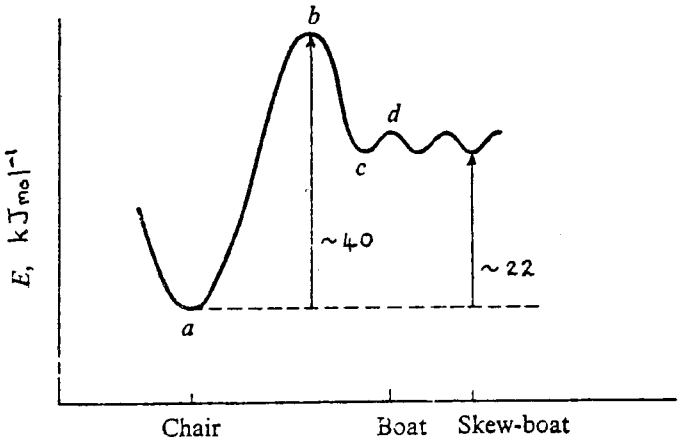
In the chair shaped molecule there are two types of bonds, namely those pointing up and down, called axial(a), and those pointing sideways which are called equatorial(e).

In the chair form, not only is there no angle strain but there is no bond opposition (eclipsing) strain either and hence the potential energy is at a minimum (See point 'a' in potential energy diagram shown in (Fig.3)). When the bottom part of the chair is bent upward (or the back bent downward), the chair is transformed into a boat. However, during the transformation, some angular distortion is required because several bonds have to be rotated at the same time, and hence, the molecule passes through a form of high potential energy (point 'b' in Fig.3.). The height of this

potential barrier has been determined[4] by N.M.R. and was found to be of the order of 40 $kJmol^{-1}$. However, at room temperature, this barrier is not high enough to prevent rapid interconversion.

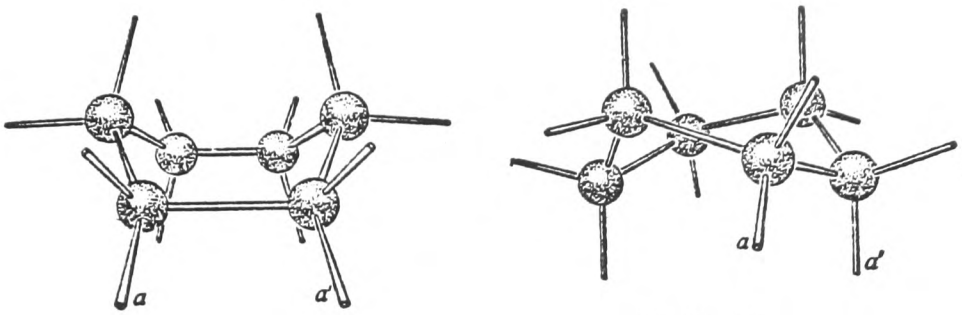
However, in the boat form although there is no angle strain there is bond opposition strain involving the four pairs of hydrogens at the side of the boat i.e. one pair being x-x in Fig.2. There is also strain due to the interference of the pair of hydrogens shown in Fig.2 as s-f, which are only 0.18nm apart (the sum of the van der Waals radii of two hydrogens being 0.24nm. This is sometimes called the "bowsprit-flagpole interaction". As a result of this the boat is considerably less stable than the chair. But by distorting the model in such a way as to pass from one boat to another, one obtains forms in which both bowsprit-flagpole interactions and eclipsings of adjacent hydrogens are somewhat alleviated (Fig.4). Hence in the energy diagram (Fig.3) these forms (sometimes called "skew-boats" or "twist-forms") correspond to the energy minimum at (point c) with the true boat being at (point d). The difference in energy between the chair form and the flexible form has been estimated[5,6] to be of the order of 22 $kJmol^{-1}$.

Fig.3.



Potential energy of cyclohexane as a function of conformation.

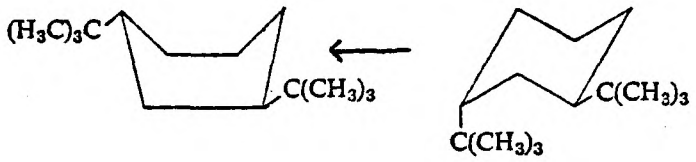
Fig.4.



(*a*) Boat (*b*) Skew-boat

There are, nevertheless, some molecules in which the cyclohexane ring exists in the flexible form. One important case being that of trans-1,3-di-tert-butylcyclohexane[5,6]. If this molecule (Fig.5) existed as a chair, there would be an intolerable interaction between the axial t-butyl group and the axial hydrogens, and hence will exist entirely in the flexible form. (The fact that the bulky t-Bu group prefers the equatorial position proves to be an invaluable asset in the following work).

Fig.5.

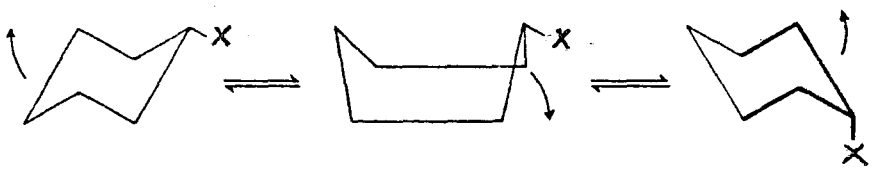


trans-1,3-di-t-butylcyclohexane

Monosubstituted Cyclohexanes

Substituents attached to axial and equatorial bonds are customarily called axial and equatorial substituents respectively. However it has been shown previously that an equatorialy substituted chair, can be readily converted into a flexible form (See Fig.2 and 4), and this, in turn, can be similarly converted into another chair in which the substituent is now axial (Fig.6).

Fig.6

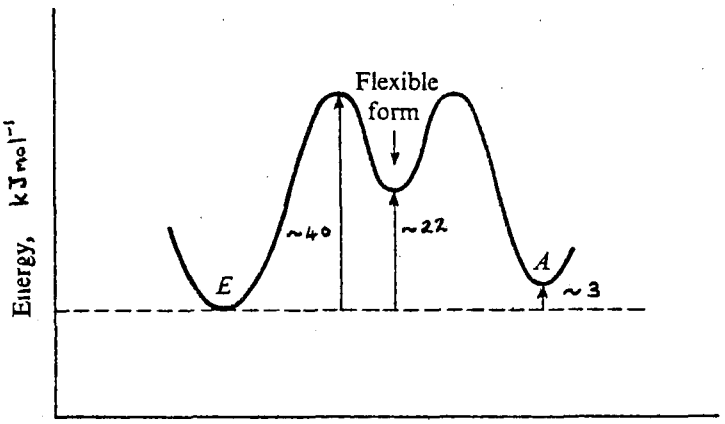


Equatorial (E) Present in very small concentration Axial(A)

Interconversion of chair forms of a monosubstituted cyclohexane.

The two isomers A and E in Fig.6, are conformational isomers, or conformers. The difference in potential energy between them can be estimated from an inspection of the models. The axial isomer,A, has two interactions of the type present in the gauche form of butane (these are shown in heavy lines in Fig.6). No such interactions are present in the equatorial isomer,E. The potential-energy difference between the axial and equatorial forms, of course, depends upon the nature of the substituent,X, and where X=OH, the value[7] is given as 2.5 to 3.5 $kJmol^{-1}$. The potential energy of cyclohexanol as a function of conformation is shown in Fig.7.

Fig.7



Disubstituted Cyclohexanes

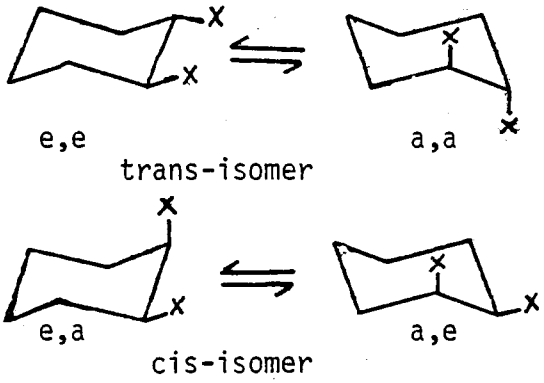
On introducing a second substituent into the cyclohexane ring, one introduces diastereoisomeric forms i.e. one cis, the other trans, Here, the substitution can be 1,2-, 1,3-, and 1,4- and all three will exist in cis and trans forms. For simplicity, these may be written in a planar form (Fig.8).

Fig.8. e.g. 1-2-di-substituted cyclohexane

trans-isomer cis-isomer

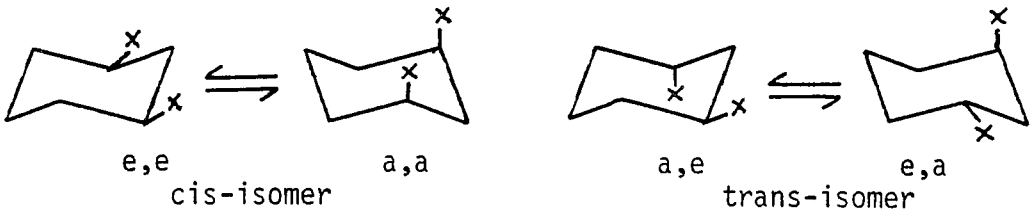
However, as the cyclohexane ring is not planar, one needs to consider these isomers in their chair forms (Fig.9).

Fig.9.

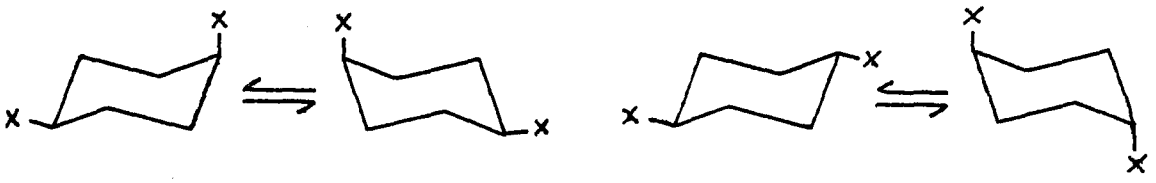


It is worthwhile, here, looking at the cis and trans forms of 1,3- and 1,4- disubstituted cyclohexanes. (Fig.10.)

Fig.10.



1,3-disubstituted cyclohexane



a,e e,a e,e a,a

cis-isomer trans-isomer

1,4- disubstituted cyclohexane

It can be seen (Table.1) that the most stable conformer is the one where the interaction energy is the lowest, indicated by the least number of interactions in this case.

Table 1.

Isomer	Conformation	No.gauche[a]	Interaction kJmol^{-1}
cis-1,2	e,a	3	11.3
	a,e	3	
trans-1,2	e,e	1	3.75
	a,a	4	15.0
cis-1,3	a,a	4	22.5*
	e,e	0	0
trans-1,3	e,a	2	7.5
	a,e	2	
cis-1,4	e,a	2	7.5
	a,e	2	
trans-1,4	e,e	0	0
	a,a	4	15.0

a- here $X=CH_3$ in the conformers, and these are the number of butane-gauche interactions. It would be expected that a similar sort of situation would occur where X=OH, but the additional interaction betweer -OH groups must be considered. (i.e. hydrogen-bonding).

*Includes diaxial methyl-methyl interaction.

Hydrogen-Bonding

The criteria for the existance of H-bonds are somewhat more clear cut than for other intermolecular interactions. Some convenient criteria for the existence of H-bonding are listed below:-

1. H-bonding occurs between a proton donor group A-H and a proton acceptor group B, where A is an electronegative atom, O, N, S, halogen or carbon, and the acceptor group is a lone electron pair of an electronegative atom, or a π-electron orbital of a multiple bond system. Generally, a H bond can be characterised as a proton shared by two lone electron pairs.

2. H-bonding is a distinctly directional and specific interaction. It is more localised than any other type of weak intermolecular interaction. (Where the acceptor group is a π-electron orbital, H-bonding is probably no more directed than a typical charge-transfer complex, such as that between iodine and benzene).

3. The total H-bond length R(A.....B) is equal to or less than the sum of the van der Waals radii of atoms A and B, that is, the total bond length contraction caused by H-bond formation is equal to or is greater than twice the van der Waals radius of the hydrogen atom.

4. The enthalpy of H-bonds generally falls in the range of 4-40 $kJmol^{-1}$. Intermolecular interactions other than H-bonding also fall within this range.

5. H-bonding is an association 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 H-bonding where the H-bond exists in the monomer state - See Figs.11,12).

6. In H-bonding a specific covalent A-H group interacts with a specific acceptor site. The A-H bond is thereby weakened but not broken, and the properties of the acceptor group are also affected.

All molecules can be conveniently classified into four types with respect to their ability to participate in H-bonding; as was classified by Pimentel and McClellan. (Table 2).

Table 2

Type	Description	Examples
I	molecules with one or more donor groups (acids) and no acceptor groups.	haloforms, highly halogenated compounds, acetylenes.
II	molecules with one or more acceptor groups (bases) and no donor groups.	ketones,ethers,esters, olefins,aromatics, tertiary amines, nitriles,isonitriles.
III	molecules with both donor and acceptor groups.	alcohols,water,phenols, inorganic and carboxylic acids, primary and secondary amines.
IV	molecules with neither donor or acceptor groups.	saturated hydrocarbons, carbon tetrachloride, carbon disulphide.

Hydrogen bonding molecules are divided into type I through III, while molecules incapable of H-bonding form type IV. The latter include compounds which are used as the so-called inert solvents in studies of H-bonded molecules. (In fact no completely inert solvent can exist, since dissolving takes place only through some interaction between solute and solvent molecules, but these "inert" solvents exert minimal solvent effects).

Type I plus type II molecules form H-bonded complexes, frequently in a simple 1:1 ratio. The strength of H-bonding depends primarily on the relative acidity of I and the basicity of II. The system chloroform - acetone is a typical example:-

$Cl_3C\text{-}H + (CH_3)_2\ C{=}O \qquad Cl_3C\text{-}H \text{ ----} O{=}C(CH_3)_2$

The bonding in chloroform is worth noting, as it was found necessary to use it as a solvent in the work carried out.

Type III molecules can self-associate by H-bonding with themselves. Two types of H-bonded complexes may be formed:-

Intermolecular (See Fig.11).

This is the widest general class of H-bonding which involves two or more molecules of the same or different substances associating. The resulting H-bonded complexes are not usually limited to dimeric linkages, but may produce chains, rings or three dimensional networks.

Intramolecular (See Fig.12).

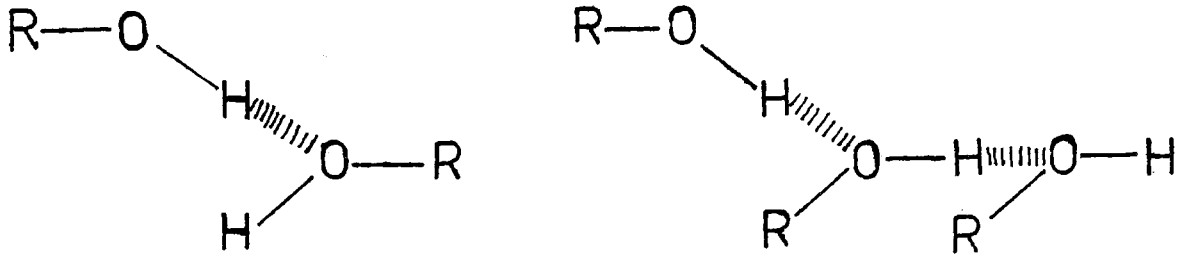
This other broad class contains those substances which have donor and acceptor sites within the same molecule, i.e. the H-bond is formed between groups within the same molecule. This process was first called "chelation", because of its pincer-like action resembling the closing of a crab's claw. However, this picturesque model is lost in proteins and larger molecules so the more general term "intramolecular H-bonding" is used.

The strength of H-bonding depends on the relative acidities and basicities of the donor and acceptor sites and in thecase of intramolecular H-bonds, on the spatial arrangement present.

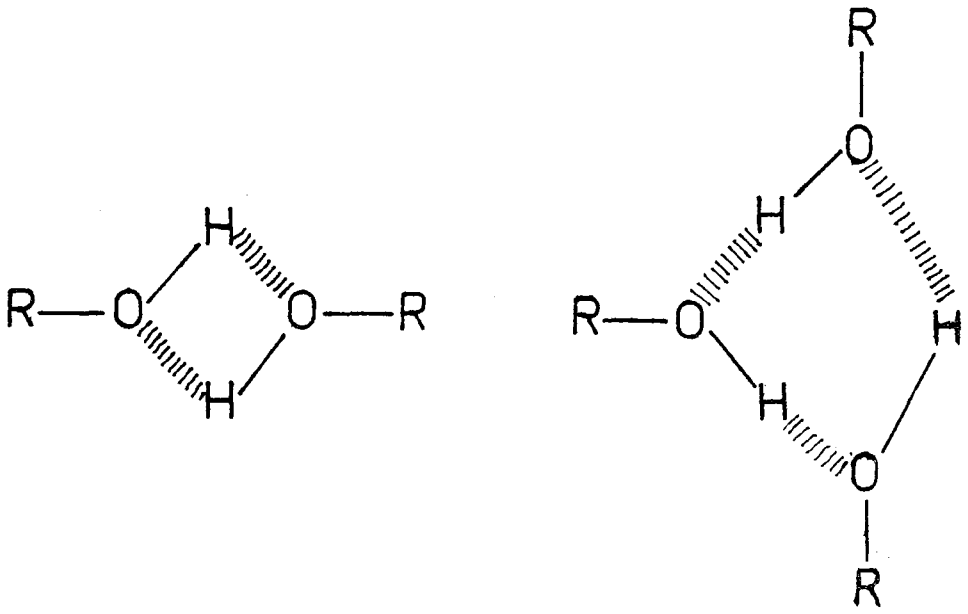
When molecules of either type I or II are added to type III molecules, several H-bonding equilibria can coexist. In the case of type I plus type III

molecules, the donor group of the type I molecules must compete with that of the type III molecule for the acceptor site(s) in the latter. This competition generally leads to a decrease in the extent of the self-association of the type III molecules, and the formation of one or more new H-bonded complexes between the two types of molecules.

Fig.11.

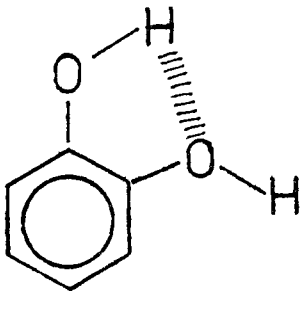


open/linear dimer and trimer.

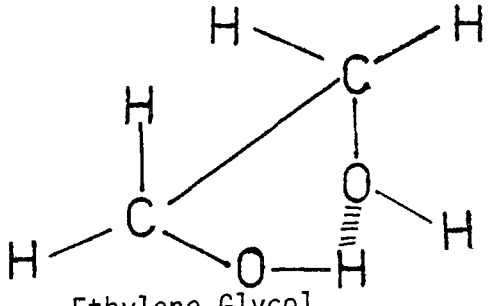


cyclic/closed dimer and trimer.

Fig.12



Catechol



Ethylene Glycol

Because of the number and complexity of the molecular species possible in such systems, experimental results are difficult to interpret. Great simplification can generally be achieved through the use of the "inert" solvent i.e. type IV. Dilution of a solution of self-associated (type III) molecule by an "inert" solvent shifts the self-association equilibria to the left, towards the monomeric species. At sufficiently low concentrations (usually 10^{-2} to 10^{-3}M) the type III molecules may be completely unassociated (this behaviour applies only to intermolecular H-bonding, since the extent of intramolecular H-bonding is little influenced by dilution with an "inert" solvent.).

Also, with molecules of type III, it should be noted that temperature will exert a great effect on the amount of association present i.e. an increase in temperature will increase the thermal motion of the molecules and hence can break down the H-bonding (note however, again, that this has the greatest effect on intermolecular H-bonding as opposed to intramolecular H-bonding).

Hence it is worthwhile,here,stating that there are 3 main criteria which will affect H-bonding, namely:-

1. Solvent
2. Concentration
3. Temperature.

Thus in order to carry out any experimental work on H-bonding, one needs to keep two of the factors constant while varying the third.

In the following work the temperature and solvent were kept constant while the concentration was varied.

Effect of Hydrogen Bonding on Spectroscopic Measurements

Proton Magnetic Resonance.

The formation of a H-bond A-H----B modifies the electron density around the proton of the A-H group and hence its shielding. In most cases the PMR absorption is displaced downfield (lower magnetic field), causing a H-bonding shift which is added to the existing chemical shift. Therefore, the H-bonding shift is usually negative, with the exception of some cases involving aromatic molecules.

There are several contributions to the H-bonding shift:-

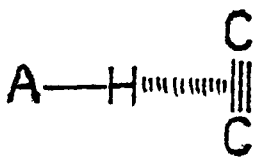
1. The electronic structure of the A-H group is distorted by the presence of the proton acceptor group B. The electric field of the latter tends to draw the H away from the bonding electrons of the A-H bond and to reduce the electron density in the immediate vicinity of H. The contribution of this effect to the H-bonding shift is always negative, since the de-shielding of the H will cause its resonance signal to occur at lower magnetic fields than in the absence of B.

II. Another contribution is also provided by group B, an effect similar to the neighbour anisotropy effect in free molecules. The secondary magnetic field at the proton due to electron currents in the group B will be non-zero when the electron cloud of group B is not spherically symmetrical and is therefore magnetically anisotropic. This contribution can be either positive or negative, but will be positive if the principal symmetry axis of B is along the A-H axis (i.e. increased shielding, requiring a stronger magnetic field). This contribution is not large, generally of the order of + 0.6 ppm. When B is an aromatic ring, a large positive contribution can occur.

III. A related effect is one that can be ascribed to the relative orientations of groups A-H and B. If A-H acts as a donor to a group B with the molecular axis of the two at the same angle, then the axial symmetry required for the

presence of contribution(II) will be partially removed and the paramagnetic high-field shift will be reduced. This will appear as a shift to low field on association. Such an effect may be important in H-bonding interactions where the A-H group associates with the π-electrons of another group.

e.g.



Generally contribution (I) is the principal one, and has been ascribed simply by Schneider, Bernstein and Pople[8] to two phenomena:-

(a) partial withdrawal of the proton from its electronic environment by the electronegative acceptor atom.

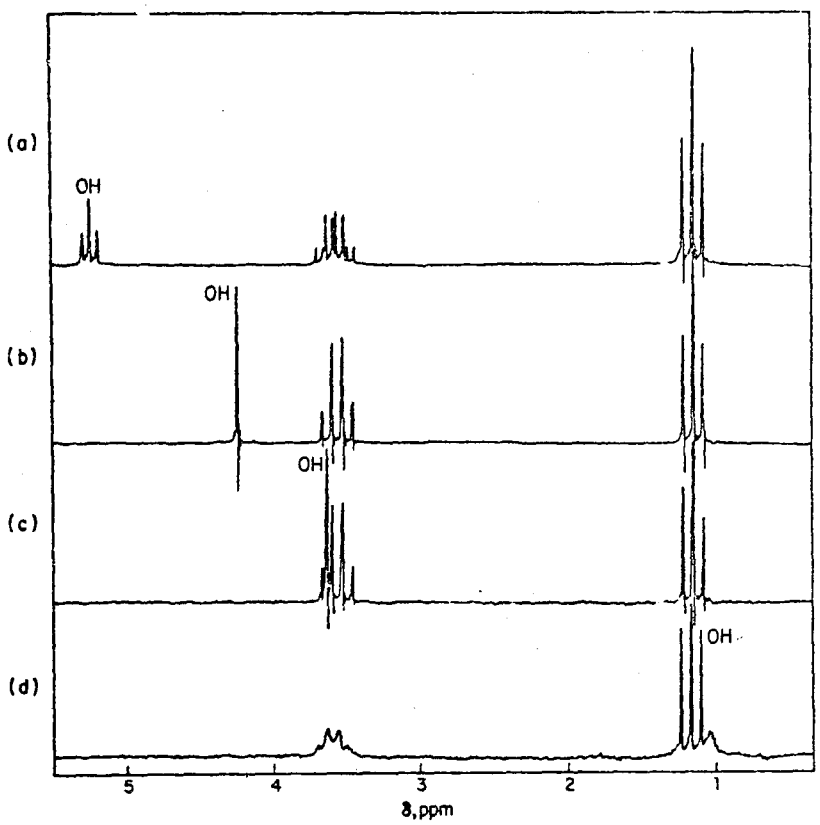
(b) inhibition of electronic circulation about the proton by the electric field of the electronegative atom.

Hence in the case of an-OH group the relative position of its resonance indicates a greater or lesser extent of H-bonding, a high field shift corresponding to less H-bonding. With some reservation this is a good approximation, although electronic screening, steric hindrance and inductive effects should not be overlooked completely.

High resolution P.M.R. spectroscopy is very useful in the study of H-bonding phenomena in liquids and solutions. In solution, concentrations are limited to about 0.01M or more, in order to provide a sufficient number of protons for a measurement. Hydrogen-bonded shifts are clearly revealed when the P.M.R. spectra of H-bonded species such as alcohols are measured as a function of temperature and concentration in "inert" solvents. (Fig.13) shows the appearance of the P.M.R. spectrum of liquid ethanol and its progressively more dilute solutions in CCl_4. The positions of the methyl

triplet and the methylene quartet are affected very little by dilution. The -OH signal, however, moves from approximately 5ppm, downfield from T.M.S., in pure ethanol to approximately 1ppm in 0.1M solution of ethanol in CCl_4.

Fig.13



PMR spectra of ethanol at 60 MHz and 40°C (a) Liquid ethanol; (b) 2.2M in CCl_4; (c) 1.1M in CCl_4; (d) 0.11M in CCl_4. (TMS standard)

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 in shielding of the -OH proton, indicated by the shift of the -OH resonance to higher magnetic fields with decrease in concentration, is due to the dissociation of H-bonded (self associated) alcohol complexes.

It might be expected that in self-associated hydroxylic compounds, individual -OH resonances would be observed for non-H-bonded hydroxyl groups in monomers, as well as for H-bonded hydroxyl groups in cyclic and open dimers, trimers, n-mers and so on. In this respect, however, P.M.R. differs significantly from I.R. spectroscopy. Usually only one P.M.R. signal is observed for the protons involved in H-bonding; this signal is a weighted average of all the protons in their environments, in the free as well as the associated forms. The time required for the resonance measurement (the time of spin orientation in the magnetic field, about 10^{-2} - 10^{-3} sec) is long compared to the lifetimes of H-bonded species, which is 10^{-12} - 10^{-13} sec, because of the very rapid formation and breaking of H-bonds in solution. In a time of the order of 10^{-3} sec the H of an AH group will participate in many H-bonds with neighbouring molecules. Accordingly it will experience at each concentration an averaged-out environment which will depend on the number and kind of proton donor species present. In the case of self-associated systems this fact decreases the usefulness of P.M.R. as a method of investigating the nature of the H-bonded dimers and n-mers and their equilibria. However, in cases where there is only one type of proton donor H-bonded to acceptor molecules in 1:1 complexes, the P.M.R. method is a very powerful method for studying H-bonding.

The main method used to obtain the unassociated value of the chemical shift is the method explained above for ethanol (i.e. successive dilution) and extrapolating the results to infinite dilution. This method undoubtedly introduces some error in the hydrogen bond shifts; however, comparisons can be made for data collected under similar conditions.

In the above, the type of H-bonding discussed is intermolecular, and successive dilution down to almost infinite dilution will ensure the presence of the monomer. However, in the case of the intramolecular H-bond, it is not affected by dilution and hence the -OH resonance will appear at a much lower

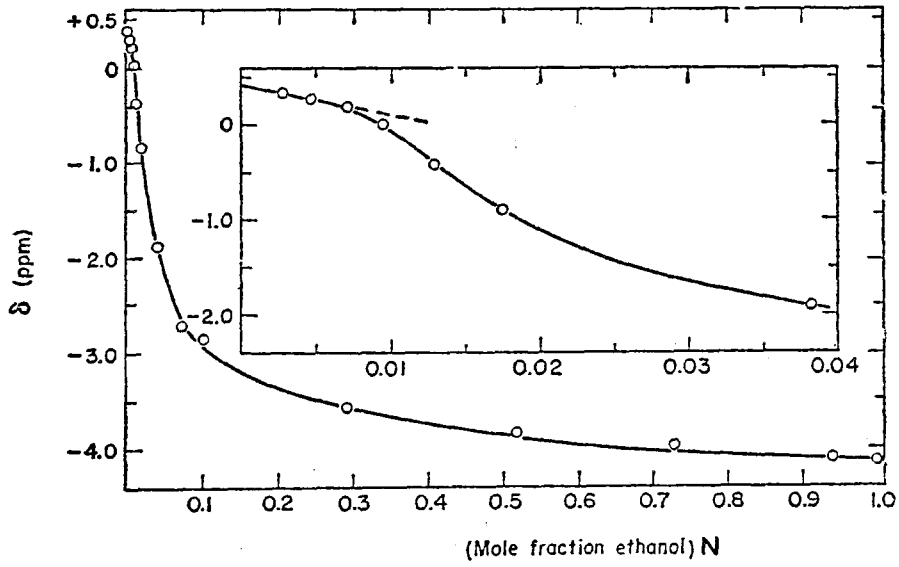
magnetic field due to the deshielding effect i.e. at infinite dilution, in the case of association (i.e. intermolecular H-bonding) the -OH groups will be 'free', whereas in the case of intramolecular H-bonding the -OH groups will not be free.

A fact worth noting is that intramolecular H-bonds tend to be bent rather than linear, and that in P.M.R. the chemical shift is also affected by geometric effects as well as the acidity of the proton in HA and the basicity of B.

Here, it is well worth mentioning the work carried out by Becker, Liddel and Shoolery,[9] in which they made a detailed study of the ethanol -OH dilution shift in carbon tetrachloride solution, with particular attention to the behaviour at low concentrations of ethanol.

Their results are shown (Fig.14).

Fig.14.



Chemical shift of hydroxyl-proton resonance vs.ethanol concentration in carbon tetrachloride at room temperature. The chemical-shift reference point is the methyl group resonance of ethanol.

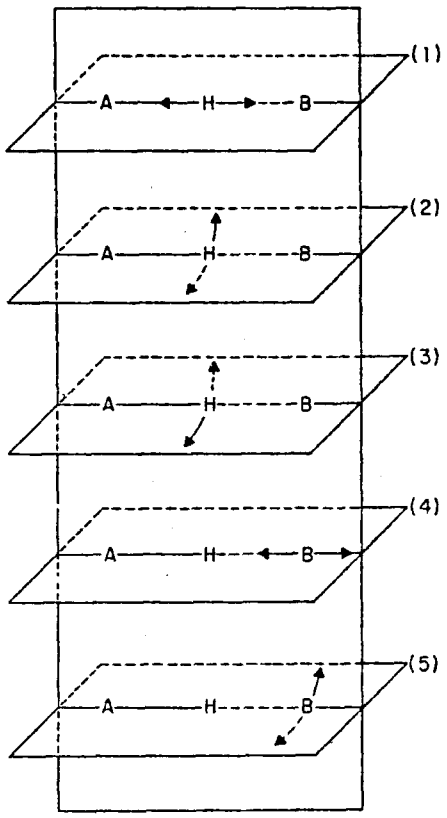
The general shape of the curve, including the reversal in curvature at N near 0.015 is of the form to be expected for a system of monomers, dimers and high polymers. The value of δm, the limiting chemical shift, corresponding to the -OH resonance of the monomer, can then be obtained by extrapolation to N = 0.

At very low concentrations of ethanol, the -OH proton shift is influenced almost entirely by the monomer-dimer equilibrium. The limiting slope of the dilution curve, i.e. from approx. N = 0.015 to infinite dilution, gives some very useful information, as will be shown later in the text.

Infra Red Spectroscopy

The -OH group may be conveniently pictured as a system consisting of point masses (atoms) held together by springs (bonds). The model is flexible and the point masses may vibrate with respect to each other. Several vibrations of the complex A-H---B are useful in H-bonding studies (See Fig.15).

Fig.15



Vibrations of the H bonded complex A—H---B.

(1) The fundamental A-H stretching frequencies.

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

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

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

(5) The AH---B deformation (bending) frequencies.

When H-bonding occurs between a proton donor group A-H and an acceptor group B, that is, a H-bonded complex A-H---B is formed, several effects are usually found in the I.R. region:-

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

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

(3) In addition to the broadening, the integrated intensity of fundamental A-H stretching bands increase, sometimes by factors of up to ten or more. However, the corresponding overtones decrease slightly in integrated intensity. The reasons for these striking intensity effects are probably related to the fact that H-bonds have substantial electrostatic character and the intensity of absorption due to I.R.active vibrations is directly proportional to the rate of change of the electrostatic dipole moment with internuclear distance.

(4) The A-H deformation modes are shifted to higher frequencies. These shifts are appreciably smaller than those found for the A-H stretching vibrations. Formation of H-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 band broadening or intensity change when H-bonding occurs.

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

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

In the following text , only the fundamental stretching frequencies in the region 4000 cm^{-1} to 3000 cm^{-1} (i.e. approx.3600 cm^{-1}) for very dilute solutions were considered in order to determine the presence or absence of intramolecular H-bonding. The intermolecular H-bonding was not studied.

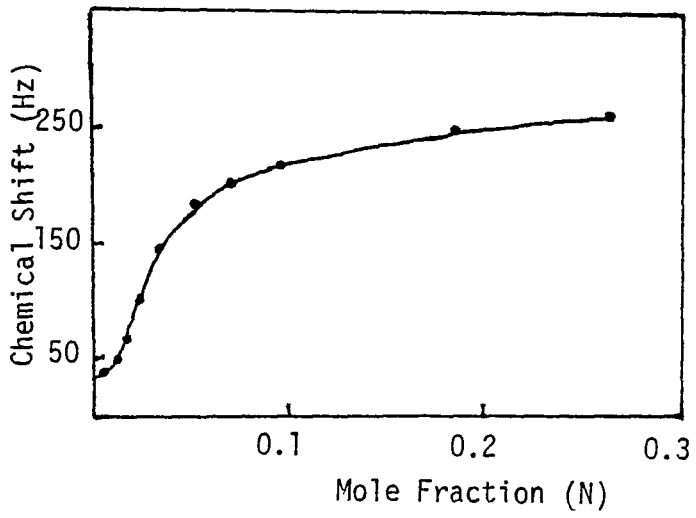
DISCUSSION

Intermolecular and Intramolecular H-bonding in ring systems (P.M.R.)

Initially the chemical shift dependence of cyclopentanol and cyclohexanol were investigated with respect to concentration in two solvents (a) carbon tetrachloride and (b) d-chloroform.

The dependence of chemical shift with concentration has been studied by Ouellette, Booth and Liptak[10], and they showed the graph obtained by plotting concentration vs-chemical shift to have the same general shape as the curve observed for ethanol (Fig.14). This graph gave a linear slope in the region 0.02 to 0.002 mole fraction range. The general shape of the curve is shown (Fig.16).

Fig.16.

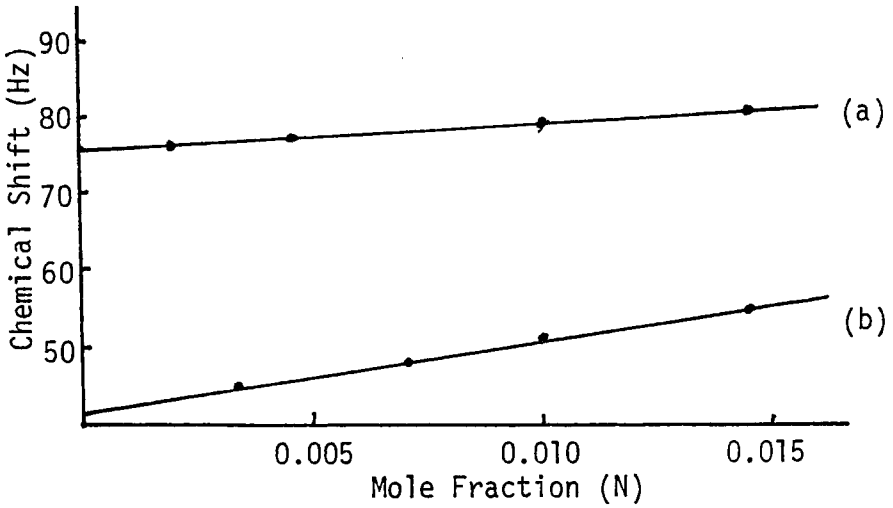


Chemical Shift vs. Concentration of cyclopentanol in CCl_4.

On investigation, a similar shaped curve was found for cyclopentanol in $CDCl_3$, and here a linear slope was obtained in the mole fraction region 0.03 to 0.003. It should be noted however that the value of this slope (i.e. Hz/N) and the limiting chemical shift are different to that obtained in CCl_4, due to the association effect of d-chloroform.

The linear portions of the graphs of cyclopentanol in carbon tetrachloride and d-chloroform are shown in (Fig.17). giving limiting chemica shifts at infinite dilution of 41.5Hz and 76.5 Hz downfield from T.M.S. respectively.

Fig.17.



(a) Cyclopentanol in $CDCl_3$ at 50^oC.

(b) Cyclopentanol in CCl_4 at 65^oC.

Although cyclopentanol is very soluble at room temperature, elevated temperatures were used. Many of the diols studied were found to be only sparingly soluble in the two solvents at room temperature, and since a comparative study was being carried out, all measurements had to be carried out at these standard elevated temperatures.

As with cyclopentanol, the same situation was found for cyclohexanol, and the limiting chemical shifts at infinite dilution were 43.5 Hz in CCl_4 at 65^oC and 82.5 Hz in $CDCl_3$ at 50^oC downfield from T.M.S. respectively.

In cyclopentanol and cyclohexanol only <u>one</u> hydroxyl group is present and hence <u>only</u> intermolecular H-bonding can occur. Hence the results given for the limiting chemical shift are a measure of the monomeric hydroxyl proton at infinite dilution and <u>are a standard value set for the absence of intramolecular H-bonding</u>.

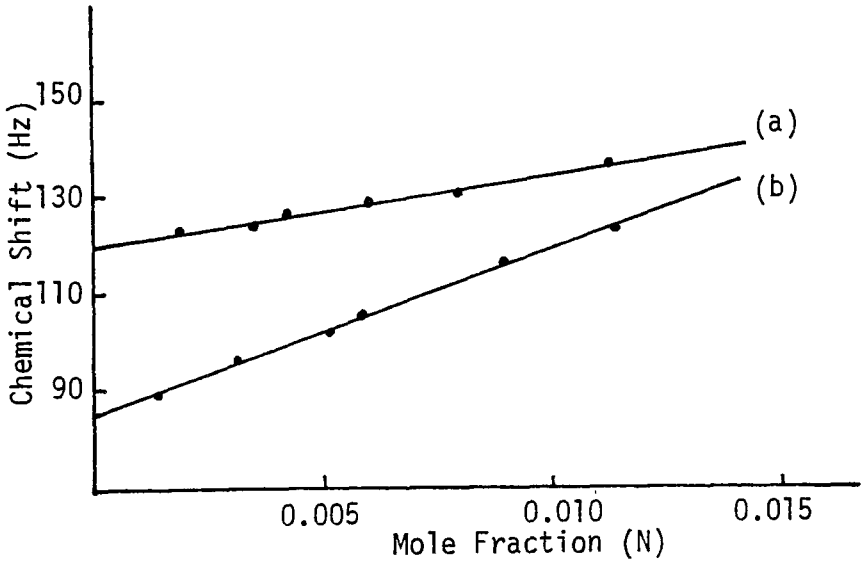
When a second hydroxyl group is introduced into the system the possibility for intramolecular H-bonding will exist.

Dilution has a great effect on intermolecular H-bonding but not on intramolecular H-bonding. Hence when intramolecular H-bonding is present in a compound the hydroxyl resonance position (limiting chemical shift) would be expected to be much larger i.e. further downfield from T.M.S. than that of a 'free' hydroxyl proton.

In order to test this, the concentration vs. chemical shift plots of (a) cis-cyclopentan-1,2-diol, and (b) trans-cyclopentan-1,2-diol were determined.

Measurements were made with each of these compounds in $CDCl_3$ at 50°C but only the cis-isomer was sufficiently soluble in carbon tetrachloride at 65°C for this latter solvent to be used. The results (Fig.18) are for the two isomers in $CDCl_3$ at 50°C.

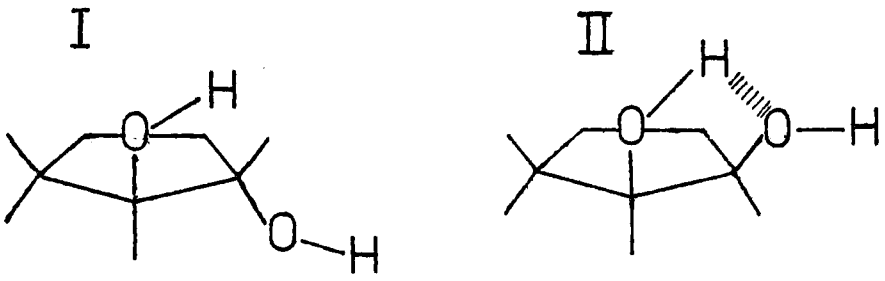
Fig.18.



(a) cis-cyclopentan-1,2-diol (b) trans-cyclopentan-1,2-diol

Considering the two isomers shown in (Fig.19) it can be seen that in the trans isomer (I) the hydroxyl groups are too far away from each other to form an intramolecular H-bond i.e. The H-bond length would be greater than the sum of the van der Waals radii of the oxygen and hydrogen atoms (>0.32nm)

Fig.19



Hence with (I) the limiting chemical shift would be expected to be of the same order as that of cyclopentanol in $CDCl_3$ at 50°C. From the graph (Fig.18) it can be seen that it is of the same order i.e. 86.6Hz downfield from T.M.S. (for I); 76.6 Hz downfield from T.M.S.(for cyclopentanol).

With the cis isomer (II) the two hydroxyl groups are in close proximity and are able to form an intramolecular H-bond (i.e. approx.0.18nm). The value of the limiting chemical shift of 120.9 Hz in $CDCl_3$ at 50°C downfield from T.M.S. clearly shows this. The value of 89.8 Hz in CCl_4 at 65°C (c.f. 41.5 Hz for cyclopentanol) substantiates this fact.

The connection between intermolecular H-bonding and the limiting chemical slope is worth noting (the limiting chemical slope being the gradient of the graph of chemical shift v.s. concentration).

In the case of the trans-isomer, where both hydroxyl groups are free to intermolecularly H-bond the value of the limiting chemical slope is 3460 Hz/N, whereas in the case of the cis-isomer the value is much less, being 1380 Hz/N. This difference in value is because in the cis isomer (II) only one of the hydroxyl groups is available for intermolecular H-bonding.

It should be noticed that the slope of the plot of the graph for the trans isomer (I) is not twice that for the cis isomer (II). This is due to the conformation of the five membered ring in that it is not completely planar. This concept will be studied in greater detail later in the text when the conformation of the six membered ring diols are discussed and this conformational factor will become more apparent, i.e. H-bonding with respect to axial and equatorial hydroxyl substituents.

The Six Membered Ring Diols

Having established the validity of the chemical shift vs. concentration technique with the five membered ring diols, the method was extended to a study of six isomersof the cyclohexan-diol system using cyclohexanol for comparison. The presence or absence of the intramolecular H-bond was determined and from this predictions of the preferred conformations of each isomer were made. The following isomerswere studied and each will be dealt with separately.

(1) cis-cyclohexan-1,2-diol

(2) trans-cyclohexan-1,2-diol

(3) cis-cyclohexan-1,3-diol

(4) trans-cyclohexan-1,3-diol

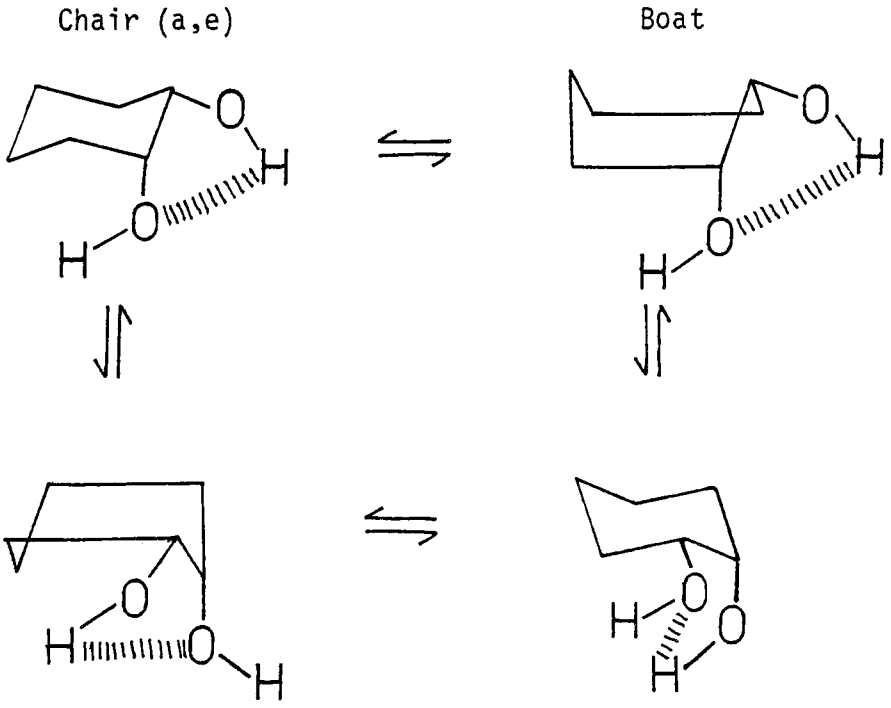
(5) cis-cyclohexan-1,4-diol

(6) trans-cyclohexan-1,4-diol

cis-Cyclohexan-1,2-diol

The possible conformations of this isomer are shown (Fig.20).

Fig.20.



It can be seen from Fig.20, that in both the chair and alternate chair conformer the hydroxyl groups are one 'axial' and one 'equatorial' and are the same energetically (chair still being more energetically favoured than the boat which will probably be present in very small concentration).

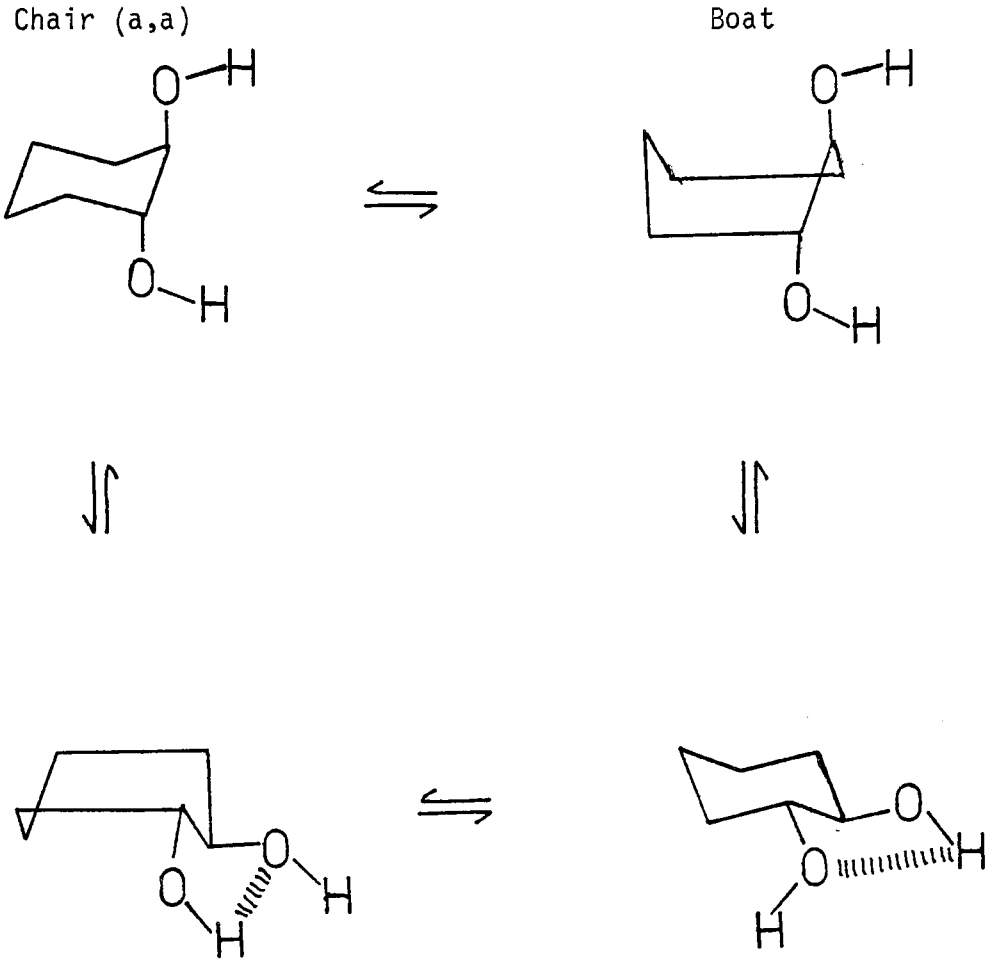
The values obtained for the limiting chemical shift were 82.1 Hz in CCl_4 at 65°C and 111.4 Hz in $CDCl_3$ at 50°C (c.f. 43.5 Hz in CCl_4 at 65°C and 82.5 Hz in $CDCl_3$ at 50°C for cyclohexanol). Hence from these results it can be seen that an intramolecular H-bond is present. The distance between the two hydroxyl groups is less than the sum of the van der Waals radii of the oxygen and hydrogen atoms i.e. < 0.32nm so it would be expected that the bond would form.

Hence it may be stated that the conformational preference of cis-cyclohexan-1,2-diol is as indicated (Fig.20) i.e. in the chair form with one hydroxyl group axial and one hydroxyl group equatorial.

Trans-Cyclohexan-1,2-diol

The possible conformations of the isomer are shown (Fig.21).

Fig.21.



From Fig.21. it can be seen that in the chair conformer the hydroxyl groups are diaxial which is energetically unfavoured whereas in the alternate chair the hydroxyl groups are diequatorial which is energetically favoured.

The limiting chemical shifts for this isomer are 84.8Hz in CCl_4 at 65^oC and 111.3Hz in $CDCl_3$ at 50^oC.

These results quite definitely show that the trans isomer forms an intramolecular H-bond. In the chair conformer the hydroxyl groups are too far apart to form a H-bond. However in the case of the alternate chair the

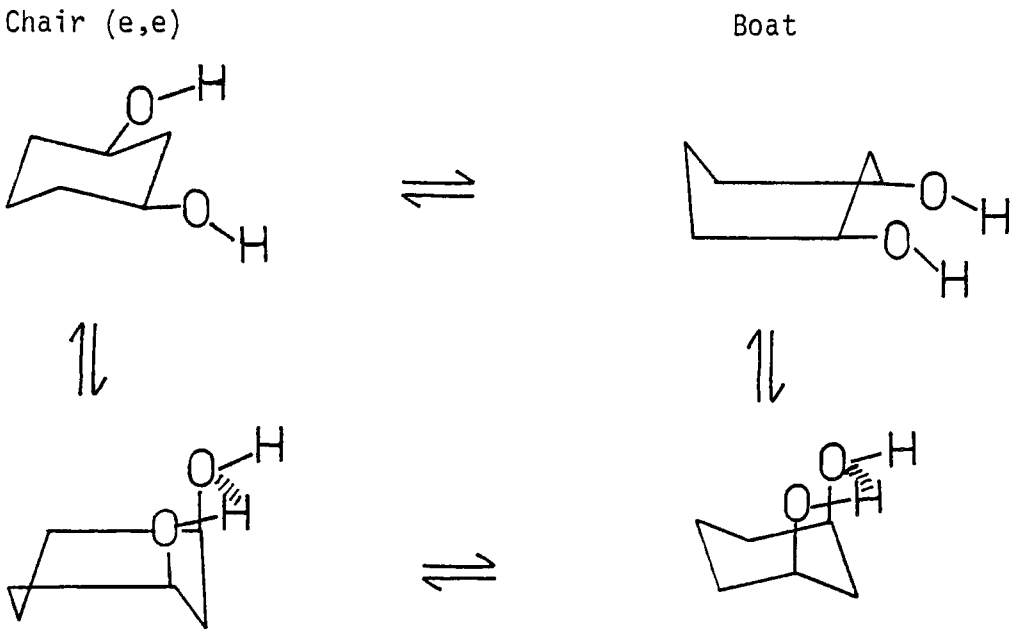
hydroxyl groups are a distance of the order <0.32nm and are therefore capable of forming an intramolecular H-bond. Although the'alternate boat' after the alternate chair conformer will have its hydroxyl groups in close enough proximity to form an intramolecular H-bond this would be energetically less favoured than the chair and probably only a very small amount would be present (See Fig.3.).

Hence, it may be stated that the conformational preference of trans-cyclohexan-1,2-diol will be in the chair form with the hydroxyl groups both being in equatorial positions.

cis-Cyclohexan-1,3-diol

The conformations possible for this isomer are shown (Fig.22).

Fig.22.



In the above it can be seen that the most energetically favoured form would be the chair form with the hydroxyl groups 'diequatorial'.

This isomer was not sufficiently soluble in CCl_4 and measurements were only carried out using $CDCl_3$ and gave a limiting chemical shift of 114.1Hz at 50°C. This result shows the presence of an intramolecular H-bond.

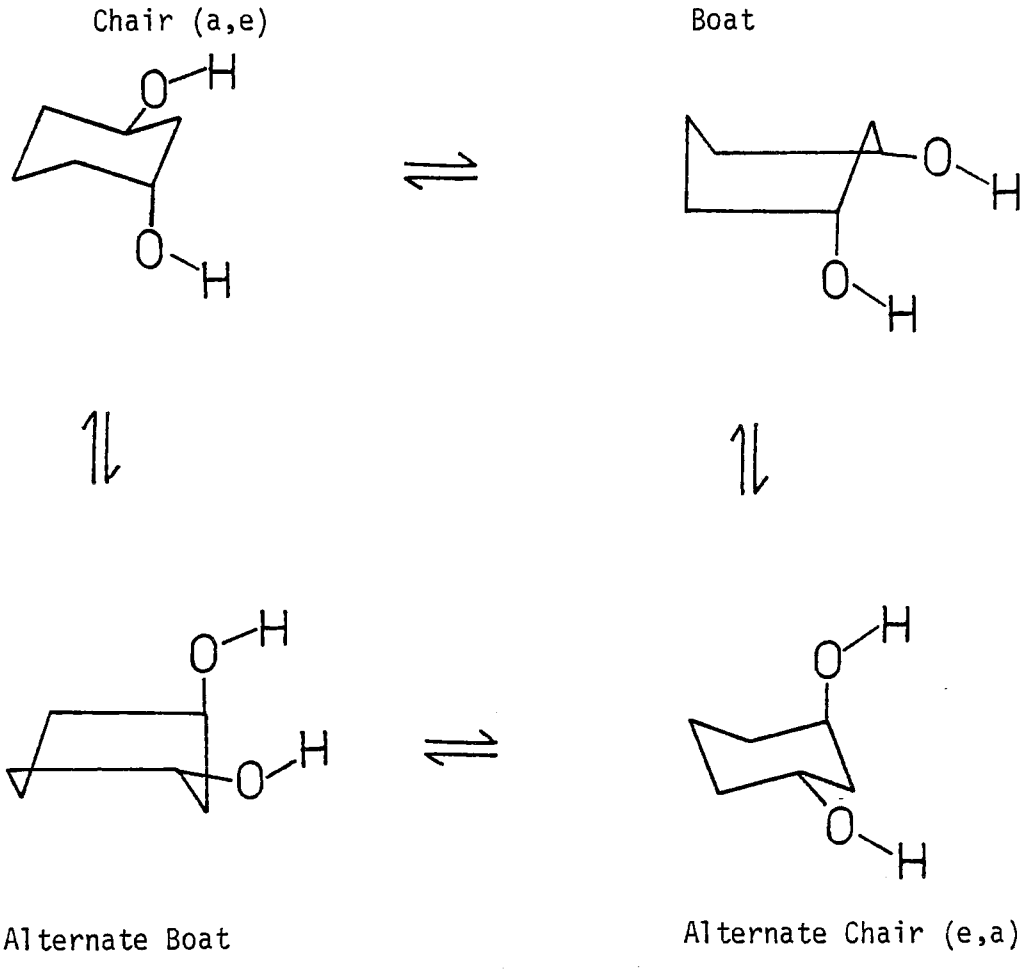
However, in the chair conformer with the hydroxyl groups diequatorial, the distance would be too great to form the bond. Only in the energetically unfavoured diaxial chair conformer would the distance factor allow the formation of the H-bond.

Although the conformation of the chair with both hydroxyl groups being axial would normally be energetically unfavoured, the formation of the intramolecular H-bond will tend to stabilise the system. Hence this would appear to be the preferred conformation of cis-cyclohexan-1,3-diol. (Again probably a very small amount of the 'diaxial' alternate boat-form with a H-bond being present).

trans-Cyclohexan-1,3-diol.

The possible conformations of this isomer are shown.(Fig.23).

Fig.23.



As in the case of the cis-1,2-diol, this particular isomer has one hydroxyl group axial and one hydroxyl group equatorial in both the chair and the alternate chair conformer and hence these are the same energetically.

This compound was only sparingly soluble in CCl_4 at 65°C but a limiting chemical shift of 48 Hz using very dilute solutions was obtained. A limiting chemical shift of 77.7 Hz in $CDCl_3$ at 50°C was also obtained and these results show the absence of an intramolecular H-bond. This is because in all conformers, the hydroxyl groups are too far apart for an intramolecular H-bond to be formed.

Hence as shown in Fig.23 the preferred conformation of trans-cyclohexan-1,3-diol is a chair with one hydroxyl group 'axial' and the other 'equatorial'. (Also no H-bond could be formed in any of the boat forms).

cis-Cyclohexan-1,4-diol

The conformations possible for this isomer are shown (Fig.24)

Fig.24.

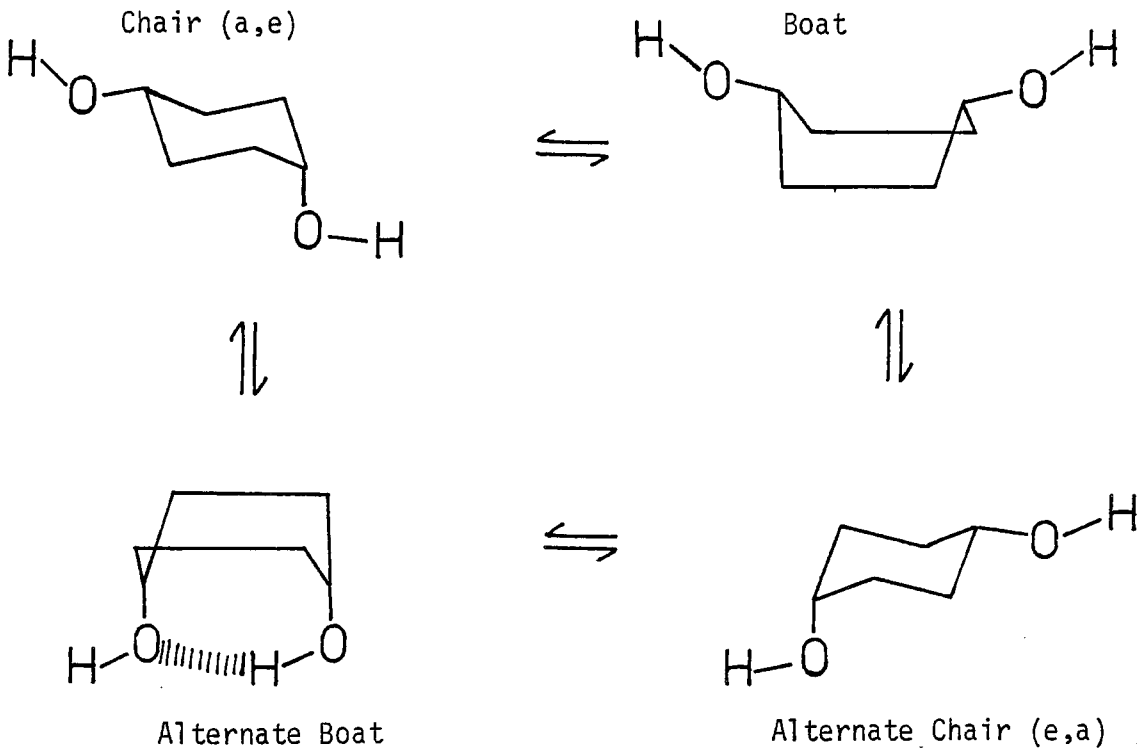


Fig.24 shows that this isomer has one hydroxyl group in the axial position and one in the equatorial position in both the chair and alternate chair conformers and hence are the same energetically.

The limiting chemical shift obtained for this isomer was 81.3Hz in $CDCl_3$ at 50°C showing the absence of an intramolecular H-bond.

In both the chair and alternate chair forms, the hydroxyl groups are too far apart to form the H-bond, but the formation of the H-bond could be envisaged in the boat-form (See Fig.24) but this is dismissed by the result obtained, showing that the preferred conformation of cis-cyclohexan-1,4-diol is that of the chair conformation with one hydroxyl axial and the other equatorial. A model of this isomer in the boat form

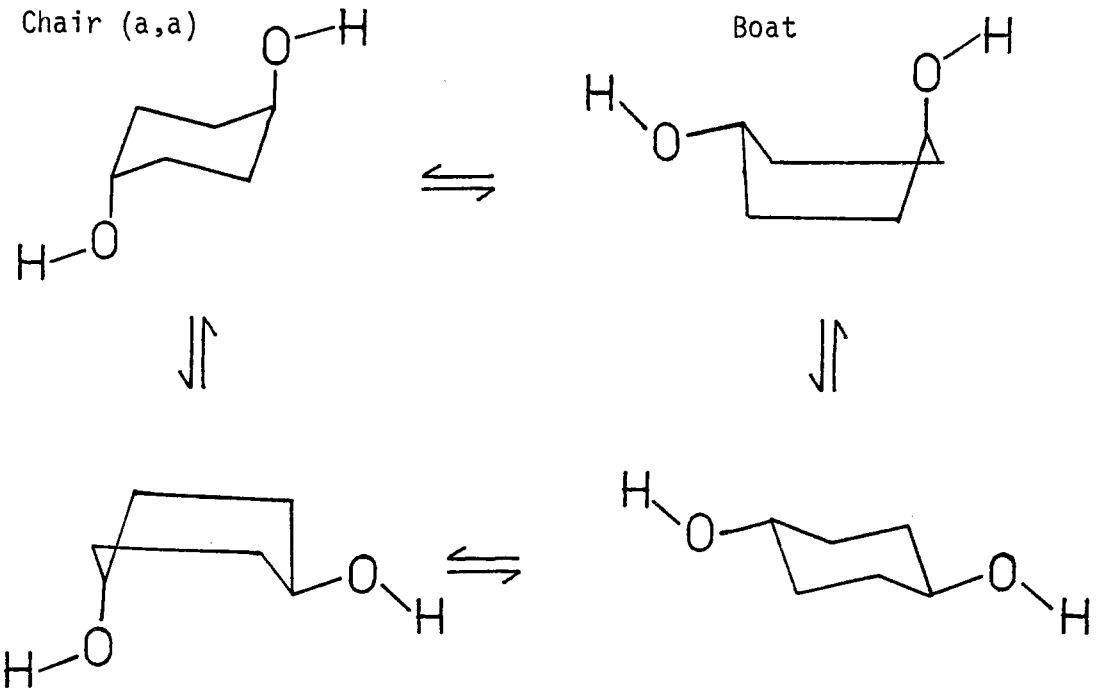
shows that the oxygen atoms are very close to each other. Because of the close proximity of these oxygen atoms, electronic repulsion between them may be the reason why the H-bond does not form. The skew boat (Fig.4) however, must be taken into consideration (being more energetically favoured than the regular boat) and the absence of the H-bond will not be due to electronic repulsion, but purely due to the energetically favoured chair conformer.

This isomer was only sparingly soluble in $CDCl_3$ at 50^oC. A scatter of points on the graph was obtained, and even though the slope of the graph is not entirely reliable, the value of the limiting chemical shift, although not absolutely accurate is reliable enough in that it is in the region of non-intramolecularly H-bonded systems.

trans-Cyclohexan-1,4-diol

The possible conformations of this isomer are shown (Fig.25.)

Fig.25.



In Fig.25 the chair conformer has its hydroxyl groups diaxial which is energetically unfavoured. The alternate chair, however has its hydroxyl groups diequatorial which is energetically favoured.

The limiting chemical shift obtained for this isomer was 78.5Hz in $CDCl_3$ at 50°C showing the absence of an intramolecular H-bond which would be expected as in all the conformers (Fig. 25.) the hydroxyl groups are too far apart.

As with the cis-1,4-diol, this isomer is also only sparingly soluble in $CDCl_3$ at 50°C, but the limiting chemical shift is reliable enough in that it is in the region of non-intramolecularly H-bonded systems.

Hence it may be stated that the preferred conformation of trans-cyclohexan-1,4-diol is in the chair form with both of the hydroxyl groups equatorial i.e. satisfied energetically in all respects.

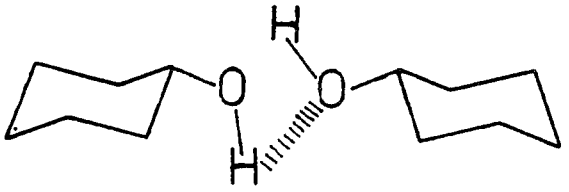
The Limiting Chemical Slopes

It has been shown by Eliel[11] and many others that there is a much more open approach of reagents to the'equatorial'position relative to the 'axial' position. Hence in the context of intermolecular H-bonding, this would occur to a greater extent if the hydroxyl groups are in equatorial positions as opposed to 'axial' positions (also shown later in the text in the determination of the conformational preference of the hydroxyl group in cyclohexanol).

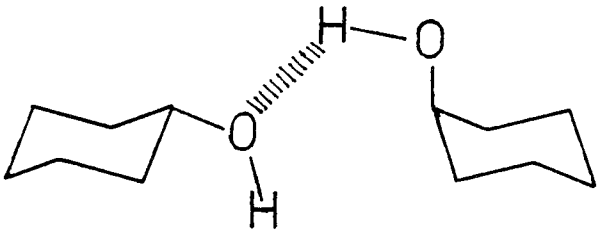
The limiting chemical slope is a measure of the amount of intermolecular H-bonding present in the system (in the low concentration range this would be mainly dimer⟶monomer). i.e. as dilution is carried out it is effectively breaking down the intermolecular H-bonding.

At first sight, this would appear to be quite straight forward, but in fact it is quite a complicated system with respect to the 'mode' of the intermolecular H-bonding. If cyclohexanol is taken as an example, then the intermolecular H-bonding can take place via three modes (see Fig.26.)

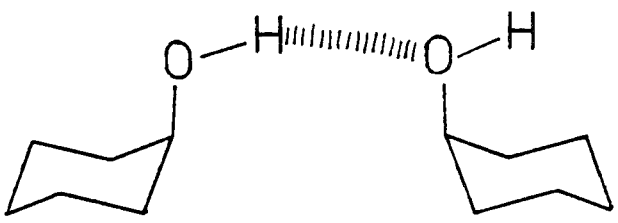
Fig.26.



equatorial-equatorial



equatorial-axial



axial-axial

Hence the limiting chemical slope will be an average of all these forms, remembering that the equatorial position is more open to approach for intermolecular H-bonding. These models are greatly simplified because the eclipsed and staggered conformations of the hydroxyl group in terms of potential energy should also be considered.

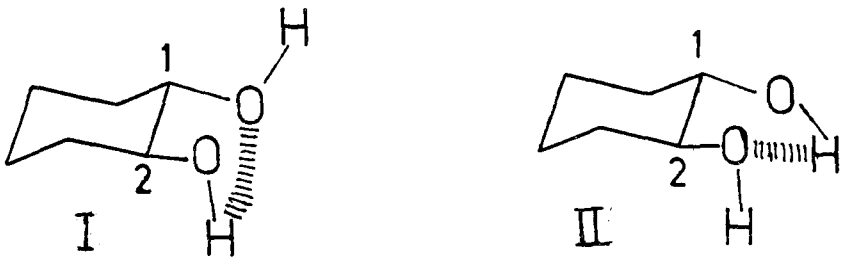
As the two 1,2-diols and the two 1,3-diols were only all soluble in $CDCl_3$ at 50°C (as opposed to the two 1,4-diols which were only sparingly soluble) then one can only realistically compare the slopes of these and from these results offer some explanation. The slopes for these four isomers are given (Table 3.)

Table 3.

Compound	Limiting chemical slope in $CDCl_3$ at 50°C (Hz/N)
cis-cyclohexan-1,2-diol	1220
trans-cyclohexan-1,2-diol	2800
cis-cyclohexan-1,3-diol	1580
trans-cyclohexan-1,3-diol	1410

Initially it is worth looking at the isomer with the largest slope of 2800 Hz/N, namely trans-cyclohexan-1,2-diol. It can be seen (Fig.27) that in this molecule intramolecular H-bonds may form in addition to intermolecular H-bonds. The intramolecular H-bond may be formed in two possible ways.

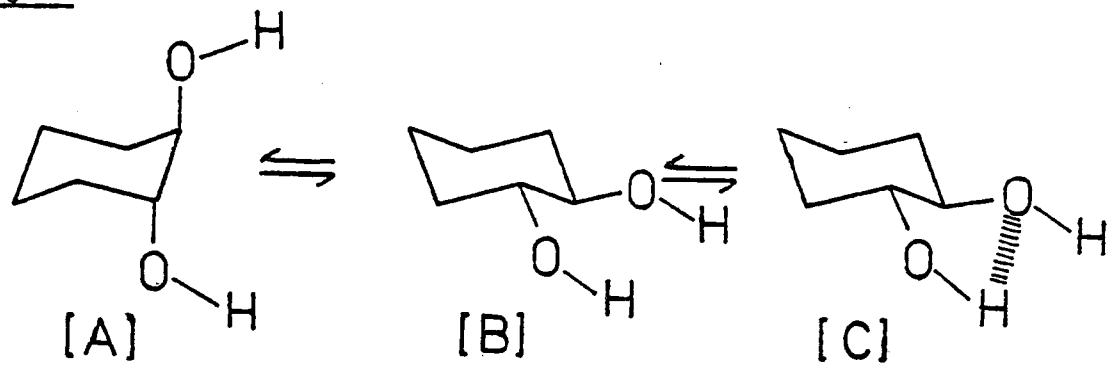
Fig.27.



However, it can be seen that whether the hydroxyl group is 'free' on C_1 as in (I) or 'free' on C_2 as in (II) both are equatorial and will be able to intermolecularly H-bond with other molecules, and, as has been stated previously, the equatorial position is more open to approach for H-bonding than the axial position.

Obviously one cannot completely ignore the equilibrium as shown in Fig.28, but purely from an energetic point of view, very little of (A) will be present (The equilibrium here being very much to the right).

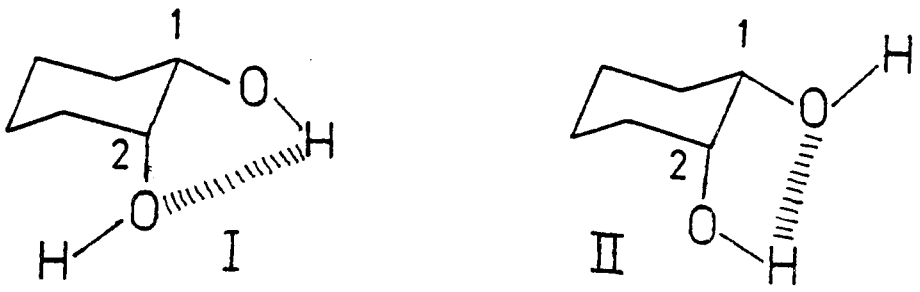
Fig.28



Diaxial (non intra H-bond) | Diequatorial (non-intra H-bond) | Diequatorial (intra-H-bond)

The cis-cyclohexan-1 2-diol has a limiting chemical slope of 1,220 Hz/N which is much less than for the trans-isomer. This may be explained by looking at the modes in which intramolecular H-bond may be formed and at the hydroxyl groups which are available for intermolecular H-bonding (Fig.29).

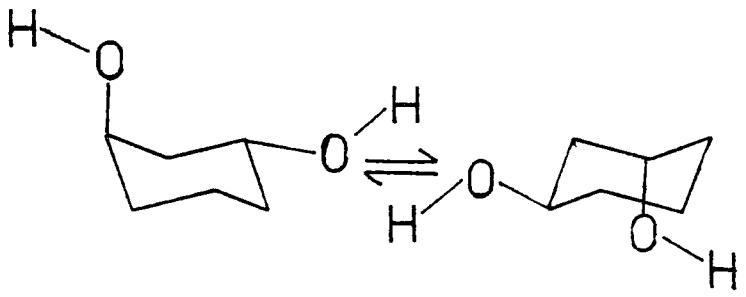
Fig.29



In (I) the hydroxyl group 'free' on C_2 is axial which can then intermolecularly H-bond with either another axial or equatorial hydroxyl group from an adjacent molecule. Similarly in (II) the hydroxyl group 'free' on C_1 is equatorial which can again associate with axial or equatorial from another molecule. Hence, due to the introduction of an axial hydroxyl group which is less prone to H-bonding than the equatorial there is a reduction in the limiting chemical slope. Also in this particular isomer, if non-intra-molecular H-bonded species are present, both chair and alternate chair have the (a,e) conformation.

The next isomer to look at is trans-cyclohexan-1,3-diol which has a limiting chemical slope of 1410 Hz/N. This isomer does <u>not</u> form an intra-molecular H-bond and hence both hydroxyl groups are 'free' hence it has a larger slope than the cis-1,2-diol. This also has the (a,e) conformation (Fig.30) hence although 'free' to intermolecularly H-bond completely, the presence of the axial hydroxyl group which is less able to intermolecularly H-bond accounts for the slope being less than for the trans-1,2-diol in which the greatly favoured conformation has the hydroxyl groups diequatorial.

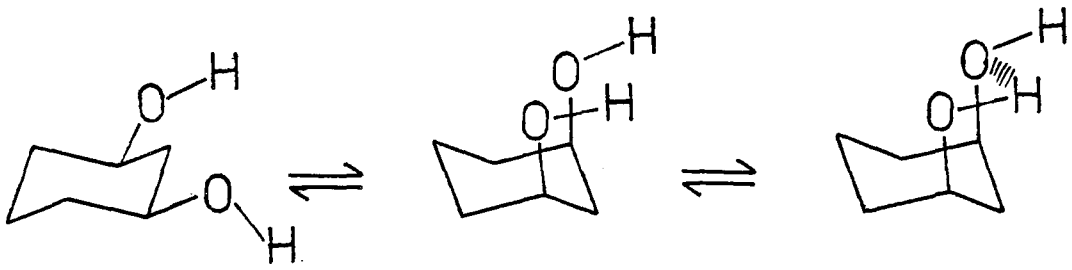
<u>Fig.30</u>.



Finally the cis-cyclohexan-1,3-diol forms an intra-molecular H-bond but this is formed in the diaxial conformation, hence it would be expected that the isomer would have the smallest slope because only axial hydroxyl groups would be present for association. However, the slope for this isomer is 1580 Hz/N.

A possible explanation for this high result is by taking into account the equilibrium (Fig.31) where, if some non-intramolecularly H-bonded species were present, then energetically the diequatorial conformation would be preferred with both hydroxyl groups free to associate. Hence if only a small amount of this is present the slope would be increased.

Fig.31.



Diequatorial (non-intra H-bond) ⇌ Diaxial (non-intra H-bond) ⇌ Diaxial (intra H-bond)

Analytical Determination

It was noticed quite early in this study that the slopes of the graphs of concentration vs. chemical shift varied from compound to compound, even when these were run in the same solvent and at the same constant temperature. This was due to the variation in the amount of intermolecular H-bonding present.

It is postulated, here, that at a specific temperature this limiting chemical slope in Hz/N (where N = mole fraction) can act as a'fingerprint' for certain isomers. If the exchange rates of the hydroxyl groups in the various isomers are similar, and if the isomers are mixed, still only one signal should be observed for the resonance of all forms of 'n'-mer present in the system. Hence, an examination of the variation of concentration with chemical shift should result in a'single graph' representation. From the slope of this graph the relative amounts of each isomer present in the mixture should be determinable. It should be noticed also that the limiting chemical shifts should give this information if the chemical shifts of the pure isomers are substantially different.

This postulation was tested by measuring the limiting chemical slopes of two pure isomers and then a mixture of the two (in the same solvent and at the same constant temperature).

Cis and trans-cyclopentan-1,2-diols were initially used to test this postulation. The results obtained in $CDCl_3$ at 50^oC are shown (Table 4).

Table 4

Compound	Limiting Chemical Slope (Hz/N)	Limiting Chemical Shift (Hz)
cis-cyclopentan-1,2-diol	1,380	120.9
trans-cyclopentan-1,2-diol	3,460	86.6
50/50 mixture of diols	2,400	102.5

From the results for the two pure isomers the theoretical expected results for the 50/50 mixture would be exactly half-way between the two limiting chemical slopes and the two limiting chemical shifts i.e. 2,420 Hz/N and 103.8 Hz respectively.

From the theoretical results and the actual results it can be calculated:-

2,420 Hz/N ≡ 50% cis isomer

$\therefore$ 2,400 Hz/N ≡ 49.6%

Also

103.8 Hz ≡ 50% cis isomer

$\therefore$ 102.5 Hz ≡ 49.4% cis isomer

Hence the original postulation would appear to be correct as these results are in good agreement.

The above method was then carried out on cis and trans cyclohexan-1,2-diols (with 50/50 and 75/25 mixtures in CCl_4 at 65°C), these having very similar limiting chemical shifts, but quite different limiting chemical slopes. The results obtained are shown (Table 5).

Table 5

Compound	Limiting Chemical Slope (Hz/N)
cis-cyclohexan-1,2-diol	4,425
trans-cyclohexan-1,2-diol	9,385
50/50 mixture of diols	7,005
75/25 mixture of diols	8,290

Exactly as calculated for the cyclopentan-1-2-diols, the results for the cyclohexan-1-2-diol mixtures are:-

(a) 50/50 mixture - slope of 7000 Hz/N gave a value of 50.7% cis isomer

(b) 75/25 mixture (i.e. 75 trans : 25 cis) - slope of 8,300 Hz/N gave a value of 23.7% cis isomer.

From the above results it can be seen, obviously that as one would move towards mixtures of 95/5 the method would become more inaccurate but this is normally found with all analytical slope techniques.

Also it may be stated that the inaccuracy of this method would probably arise from three major factors:-

(a) impurity of samples - probably unlikely as compounds used had been previously purified by vacuum sublimation or distillation over nitrogen.

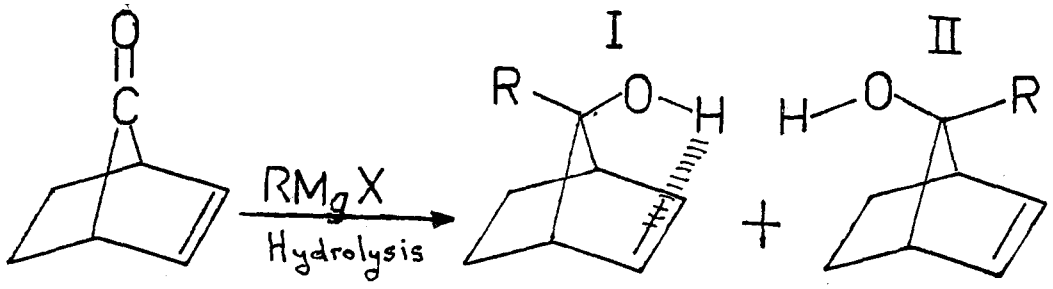
(b) chemical shift measurement - again unlikely as the accuracy of measurement is of the order of 0.2 Hz.

(c) weighing of samples - due to the relative insolubility of the samples in the solvent very small quantities (usually a few milligrammes) had to be weighed. Hence, any inaccurancy in the method could probably arise in the weighing even though a five-figure balance was used.

However, apart from this it may be appreciated that this technique could be useful for the determination of the amount of hydroxyl isomers present in a system provided that either the limiting chemical shifts or limiting chemical slopes of the pure isomers are known (Also the larger the difference in either of these values, the more accurate the method becomes).

A general example of the possible use of the technique would be in a $LiAlH_4$ reduction or a Grignard as shown in (Fig.32).

Fig.32.



In the syn isomer (I) the hydroxyl group is close enough to form an intramolecular H-bond with the π-bond , whereas in the anti isomer (II) it is too far away. This is clearly shown by the slope and limiting chemical shift of (I) being 320Hz/N and 121.0Hz respectively, whilst the corresponding values of (II) are 2380Hz/N and 60.5Hz respectively. These values were obtained by Ouellette et al[12] in carbon tetrachloride at 40°C (for R=H i.e. $LiAlH_4$ reduction).

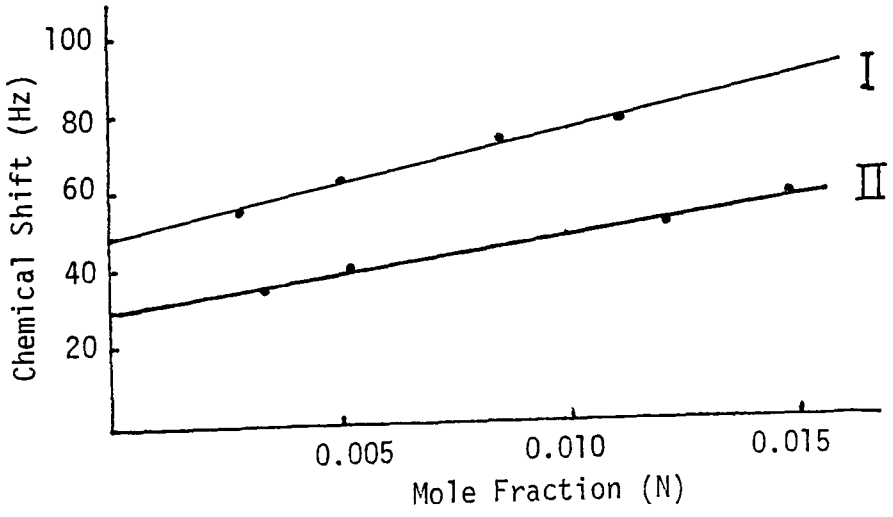
Usefulness of the concentration vs. chemical shift graph in the differentiation between (a) axial and equatorial hydroxyl groups and (b) endo and exo hydroxyl groups.

Axial and equatorial hydroxyl groups

This may be demonstrated quite easily by the use of the isomers cis and trans-4-tert-butyl-cyclohexanols. (Here the terms cis and trans refer to the hydroxyl groups with respect to the tert-butylgroup). As described previously (Page 4) the tert-butyl group will ensure conformational homogeneity in the cyclohexane system because the size of the group ensures that it will be entirely in the equatorial position. Also it has been shown that the tert-butyl group in the 4-position with respect to the hydroxyl group has no effect on the chemical shift associated with the hydroxyl group.

The study was carried out in carbon tetrachloride at a probe temperature of +40^{o}C. The resulting graphs are shown (Fig.33).

Fig.33



The resulting limiting chemical slopes obtained from the computer plotted graphs are 2750 Hz/N from the trans isomer (I) which has its

hydroxyl group equatorial, and 1900 Hz/N for the cis isomer (II) which has its hydroxyl group axial. These results lend support to the accepted fact that an hydroxyl group in an axial position is less intermolecularly H-bonded than an hydroxyl group in an equatorial position. Also the resulting limiting chemical shifts for the cis isomer (II), and the trans isomer (I) are 27.6 Hz and 46.0 Hz respectively which again are a function of the stereochemistry.(See Page 50)

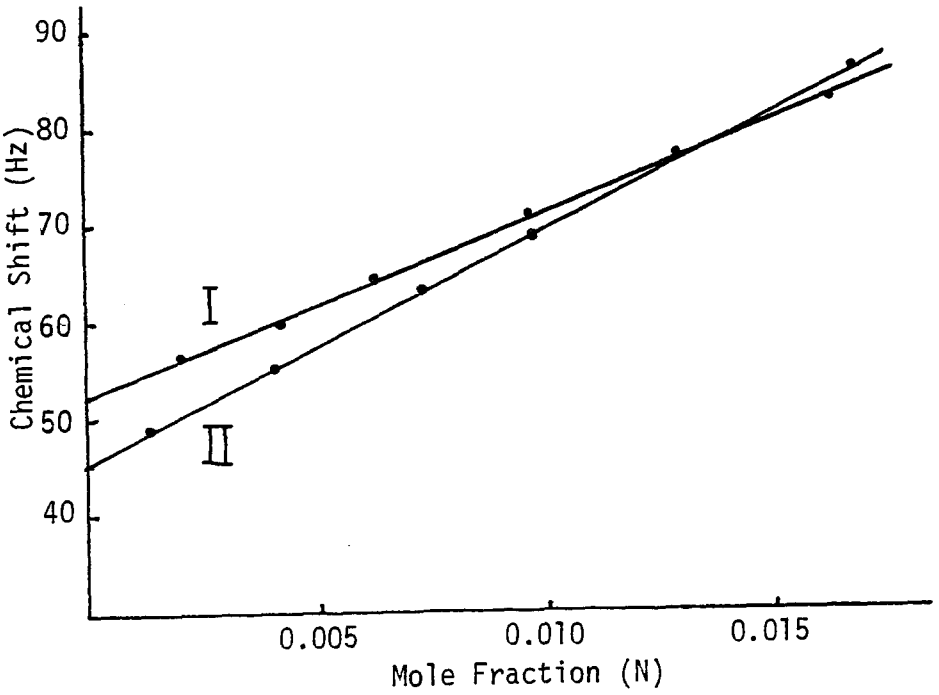
At first sight this method of dilution and the monitoring of the chemical shift of the hydroxyl proton, would appear to be elaborate and time consuming, when all that it may be necessary to do, is to observe the chemical shift of the α-proton (i.e. α to the hydroxyl group) to differentiate between axial and equatorial forms. However, when the group at the α-position is not a proton this can create difficulties in finding the actual chemical shift of the group. If this group is aliphatic the chemical shift will be in the middle of the resonance positions of the various ring protons. In a situation like this, the usefulness of the hydroxyl group dilution studies have distinct advantage. Also the precise position of the hydroxyl peak in the spectrum is much easier to measure than the position in the spectrum of the α-proton.

Exo and endo hydroxyl groups

The application of this technique is illustrated by exo-bicyclo (2,2,1) heptan-2-ol (isonorborneol) and endo-bicyclo (2,2,1) heptan-2-ol (norborneol). Because the skeleton of the bicyclo (2,2,1) heptane system is rigid then the positions of the hydroxyl groups are fixed i.e. endo and exo.

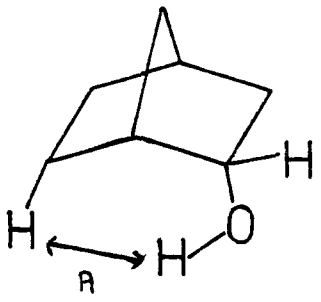
The study was carried out in carbon tetrachloride at a probe temperature of + 40°C. The resulting graphs are shown (Fig.34).

Fig.34

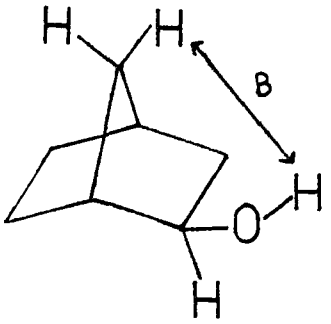


Similarly, here the resulting chemical slopes obtained from the computer plotted graphs are 2350 Hz/N for isomer (II) which has its hydroxyl group exo, and 1850 Hz/N for isomer (I) which has its hydroxyl group endo. Hence it may be concluded that the endo side of the bicyclo (2,2,1) heptane system is more hindered than the exo side; a conclusion which has long been accepted.[14]

Fig.35



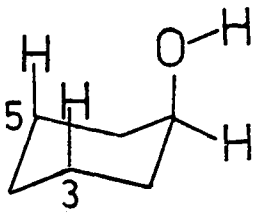
endo



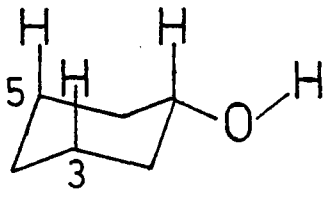
exo

However it should be noticed that the limiting chemical shift of the 'endo' hydroxyl group is 52.1 Hz whereas that of the 'exo' hydroxyl group is 45.5 Hz i.e. the 'endo' hydroxyl group resonates at a position downfield from that of the 'exo' hydroxyl group. In the diagrams (Fig.35) the distance 'A' in the endo isomer is much smaller than the corresponding distance 'B' in the exo isomer. Hence the steric interactions A and B lead to van der Waals deshielding which will be greater for the endo isomer because of the closer proximity and thus causing resonance at a lower field.

Fig.36



axial

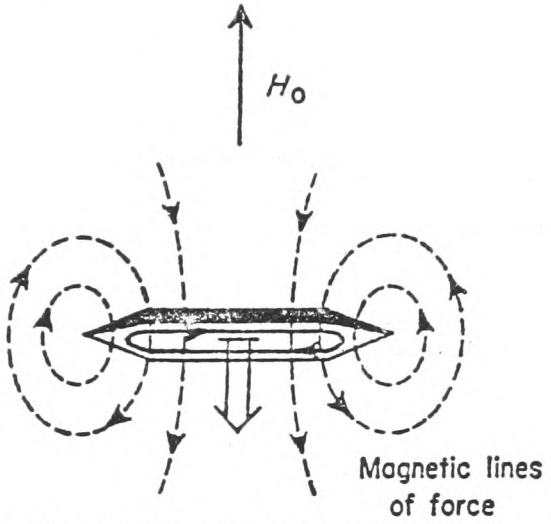


equatorial

In the cyclohexanol system (Fig.36), purely from a steric point of view, it would be expected that the hydroxyl group in the axia position would have a greater steric interaction than the equatorial

hydroxyl group (i.e. due to the protons at C_3 and C_5) and hence resonate further downfield. However, the opposite is actually found. The explanation given by Pople, Schneider and Bernstein attributes this to the ring current effect (Fig.37) These workers drew a parallel between the cyclohexane system and the benzene ring where ring currents are known to be set up.

Fig.37



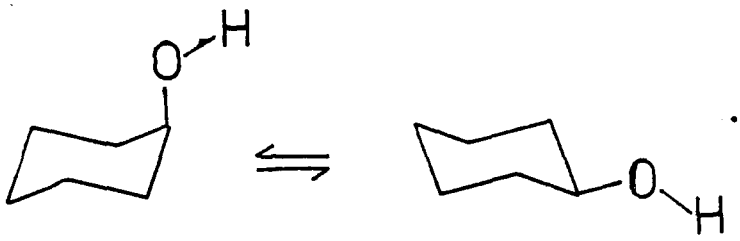
Current and magnetic lines of force induced in benzene by a primary field H_0.

The secondary magnetic field at the positions of the aromatic protons at the side of the ring will reinforce the primary field H_0 and will therefore give a negative contribution to the screening constant. Hence the aromatic protons will resonate at lower field than others.

Although there is no direct magnetic evidence on the magnitude of saturated ring currents, this could well be an explanation as to why the equatorial groups in the cyclohexane system appear at a lower field than axial groups (although only of the order of $\sim$1 ppm). The equatorial protons are considered to be in positions analogous to the ring protons in benzene. It must also be appreciated that this ring current effect must be greater than the effect of the van der Waal's deshielding.

The conformational preference of the hydroxyl group in the cyclohexanol system

The equilibrium involved here is:-



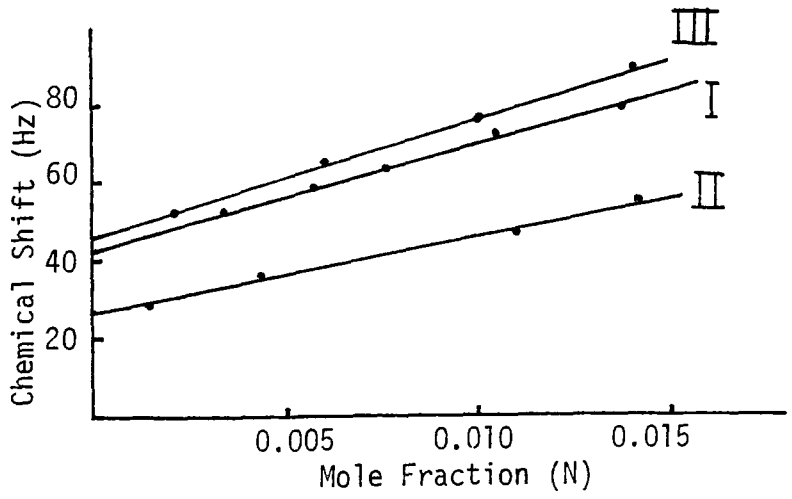
..... (1)

The use of the cis and trans isomers of 4-t-butyl-cyclohexanol to differentiate between axial and equatorial hydroxyl groups was described earlier in the text (Page.47). Exactly the same method of chemical shift measurement with dilution was carried out on cyclohexanol in carbon tetrachloride at 40°C. The results (Table 6) of cyclohexanol and the cis and trans 4-t-butyl cyclohexanol isomers are given below; which were obtained from the graphs shown in Fig.38.

Table 7

Compound	Limiting Chemical Shift (Hz)	Limiting Slope(Hz/N)
trans-4-t-butyl-cyclohexanol (III)	46.0	2725
Cyclohexanol (I)	41.8	2575
cis-4-t-buty-cyclohexanol (II)	27.6	1910

Fig.38



It can be seen from equilibrium (1) that the value of the chemical shift of 41.8 Hz at infinite dilution, for cyclohexanol is an average position of the pertinent hydroxyl groups in the two conformations. This average position gives rise to a chemical shift (i.e. 41.8 Hz) which will be given by the equation:-

$$\delta = N_e\delta_e + N_a\delta_a \quad \ldots\ldots\ldots\ldots (2)$$

where N_e is the mole fraction of cyclohexanol molecules with the hydroxyl group in the equatorial position and N_a the mole fraction with the hydroxyl group in the axial position. δ_e and δ_a are the chemical shifts for the hydroxyl groups in the pure equatorial and pure axial conformations.

Now:- $N_a + N_e = 1$ and $N_e/N_a = K$

$$\therefore \quad \delta = \frac{\delta_a + K\delta_e}{(K+1)} \quad \ldots\ldots\ldots\ldots (3)$$

Hence:-

$$K = \frac{\delta_a - \delta}{\delta - \delta_e} \quad \ldots\ldots\ldots\ldots (4)$$

where K is the equalibrium constant for equation (1)

Hence from the results obtained:-

$$K = \frac{\delta_{II} - \delta_I}{\delta_I - \delta_{III}} = \frac{27.6 - 41.8}{41.8 - 46.0}$$

$$\therefore \quad K = 3.38$$

Now:- $-\Delta G_{OH} = RT\ell nK$

Hence:- $-\Delta G_{OH} = 8.314 \times 313.15\ \ell n\ 3.38$

$$= 3.17\ kJmol^{-1}$$

This value for the conformational preference of the hydroxyl group is in very good agreement with the value of Winstein[13] of 3.26 $kJmol^{-1}$.

This particular work was originally carried out by Ouellette[15] in which he obtained a value of 3.14 $kJmol^{-1}$. However, his results quote the limiting slope of the graph for cyclohexanol as being exactly the same as that for the pure equatorial isomer, trans-4-t-butyl cyclohexanol. In the results quoted in this work the slope is slightly less i.e. 2575 Hz/N as compared to 2725 Hz/N which is much more realistic, as there is approximately 20% of the axial conformation present at $40^{o}C$.

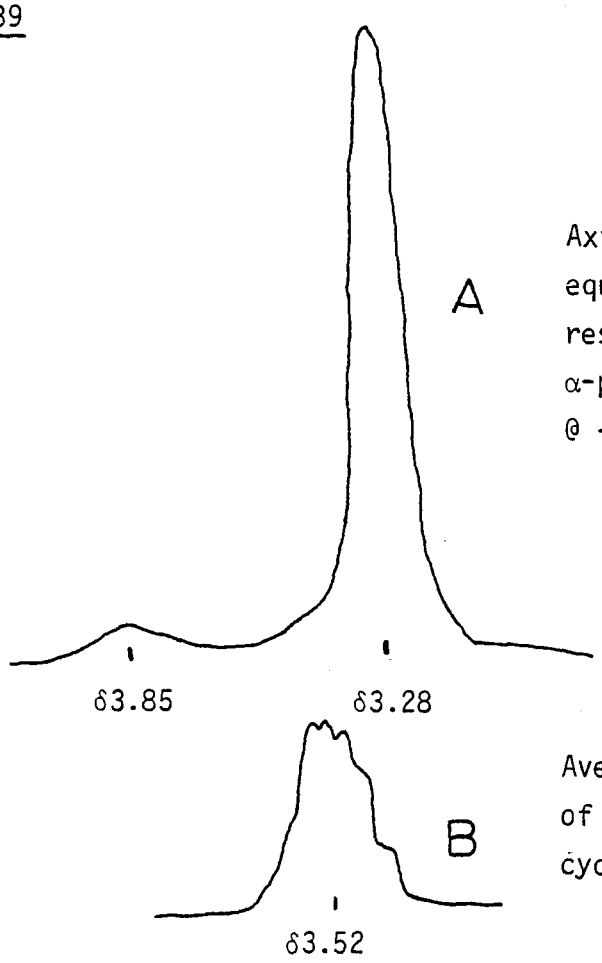
By the same experimental method Ouellette et al were able to determine the conformational preference of both the ethynyl[16] and vinyl[17] groups the results obtained being 0.75 $kJmol^{-1}$ and 5.82 $kJmol^{-1}$ respectively. To obtain these values Ouellette assumed that the conformational preference of two groups attached to the same carbon atom on a cyclohexane ring are additive. Hence by using the respective 1-substituted cyclohexanols they were able to utilise the value of 3.14 $kJmol^{-1}$ calculated for the conformational preference of the hydroxyl group in cyclohexanol.

However before proceeding, it is worthwhile noting that the conformational preference of the hydroxyl group has been calculated by many methods and Eliel[18] has quoted a range of values for this group i.e. $1.05 \rightarrow 5.23$ $kJmol^{-1}$ showing a large variation. To emphasise this fact further other N.M.R. experiments were carried out to determine the conformational preference of the hydroxyl group, all of which are accepted.

The conformational preference of the hydroxyl group in cyclohexanol determined by the N.M.R. peak area method[19] at -83°C.

Examination of the N.M.R. spectrum of cyclohexanol in carbon disulphide at -83°C revealed two resonances corresponding to equatorial α-proton H_1 at approximately δ3.85 and to the axial α-proton H_1 at approximately δ3.28 as shown, together with the "average" position of δ3.52 at + 40°C. (Fig.38).

Fig.39



Axial (δ3.28) and equatorial (δ3.85) resonances of the α-proton in cyclohexanol @ -83°C.

Average resonance position of the α-proton in cyclohexanol @ +40°C.

Electronic integration and measurement by assumption of triangulation under the peaks gave a ratio of 3005:215 which in turn gives a value of K = 14.0 and hence a value of $-\Delta G_{OH}$ = 4.17 $kJmol^{-1}$ at -83°C. This value is quite high because the concentration used (2.5 mol l^{-1}) will give rise to quite considerable intermolecular H-bonding at -83°C.

Measurement of the axial-equatorial chemical shifts at -83°C and that of the average chemical shift[20] at + 40°C.

As shown in Fig.39, at -83°C the chemical shifts of the axial δ3.28, and equatorial δ3.85 may be easily measured. However the position of the resonance at + 40°C at δ3.52 is an averaged one for the two conformers. The proportions of these may be obtained by linear interpolation between the equatorial and axial shifts which are known from the low-temperature measurement.

Hence:-

δ3.28 corresponds to 100% axial conformer

δ3.85 corresponds to 0% axial conformer (100% equatorial)

$\therefore$ δ3.52 corresponds to $\frac{3.52 - 3.28}{3.85 - 3.28} \times 100\%$

= 23.8% of axial conformer at + 40°C.

Hence :- $K = \frac{76.2}{23.8} = 3.20$

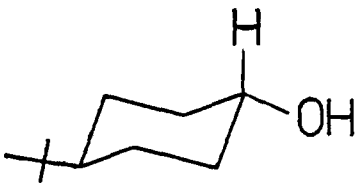
Thus:- $-\Delta G_{OH} = RT\ell nK$

$= 8.314 \times 313.15\ \ell n\ 3.20$

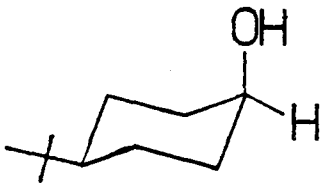
$= \underline{3.03\ kJmol^{-1}}$

Measurement of the chemical shifts of the α-protons of pure axial and equatorial isomers of 4-t-butyl-cyclohexanols and cyclohexanol[21] at + 40°C.

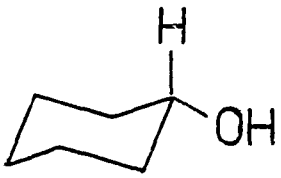
Here the cis and trans isomers of 4-t-butyl cyclohexanol were used to measure the chemical shifts of the pure equatorial and pure axial α-protons respectively, assuming (1) complete conformational homogeniety and (2) that the 4-t-Bu group does not affect the chemical shifts of the α-protons.



axial α-proton
δ3.38

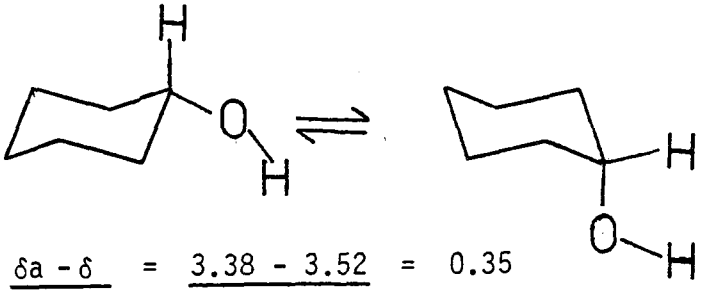


equatorial α-proton
δ3.92



α-proton variable at + 40°C
δ3.52

Hence for the following equilibrium:-



$$K = \frac{\delta a - \delta}{\delta - \delta e} = \frac{3.38 - 3.52}{3.52 - 3.92} = 0.35$$

i.e. equilibrium is further to the left-hand-side of the equation with an equilibrium constant K = 2.85

Hence $-\Delta G_{OH} = 2.73\ kJmol^{-1}$

With all the methods quoted beforehand both area measurement and shift measurement are fairly unreliable, especially with the shift measurements of the α-protons which are unresolved. In the case of the hydroxyl group shift measurements the sharp line gives a much more accurate result.

Conformational analysis with Lanthanide shift reagents

Originally Damarco et al.[22] used tris(dipivalomethanato) europium (III) i.e. $Eu(DPM)_3$ to measure the chemical shifts of cis and trans-4-t-butyl-cyclohexanols. They added increasing amounts of the shift reagent to the alcohols in $CDCl_3$. Because of limiting solubility, a least squares method had to be used in order to obtain the chemical shifts of the various protons of the alcohols at a molar ratio of complex to solute of one (i.e. n = 1). Each chemical shift was obtained from the difference in resonance when dissolved in inert $CDCl_3$ from that when an equimolar amount of $Eu(DPM)_3$ was present in the same solvent.

i.e. $\Delta Eu = \delta_{CDCl_3} - \delta^{n=1}_{Eu(DPM)_3}$

The results obtained are given below (Table 7).

Table 7

Compound		H_1	H_2/H_6eq	H_6/H_{2ax}	H_5/H_{3eq}	H_5/H_{3ax}
trans-isomer	ΔEu	-21.7	-13.6	-14.7	-4.4	-5.4
cis-isomer	ΔEu	-24.7	-14.9	-8.2	-6.7	-13.6

Groves et al[23] carried out the same addition of $Eu(DPM)_3$ to cyclohexanol and the observed shift (ΔEu^{obs}) was related to the equatorial-axial equilibrium according to the expression:-

$$\Delta Eu^{obs} = N_{eq}\Delta Eu^{eq} + N_{ax}\Delta Eu^{ax}$$

Comparison of ΔEu values for each position of cyclohexanol with these reported by Demarco et al for cis and trans-4-t-butylcyclohexanol (as shown in Table 8 below) led to a best fit of the data with Neq = 73 and Nax = 27.

Table 8

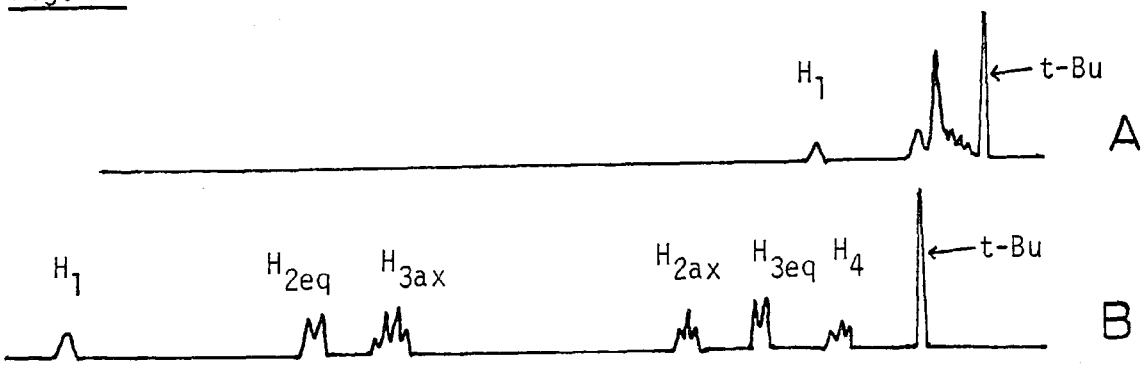
Compound	H_1	H_2-cis	H_2-trans	H_3-cis	H_3-trans
trans-4-t-butylcyclohexanol	-21.7	-14.7	-13.6	-4.4	-5.4
cis-4-t-butylcyclohexanol	-24.7	-14.9	-8.2	-13.6	-6.7
Cyclohexanol (observed)	-22.5	-16.1	-13.1	-6.9	-5.8
Cyclohexanol (calcd for 73:27)	-22.5	-14.8	-12.1	-6.9	-5.8

From the calculated values of Neq = 73 and Nax = 27 a value of K = 2.70 is obtained which then gives $-\Delta G_{OH} = 2.59$ kJmol^{-1}.

This lower value for the conformational preference of the hydroxyl group is attributed to the absence of H-bonding due to the complexation. Further, they suggest that the conformational equilibrium is not affected appreciably in $Eu(DPM)_3$ or $Eu(fod)_3$ complexes.

An example of the lanthanide shift technique is given below in Fig.40 for cis-4-t-butylcyclohexanol.

Fig.40

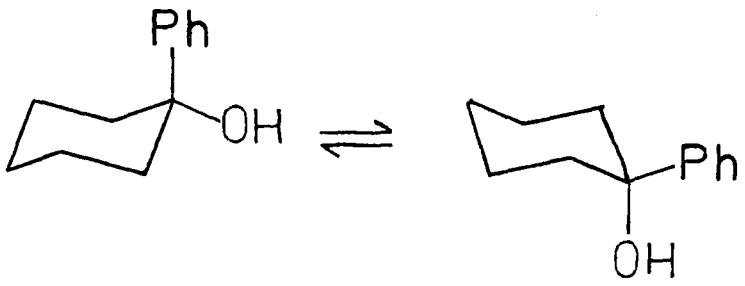


A:- N.M.R. Spectra of cis-4-t-butylcyclohexanol in $CDCl_3$

B:- N.M.R. Spectra of cis-alcohol + ∿ 0.6 mol ratio $Eu(DPM)_3$

The Conformational Preference of the Phenyl group in the Cyclohexyl system

The equilibrium involved here is:-



To determine this conformational preference the previously mentioned graphical method of chemical shift vs. concentration for 1-phenylcyclohexanol was utilized together with the pure axial and equatorial hydroxyl groups of the trans and cis-4-t-butyl-1-phenyl cyclohexanols respectively. The dilution-chemical shift studies were carried out in carbon tetrachloride at a probe temperature of + 40°C, and the results obtained (Table 9) from the graph shown in (Fig.41) are given below:-

Table 9.

Compound	Limiting Chemical Shift (Hz)	Limiting Slope (Hz/N)
cis-4-t-butyl-1-phenylcyclohexanol (III)	73.7	1000
1-Phenylcyclohexanol (I)	68.1	520
trans-4-t-butyl-1-phenylcyclohexanol(II)	67.8	415

From the above results:-

$$K = \frac{\delta_{II} - \delta_{I}}{\delta_{I} - \delta_{III}} = \frac{67.8 - 68.1}{68.1 - 73.7}$$

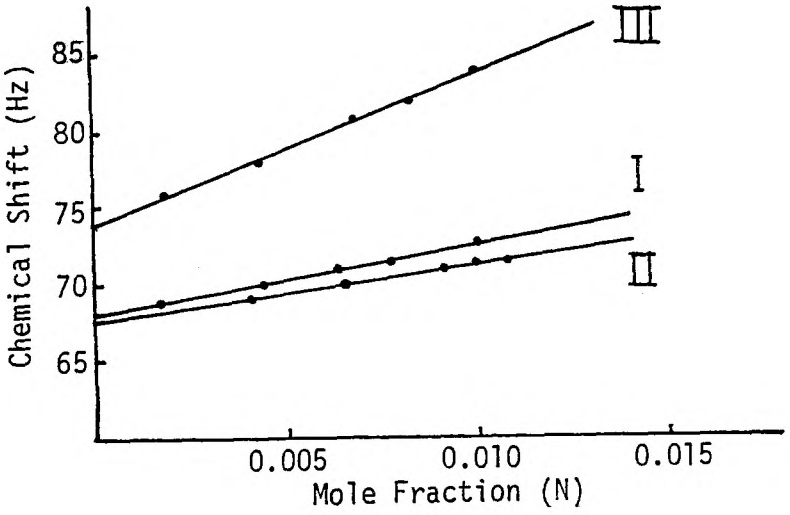
$$\therefore K = 0.05357 \quad (\text{for equilibrium } R \rightarrow L)$$

$$\therefore -\Delta G = -7.62 \text{ kJmol}^{-1}$$

Hence by making the assumption that the conformational preference of two groups attached to the same carbon atom on a cyclohexane ring are additive, and the conformational preference of the hydroxyl group in carbon tetrachloride at infinite dilution and at +40°C is 3.17 kJ mol^{-1}, then the conformational preference of the phenyl group in phenylcyclohexane is 10.79 $kJmol^{-1}$.

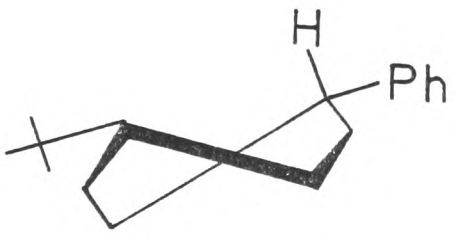
This is in very good agreement with the value of 10.88 $kJmol^{-1}$ obtained by Eliel and Rerick[24] at + 35°C.

Fig.41



However it should be noted that Garbisch and Patterson[25] have postulateda value of 12.97 $kJmol^{-1}$, for the conformational preference of the phenyl group in phenylcyclohexane, and also suggest that a small amount (∿10%) of the boat form is present (Fig.42) at room temperature.

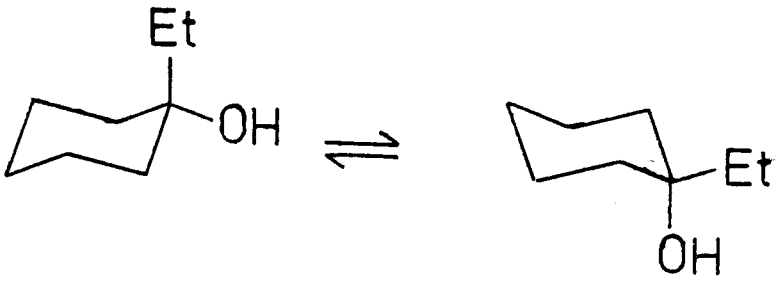
Fig.42



Boat form present at room temperature.

The Conformational Preference of the Ethyl group in the Cyclohexyl System

The equilibrium involved here is:-



To determine this conformational preference the isomers cis and trans-4-y-butyl-1-ethylcyclohexanol were used together with 1-ethylcyclohexanol. The dilution-chemical shift studies were carried out in carbon tetrachloride at a probe temperature of + 40°C and the results obtained (Table 10) for the graph shown in (Fig.43) are given below:-

Table 10.

Compound	Limiting Chemical Shift (Hz)	Limiting Slope (Hz/N)
cis-4-t-butyl-1-ethylcyclohexanol (III)	41.6	735
1-Ethylcyclohexanol (I)	36.5	600
trans-4-t-butyl-1-ethylcyclohexanol (II)	35.1	535

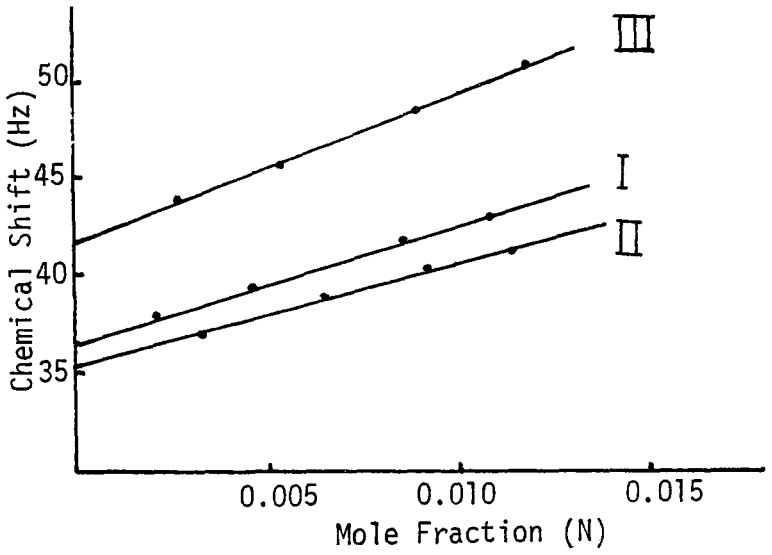
From the above results:-

$$K = \frac{\delta_{II} - \delta_{I}}{\delta_{I} - \delta_{III}} = \frac{35.1 - 36.5}{36.5 - 41.6}$$

$\therefore$ K = 0.2744 (for equilibrium R→L)

$\therefore$ $-\Delta G = -3.37\ kJmol^{-1}$

Fig.43



Hence by making the assumption that the conformational preference of two groups attached to the same carbon atom on a cyclohexane ring are additive, and the conformational preference of the hydroxyl group in carbon tetrachloride at infinite dilution and at + 40°C is 3.17 $kJmol^{-1}$, then the conformational preference of the ethyl group in ethylcyclohexane is 6.54 $kJmol^{-1}$.

This is within the values of 6.3 - 8.8 $kJmol^{-1}$ quoted by Eliel[18], his own value being 7.53 $kJmol^{-1}$, recommended from the work of Allinger and Hu[26].

The Conformational Preference of the Ethyl group by the Lanthanide Shift method of Groves and Van der Puy[22]

In the original work of Groves and Van der Puy, they used the lanthanide shift reagent $Eu(DPM)_3$ which has a limited solubility and a graphical least squares method had to be used for extra polation to obtain the molar ratio of one for complex to solute. However $Eu(fod)_3$ is much more soluble in $CDCl_3$, and here the molar ratio of one may be achieved by direct addition. The original spectra of alcohol in $CDCl_3$ and the spectra after addition of $Eu(fod)_3$ to n = 1, of trans-4-t-butyl-1-ethylcyclohexanol, cis-4-t-butyl-1-ethylcyclohexanol and 1-ethylcyclohexanol are shown in Figs,44,45 and 46, respectively. As stated before:-

$$\Delta Eu = \delta_{CDCl_3} - \delta^{n=1}_{Eu(fod)_3}$$

The relevant results obtained are given below for ΔEu (Table 11).

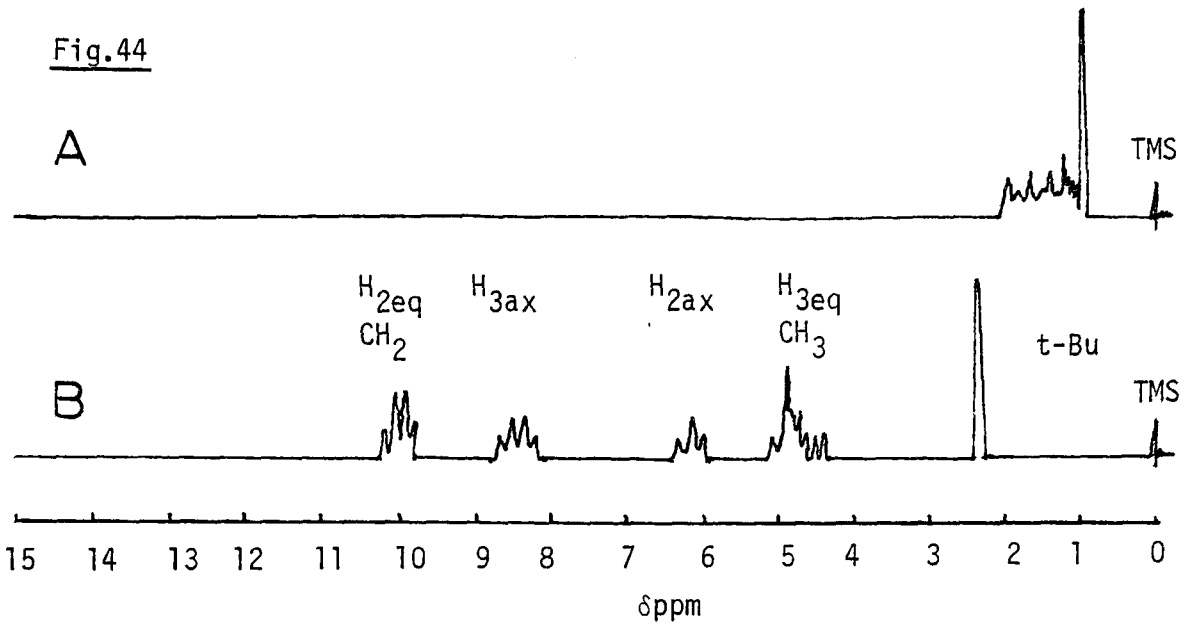
Table 11.

Compound	H_2-cis *	H_2-trans *	H_3-cis	H_3-trans	$-CH_2-$
trans-4-t-butyl-1-ethylcyclohexanol	-8.4	-4.7	-6.8	-3.5	-8.5
cis-4-t-butyl-1-ethylcyclohexanol	-12.1	-11.1	-3.5	-4.5	-8.2
1-ethylcyclohexanol (observed)	-10.4	-7.1	-6.2	-4.0	-8.4
1-ethylcyclohexanol (calc^d for 64:36) †	-10.7	-7.0	-5.6	-4.1	-8.3

* Here cis and trans refer to the protons with respect to the hydroxyl group.

† Calculated by the least squares method shown later.

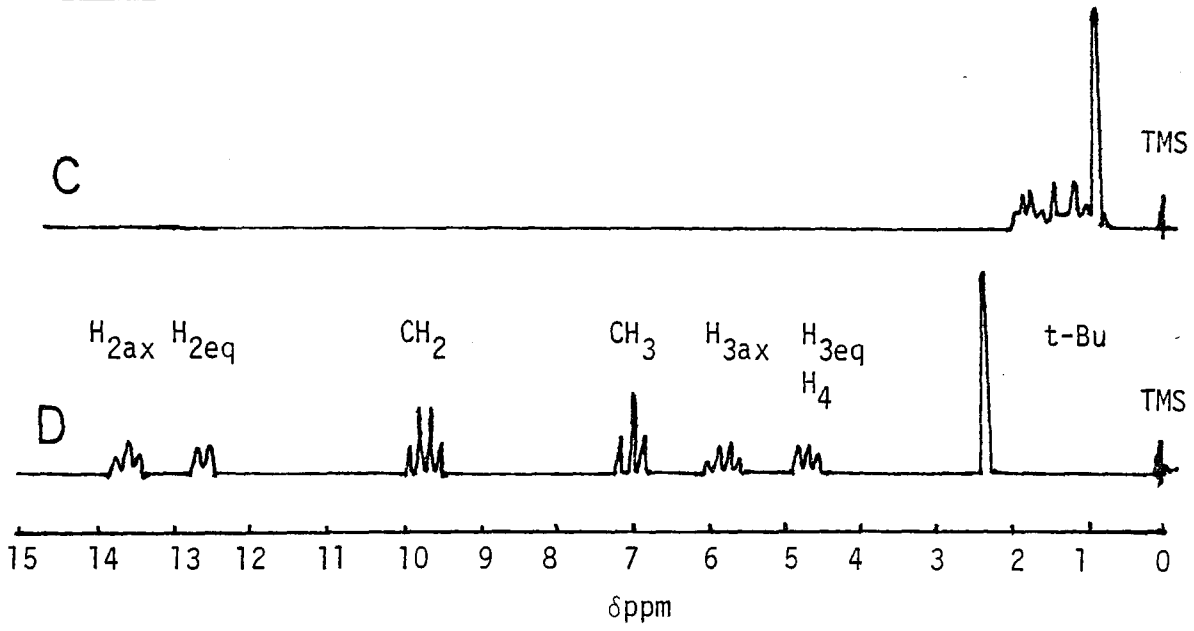
Fig.44



Spectrum A:- 10mg. of trans-4-t-butyl-1-ethylcyclohexanol in 0.5 ml of $CDCl_3$.

Spectrum B:- Addition of 55.2 mg $Eu(fod)_3$.

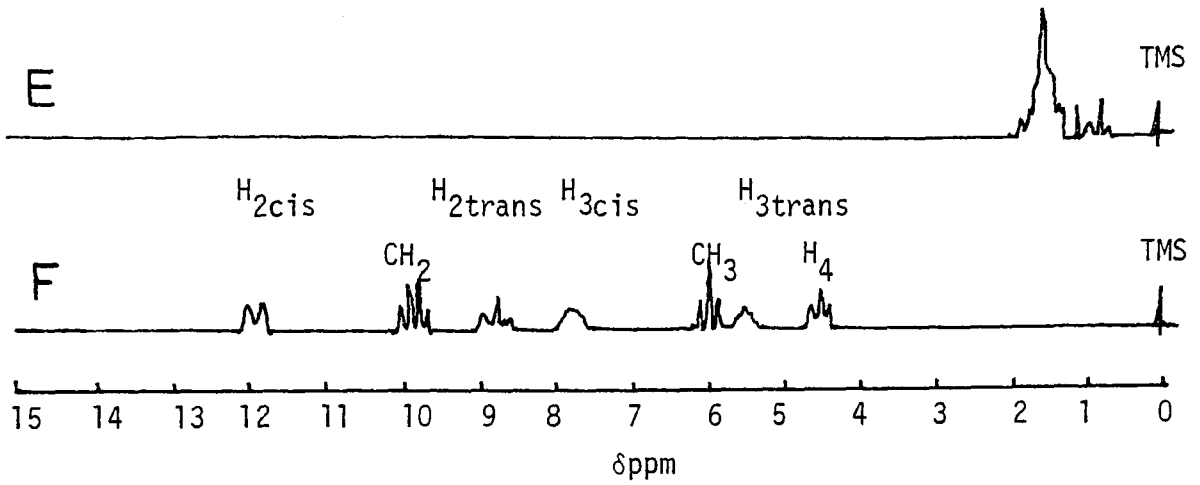
Fig.45



Spectrum C:- 10mg of cis-4-t-butyl-1-ethylcyclohexanol in 0.5ml of $CDCl_3$.

Spectrum D:- Addition of 55.2 mg $Eu(fod)_3$.

Fig.46



Spectrum E:- 10mg of 1-ethylcyclohexanol in 0.5 ml of $CDCl_3$

Spectrum F:- Addition of 82 mg. $Eu(fod)_3$

Least squares method for 'best fit' determination.

From the eqn:-

$$\Delta Eu^{(obs)} = N_{ax}\Delta Eu_{ax} + N_{eq}\Delta Eu_{eq}$$

or:- $y = bz + ax$ where $b = (1-a)$

$\therefore\ y = (1-a)z + ax.$

Hence for least squares:-

$$V_i = z - az + ax - y.$$

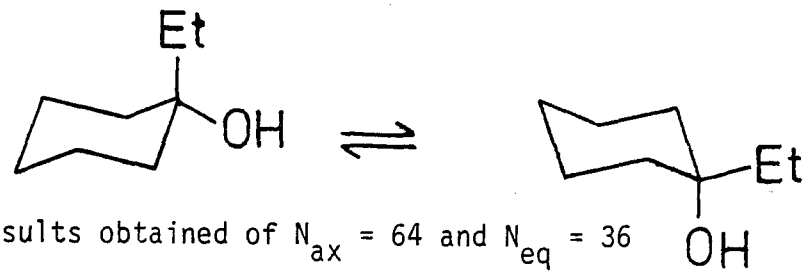
$$\therefore\ \Sigma v_i^2 = \Sigma z^2 - 2a\Sigma z^2 + 2a\Sigma xz - 2\Sigma yz + a^2\Sigma z^2 - 2a^2\Sigma zx + 2a\Sigma zy + a^2\Sigma x^2 - 2a\Sigma xy + \Sigma y^2$$

$$\therefore\ \frac{\delta\Sigma V_i^2}{\delta a} = -2\Sigma z^2 + 2\Sigma xz + 2a\Sigma z^2 - 4a\Sigma zx + 2\Sigma zy + 2a\Sigma x^2 - 2\Sigma xy = 0$$

$$\therefore\ a = \frac{\Sigma z^2 - \Sigma xz - \Sigma zy + \Sigma xy}{\Sigma z^2 - 2\Sigma xz + \Sigma x^2}$$

$$\text{i.e. } a = \frac{\Sigma\Delta Eu_{ax}^2 - \Sigma\Delta Eu_{eq}\Delta Eu_{ax} - \Sigma\Delta Eu_{ax}\Delta Eu^{obs} + \Sigma\Delta Eu_{eq}\Delta Eu^{obs}}{\Sigma\Delta Eu_{ax}^2 - 2\Sigma\Delta Eu_{eq}\Delta Eu_{ax} + \Sigma\Delta Eu_{eq}^2}$$

Hence for the equilibrium:-



Using the results obtained of N_{ax} = 64 and N_{eq} = 36

$\therefore$ K = 0.5625 (for equilibrium R→L)

Hence

$$-\Delta G = \underline{-1.5\ kJmol^{-1}}$$

Therefore assuming additivity of conformational preferences of groups on the same carbon atom of the cyclohexane ring, and using the value of 2.59 $kJmol^{-1}$ for the conformational preference of the hydroxyl group, as obtained by Groves and Van der Puy.

$$-\Delta G_{Et} = \underline{4.09\ kJmol^{-1}}$$

This value however is vastly outside the range of values quoted by Eliel[18] i.e. 6.3→8.8 $kJmol^{-1}$ for the conformational preference of the ethyl group in the cyclohexane system.

In the lanthanide shift method of Groves and Van Der Puy, they give a value of 2.59 $kJmol^{-1}$(Pg.59) for the conformational preference of the hydroxyl group in cyclohexanol. They made a comparison of this result with that of 4.17 $kJmol^{-1}$(Pg.55) obtained by Bushweller et al, stating that his result is inaccurate due to the large amount of H-bonding present because of high concentration and low temperature. They do not however compare their value with the value of 3.17 $kJmol^{-1}$ (Pg.53) obtained from the concentration against chemical shift technique where H-bonding is eliminated by dilution.

Furthermore Groves and Van Der Puy state that the complexing of the $Eu(fod)_3$ does not affect the axial-equatorial equilibrium but this would appear to be unlikely because a large group complexing with the oxygen of an hydroxyl group would almost certainly prefer the equatorial position. Although their results do not show this effect, the experiments carried out on 1-ethylcyclohexanol would tend to cast some doubt on their observations. The value of K obtained for the equilibrium of 1-ethylcyclohexanol by the concentration against chemical shift method is 0.2744 (Pg.62) giving rise to a good value of $-\Delta G$ for the conformational preference of the ethyl group in ethylcyclohexane. However, the value of the equilibrium constant K obtained via the lanthanide shift method of Groves and Van Der Puy is 0.5625 (Pg.67) showing that the complexing does increase the amount of equatorial hydroxyl group in the equilibrium.

The accuracy of NMR conformational anaylsis and the Equilibrium constant

In the NMR methods of Bushweller et al[19] and Jensen et al[20] where a value of K is calculated by (i) integration of peaks and (ii) chemical shift of the axial and equatorial protons at a lowered temperature of approximately - 80°C Bushweller quotes his values of K to an accuracy of ± 1 (approximately) whereas Jensen does not quote his accuracy.

However, work recently published by Sergeyev[27] would tend to cast some doubt on the accuracy of both these methods. Sergeyev gives an equation for the absolute error in K values by the integration method as:-

$$\sigma K = \left[\frac{\sigma I}{I}\right] \cdot 1 + K.\sqrt{1 + K^2} \qquad \ldots\ldots\ldots\ldots\ldots \quad 1$$

where σK = absolute error in the value of K

$(\sigma I/I)$ = standard error of integration (dependent on manufacturer's) (machine specification)

Hence the relative error $\sigma K/K$ is given by

$$\frac{\sigma K}{K} = \left[\frac{\sigma I}{I}\right] \cdot \frac{1 + K.\sqrt{1 + K^2}}{K} \qquad \ldots\ldots\ldots\ldots\ldots \quad 2$$

The normal value of $(\sigma I/I)$ is approximately 0.05 (or 5%). Hence from equation (2) it can be seen that the minimum relative error would be at a value of K = 1. If the value of K = 10 as in the case of the low temperature work of Bushweller, the value of $\sigma K/K = 0.5$ and hence K would have to be quoted as an uncertainty of K = 10 ± 5 (and not as 10 ± as stated).

The other equation quoted by Sergeyev concerns the inaccuracy of the chemical shift method of Jensen, being:-

$$\frac{\sigma K}{K} = \sigma_{cs} \cdot \frac{1}{\delta_2} \cdot \frac{1 + K\sqrt{2(1+K+K^2)}}{K} \quad \ldots\ldots\ldots\ldots \quad 3$$

where σ_{cs} = instrumental error in chemical shift measurements.

δ_2 = difference in the chemical shifts of axial and equatorial protons (i.e. setting δ_1 at zero)

Hence, once again it may be seen that as σ_{cs} will be a constant, then the minimum error will be at a value of K = 1 and increase with change in K. Also, it should be noted that the larger the value of δ_2, then the smaller the error.

Finally, Sergeyev quotes the error in the determination of $-\Delta G$ as:-

$$\sigma_{\Delta G} = RT(\sigma K/K) \quad \ldots\ldots\ldots\ldots \quad 4$$

(Table.13)displays the accuracy of the values of K and $-\Delta G$ by the methods of Bushweller, Jensen, Eliel and Ouellette respectively as obtained previously in the text, with respect to the cyclohexanol system.

Table 13.

Method	Accuracy of K value	Range in $-\Delta G$ value ($kJmol^{-1}$)
Bushweller	14 ± 10	2.97 - 5.37
Jensen	3.2 ± 0.5	2.60 - 3.46
Eliel	2.9 ± 0.45	2.31 - 3.15
Ouellette	3.2 ± 0.8	2.34 - 4.00

Hence from the figures shown in (Table 13) it can be seen that the method of Ouellette (i.e. concentration vs. chemical shift extrapolated to infinite dilution) is no better or worse than the accepted methods of Jensen and Eliel, although the method of Bushweller does leave little to be desired, as the integration method would appear to be the most inaccurate.

(N.B. See the results section for the variation of $\sigma K/K$ with K and $\sigma\Delta G$ with K by the method of Bushweller).

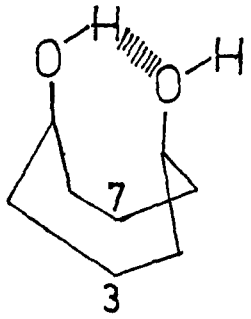
Also at this point, it is worthwhile noting that the methods involving measurements whether by chemical shift or integration, of the α-proton are restricted to certain groups on the cyclohexane ring i.e. those groups which are capable of deshielding the α-proton sufficiently downfield to enable observation to be distinct from the rest of the cyclohexane ring protons e.g. groups such as halogen, OH, OR, etc. Hence it can be seen that the method of -OH shift vs. concentration may be utilised for groups like methyl, ethyl, phenyl etc.

Examples of the usefulness of the technique

1. Does cis-cyclooctan-1-5-diol form an intra molecular H-bond?

The cyclooctane system is a very flexible system and it may easily be envisaged how an intramolecular H-bond may be formed in the cis-1-5-diol isomer, especially so,as it would form a very stable eight-membered ring system (Fig.47).

Fig.47



In fact, the results of the concentration vs. chemical shift graph, give limiting chemical shifts of 46.5 Hz in CCl_4 at + 65°C and 80.5 Hz in $CDCl_3$ at + 50°C, (i.e. no intra-H-bond)

The probable reason for the absence of the intramolecular H-bond being the steric interference of the protons at C_3 and C_7.

2. Does the double bond in 2-cyclohexen-1-ol possess an intramolecular H-bond and/or affect the intermolecular H-bonding?

The results of the concentration vs. chemical shift graph are given (Table 12) below and are compared with those of cyclohexanol itself in CCl_4 at + 40°C.

Table 12

Compound	Limiting Chemical Shift (Hz)	Limiting Slope (Hz/N)
Cyclohexanol	41.8	2575
2-Cyclohexen-1-ol	43.3	2550

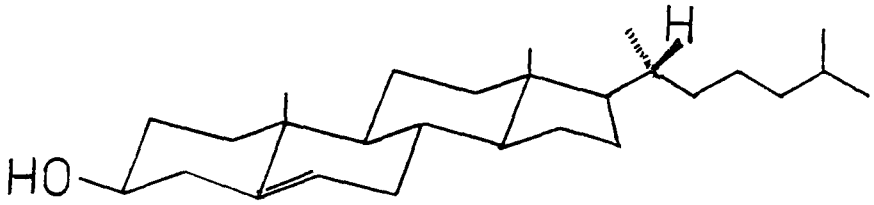
It may be seen from the above results that the compound 2 - cyclohexene-1-ol does not form an intramolecular H-bond which would

probably be expected due to the distance factor between the π-bond and the hydroxyl group. More important however, is the fact that the intermolecular H-bonding is not affected by the introduction of the double bond.

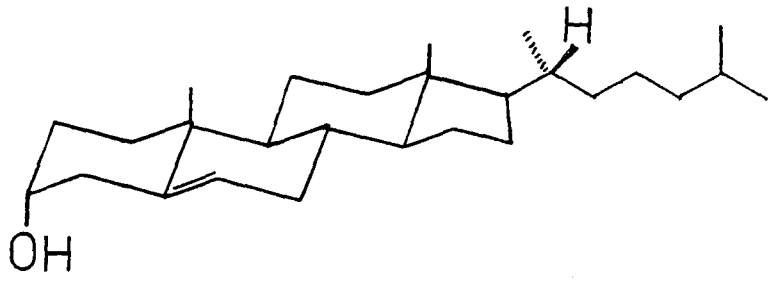
From this fact it is quite reasonable to assume that one could differentiate between steroids containing hydroxyl groups which may be 'alpha' or 'beta' even if they also contain double bonds. The hydroxyl group in the steroid system will be 'fixed' because e.g. in cholesterol only the chair (no alternate chair) or boat (which would be very energetically unfavoured could be present). (Fig.48).

Fig.48

β-hydroxyl group



α-hydroxyl group



Obviously one could differentiate between the α or β isomers by the chemical shift of the 3-proton alone, but if the steroid has a group R in the 3-position then the chemical shift vs. concentration technique would be valid.

Infra Red Spectra of the cyclohexane diols at low concentration

The spectra obtained from the eight diols (including the cis and trans cyclopentan-1-2-diols) are shown for very dilute solutions (~0.0005M) in the results section and it can be seen that where an intramolecular H-bond occurs two bands occur on the spectrum namely one at a wavenumber of approximately 3620 cm^{-1} due to the free hydroxyl group and the other at a lower wavenumber due to the hydrogen bonded hydroxyl group. Obviously, where no H-bond is found only one band is observed due to the 'free' hydroxyl groups.

The observed differences, between the free and bonded OH bands, $\Delta\nu$ are attributed to differences in the O---H distance. Badger[28] has shown that the stronger the hydrogen bond the greater is $\Delta\nu$, and hence one would expect that the value of $\Delta\nu$ would vary inversely with the length of the hydrogen bond. (Table 14) shows the calculated H----O distances, the values of the wavenumbers of the bands observed and $\Delta\nu$ values as observed by Kuhn[29] and myself.

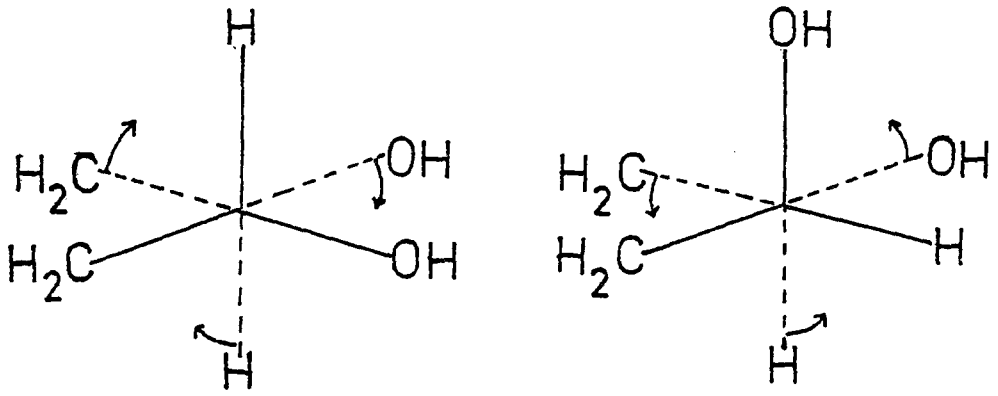
Table 14

Compound	Free OH(cm^{-1})		Intramol. Bonded OH(cm^{-1})		Δν		H----O* dist(nm)
	Kuhn	Williams	Kuhn	Williams	Kuhn	Williams	
cis-Cyclopentan-1,2-diol	3633	3636	3572	3575	61	61	0.184
trans-Cyclopentan-1,2-diol	3620	3628			0	0	0.330
cis-Cyclohexan-1,2-diol	3626	3628	3587	3589	39	39	0.234
trans-Cyclohexan-1,2-diol (equatorial)	3634	3632	3602	3600	32	32	0.234
(axial)							>0.330
cis-Cyclohexan-1,3-diol (axial)	3619	3623	3544	3547	75	76	0.164
(equatorial)							>0.330
trans-Cyclohexan-1,3-diol	3620	3627			0	0	> 0.330
cis-Cyclohexan-1,4-diol	3629	3626			0	0	> 0.330
trans-Cyclohexan-1,4-diol	3629	3627			0	0	> 0.330

* These values were calculated for bond distances and bond angles: C-C 0.154, C-O 0.142, O-H 0.096nm., C-C-O $109^{o}28^{1}$, C-O-H 108^{o}. The assumption is made that the orientation around the C-O bond is such that the H----O distance is a minimum.

In (Table 14) it is worth noting the cis and trans cyclohexan-1,2-diol isomers which although having the same calculated H---O distance of 0.234 nm, gives values of $\Delta\nu$ of 39 and 32 respectively. The attraction between the OH groups in forming a hydrogen bond will tend to produce a rotation around the C-C bond thus reducing the angle bounded by the two C-O bonds. As shown in Fig.49, this will make the ring more planar in the cis-isomer and more puckered in the trans-isomer.

Fig.49



The potential energy curve for rotation around a C-C bond of cyclohexane has two minima and the ring goes through the planar form in going from one minimum to the other, hence the curve is not symmetrical around a minimum but has a steeper slope in going toward the more puckered shape as compared with going toward the more planar shape.

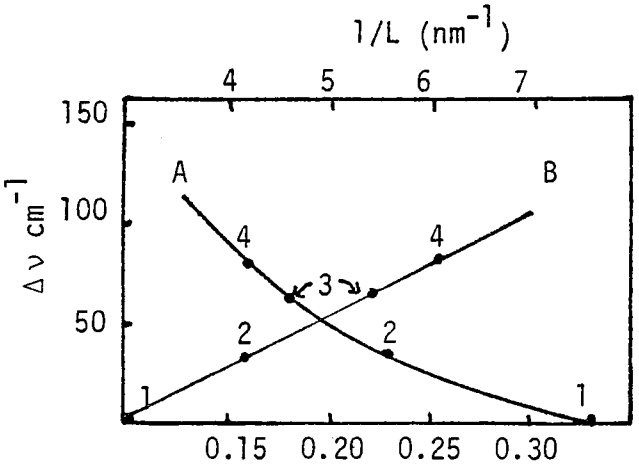
For a given expenditure of energy the OH groups of the cis-isomer can get closer together than those of the trans-isomer, and this explains why the $\Delta\nu$ is larger for the cis than for the trans-isomer.

The data relating H----O distance with $\Delta\nu$ which are given in(Table 14) are shown graphically in Fig.50. A curve is shown of somewhat similar shape as has been found for $\Delta\nu$ versus energy of the hydrogen bond[27]. In the range of value of H----O distance which was available, namely 0.16 to 0.33 nm, a linear relationship was found between $\Delta\nu$ and the reciprocal of the H---O distance as shown in Fig.50. This relationship can be expressed by the equation[29]:-

$$\Delta\nu = \frac{250 \times 10^{-8}}{L} - 74$$

where L is the H---O distance in cm.

Fig.50



A:- H----O distance vs.$\Delta\nu$

B:- 1/L vs. $\Delta\nu$

1. trans-cyclopentan-1,2-diol; 2. trans-cyclohexan-1,2-diol;

3. cis-cyclopentan-1,2-diol; 4. cis-cyclohexan-1,3-diol.

Comparison of I.R. and P.M.R. methods

In the case of detection of the intramolecular H-bond in the cyclic diol systems the infrared method is much better as it is less time consuming than the N.M.R. method although NMR can give rise to extra information from the point of view of the slopes of the concentration vs. chemical shift graphs. Also, in self-associated systems, each hydrogen-bonded species (i.e. monomer, dimer, trimer etc.) can, in principle, be individually distinguished by I.R. spectroscopy. This is a distinct advantage of the I.R. method over N.M.R. spectroscopy, which generally exhibits an average signal for all the species. However, band broadening, overlapping bands and anharmonicity, do complicate the interpretation of I.R. results. As mentioned above, in the N.M.R. method the slopes of the concentration vs. chemical shift graph can give information on the amounts of hydroxyl species in a mixture which is an advantage over the I.R. method. Another advantage of the N.M.R. method is the ability to differentiate between axial and equatorial hydroxyl groups in the cyclohexane system and the endo and exo hydroxyl groups in the rigid bicyclo systems, which is not so apparent by I.R. spectroscopy.

The main advantage of the N.M.R. technique would appear to lie in the field of conformational analysis of the cyclohexane system and the ability to measure equilibrium constants and hence calculate the conformational preference of groups in the system.

Also the fact that N.M.R. is very useful in the detection of weaker H-bonds such as with π-bond systems should not be disregarded.

Finally it may be stated that the use of both methods should provide a more complete and less ambiguous picture of a H-bonded system than either method alone, and is recommended wherever possible.

CONCLUSION

The concentration vs. chemical shift technique via NMR has proved to give good results in the determination of the presence of intramolecular hydrogen-bonding and hence the preferred conformations of the six cyclohexan-diol isomers studied. Also,these results are in total agreement with those obtained via the Infra Red method,the preferred conformations being:-

(a) cis-Cyclohexan-1-2-diol ——— Chair (a,e)
(intramolecularly H-bonded)

(b) trans-Cyclohexan-1-2-diol ——— Chair (e,e)
(intramolecularly H-bonded)

(c) cis-Cyclohexan-1-3-diol ——— Chair (a,a)
(intramolecularly H-bonded)

(d) trans-Cyclohexan-1-3-diol ——— Chair (a,e)
(non-intramolecularly H-bonded)

(e) cis-Cyclohexan-1-4-diol ——— Chair (a,e)
(non-intramolecularly H-bonded)

(f) trans-Cyclohexan-1-4-diol ——— Chair (e,e)
(non-intramolecularly H-bonded)

The slopes of the concentration vs. chemical shift graphs have proved useful as an analytical method in determining the amounts of alcohols in mixtures,as long as the slopes or limiting chemical shifts of the pure isomers are substantially different.

The conformational preference of the hydroxyl group in cyclohexanol has been determined by the concentration vs. chemical shift method as 3.2 ± 0.8 $kJmol^{-1}$. This has been compared with other NMR methods:-

(1) peak area measurement of axial and equatorial α-protons at -83°C.
(2) chemical shift of the α-protons (axial and equatorial) at -83°C and the average chemical shift at +40°C.
(3) chemical shift of the α-protons (axial and equatorial) using fixed cis and trans-4-t-Bu-cyclohexanol isomers and cyclohexanol at +40°C.
(4) a lanthanide shift method.

The value of 3.2 ± 0.8 $kJmol^{-1}$ has proved to be as good as and often better than the other results obtained.

Similarly, the conformational preference of the phenyl group in phenylcyclohexane has been calculated by the concentration vs. chemical shift method to give a good value of 10.79$kJmol^{-1}$. By this same method a good value 6.54$kJmol^{-1}$ has been determined for the ethyl group in ethylcyclohexane. The lanthanide shift technique was also carried out on this compound and the results obtained tend to cast doubt on the postulation of Groves and Van der Puy that the axial-equatorial equilibria is not affected by complexation.

The work of Sergeyev has shown that the determination of the equilibrium constant K by NMR will be more inaccurate as the value deviates from K=1.

However, it must be stated that the concentration vs. chemical shift technique is a useful and valid method which can be used in the quantitative and qualitative studies of hydroxyl containing compounds.

Experimental Conditions

1. Nuclear Magnetic Resonance

Spectroscopic grade carbon tetrachloride was distilled at atmospheric pressure into a dry system over nitrogen. The fraction boiling at 76.5°C was collected and stored over Molecular Sieve 5A in a vacuum desiccator. Tetramethyl-silane was added to form a 1% solution. In the case of d-chloroform, the D_1 Gold Label from Aldrich Chemical Co. was used which contained 1% TMS, which was again stored in a vacuum desiccator.

All compounds used were either distilled under an atmosphere of nitrogen or vacuum sublimed prior to use. Compounds and solvent were prepared in 1- and 2- cm^3 volumetric flasks except the cases when solubility was a problem and compound and solvent were weighed directly into the N.M.R. tubes.

The spectra were obtained on a JEOL C-60HL instrument and the chemical shifts of the hydroxyl protons were determined relative to the internal TMS standard. Using the x 1/2 scale the chemical shifts were determined to 0.2 Hz. Each compound was run at the same sweep rate and in precision Loxford N.M.R. tubes. In cases of doubt as to the position of the hydroxyl group, deuterium oxide was added.

All graphs were obtained using the graph-plotting facilities of the IBM 1130 computer.

2. Infra Red

The diols were made up in dried carbon tetrachloride at a concentration of approximately 0.0005M in order to eliminate any intermolecular H-bonding. The spectra were obtained on a Perkin Elmer 580 machine using 10cm cells with sodium chloride windows. The spectra were recorded only in the region 2800-4000cm^{-1}.

Preparation and purification of the compounds used in the study

cis-Cyclopentan-1-2-diol[30]

The method of Milas and Sussman (see preparation of cis-Cyclohexan-1-2-diol) was tried with cyclopentene but gave little success and a very small yield. Hence the method of Owen and Smith was utilised.

A solution of cyclopentene (5.5g) in ethanol (150 cm^2) was cooled to -40°C (solid CO_2/acetone); and a solution of potassium permanganate (10g) and anhydrous magnesium sulphate (7g) in water (200cm^2) was added with vigorous stirring over 2 hours. The manganese dioxide was filtered off and the filtrate evaporated to approximately 60cm^3 and continuously extracted with ether for 48 hours. The dried extract was then evaporated and distilled to give cis-cyclopentan-1-2-diol (b.p.82-84°C/1mm) Yield = 2g.

trans-Cyclopentan-1-2-diol [30]

A mixture of 30% aqueous hydrogen peroxide (6.5g) and formic acid (53g) was added to cyclopentene (3.3g) with much heat being generated. The temperature was allowed to fall to 40°C and was so maintained for 4 hours. After this period the mixture was tested for unchanged peroxide before proceeding. The formic acid was removed under reduced pressure and the residue was dissolved in ice-cold 10% aqueous sodium hydroxide (25cm^3) and boiled under reflux for 45 minutes. After extraction with ethyl acetate (4 x 25cm^2) and drying, the ethyl acetate was removed under reduced pressure and the trans isomer isolated after distillation twice under reduced pressure (b.p.93°C / 2mm; m.p.50°C) Yield = 1.5g.

cis-Cyclohexan-1-2-diol[31]

Cyclohexene, previously freed from peroxides by washing with sodium meta-bisulphite was dried and distilled. The fraction collected at b.p. 81-83°C was used. Hydrogen peroxide (30%, 6.5cm^3) was dissolved in tert-butyl alcohol (25 cm^3), dried twice with 'drierite' and filtered. This was used as the oxidation reagent.

Cyclohexene (4.1g) was mixed with the oxidation reagent ($30cm^3$) and a solution of osmium tetroxide (0.015g) in tert-butyl alcohol added. The mixture was cooled to 0^oC and left overnight at room temperature. The solvent and unused cyclohexene was removed by distillation at atmospheric pressure and the residue fractionated under reduced pressure (b.p.= 120-40/15mm). The solidified distillate was recrystallised from ethyl acetate and then refractionated under reduced pressure to give a white solid (2.5 gms. m.p. = 95^oC).

trans-Cyclohexan-1-2-diol[31]

This was prepared by the same method as the trans-cyclopentan-1-2-diol. Using formic acid (90%, 30 cm^3); hydrogen peroxide (30%, $7cm^3$) and cyclohexene (5.1 cm^3) the trans-cyclohexan-1-2-diol was obtained, after distillation (b.p. 128-132^oC/15mm) and recrystallisation from ethyl acetate, as a white solid (m.p.103^oC) Yield = 2.5g.

cis and trans-Cyclohexan-1-3-diols[32]

A mixture of the two diols (prepared by hydrogenation of resorcinol by the method of Pavlic and Adkins)[33] was dissolved (20g) in pyridine (70g), and benzoyl chloride (57g), was slowly added with stirring at 0^oC. The mixture was left overnight at room temperature, and then heated on a steam bath for 1 hour, cooled and diluted with 2M, sulphuric acid ($400cm^3$). The precipitated oil was taken up in chloroform and the extract was washed with dilute sulphuric acid, aqueous sodium carbonate and finally with water. After drying and evaporating back to the oil, this was treated with ethanol (3 cm^3) and a solid crystallised. This was collected and 12g was recrystallised from methanol to give the trans-dibenzoate (m.p.= 123^oC). The ethanolic solution was concentrated and treated with a little light petroleum (40-60) and set aside in the refrigerator. The solid crystallised slowly and after trituration with cold methanol, the solid was recrystallised from the minimum amount of boiling methanol, to give short, thick needles of the cis-dibenzoate (m.p = 67^oC) Yield = 6g.

The trans-dibenzoate (10g) was dissolved in dry methanol ($30cm^3$) and a 5% solution of sodium in dry methanol ($0.1cm^3$) was added. The mixture protected from the atmosphere was kept at 50^oC for 24 hours. Water ($0.5\ cm^3$) was added and the alkali was neutralised with carbon dioxide. After filtration and removal of the methanol by distillation, the remaining liquid, on fractionation, gave methyl benzoate (b.p.91^o/15mm); and trans-cyclohexan-1-3-diol (b.p. 140-2/15mm). This solidified and on recrystallisation from ethyl acetate gave 2.5g of plates of the diol (m.p. = 115^oC).

6.g. of the cis-dibenzoate was treated as above, but here the cis-diol crystallised from the methyl benzoate. $30cm^3$ of light petroleum (40-60) was added and the diol filtered and washed with light petroleum. After recrystallisation from acetone 1.8g of the cis-1-3-diol were obtained (m.p. = 85.5^oC).

cis and trans-cyclohexan-1-4-diols[34]

A mixture of the two diols (prepared by the hydrogenation of quinol) (21 gms) was acetylated, by refluxing for 4 hours with acetic anhydride (40g) and the crude diacetate crystallised from boiling acetone ($20cm^3$) to give long prisms of the trans-diacetate (10g, m.p. = 102^oC). This was covered with anhydrous methanol ($20cm^3$) and treated with 20% methanolic sodium methoxide ($0.25cm^3$). After 24 hours standing at room temperature, the solution was concentrated to $\sim 10cm^3$ and treated with ether ($40cm^3$) and cooled to 0^oC to give small prisms of the trans-diol (Yield = 2g, m.p. = 141^oC).

The cis-isomer was obtained cheaply from a chemical firm, but was crystallised twice from boiling acetone to give crystals (m.p. = 108-110^oC).

cis and trans-4-tert-butyl-cyclohexanols[6]

A mixture of these two isomers was obtained from the Aldrich Chemical Company. They were separated chromatographically by a column using 30g of activated alumina per gram of alcohol. The 'cis' isomer was eluted first with pentane, whereas elution of the 'trans' isomer required a solvent containing 10-20% of ether. Fractions from the column were able to be checked by N.M.R. as the α-proton i.e. one isomer 'axial' the other 'equatorial', have different chemical shifts.
N.B. Also it should be stated here that cis and trans refer to the -OH group with respect to the tert-butyl group.

cis and trans-4-tert-butyl-1-phenyl-cyclohexanols[35]

A mixture of the isomers were prepared via a Grignard reaction using 4-tert-butyl-cyclohexanone (14g), bromobenzene (18g) and magnesium (3g). The product (1.5g) was placed on the top of a column containing silica gel (70g) as a slurry in (60-80) petroleum ether. This was successively eluted with petroleum ether ($1000cm^3$); 5% benzene/petroleum ether ($500cm^3$); 10% benzene/petroleum ether ($500cm^3$); 30% benzene/petroleum ether($500cm^3$); 50% benzene/petroleum ether ($500cm^3$) and 70% benzene/petroleum ether ($1000cm^3$) to give 200mg. of the trans isomer which had a m.p.= 116^oC after recrystallisation from pentane (eluted with 10-30% benzene/petroleum ether).

The fraction at 50% benzene/pet. ether gave a mixture of the isomers, and then at 70% benzene/pet. ether gave 300mg. of the cis-isomer which had a m.p. = 158^oC after recrystallisation from hexane. As would be expected, the trans-isomer came off the column first as an -OH group in the 'axial position is known to be less strongly adsorbed on silica-gel or alumina than an -OH group occupying the equatorial position[35]. The purity of each isomer was checked by N.M.R. as the tert-butyl group of each isomer have slightly different resonance positions i.e. 0.8 ppm for the 'cis' and 0.9 ppm for the 'trans' N.B. Here the cis and trans refer to the phenyl group with respect to the tert-butyl group.

cis and trans-4-tert-butyl-1-ethyl-cyclohexanols

A mixture of the isomer was prepared via a Grignard reaction using 4-tert-butyl-cyclohexanone(11.5g) iodoethane (15.6g) and magnesium (2.35g) 4g of the product as a yellow oil was dissolved in the minimum amount of (40-60) petroleum ether and placed on the top of a column of alumina (200g in a slurry of (40-60) petroleum ether) This was successively eluted with 800cm^3 of (40-60) petroleum ether;1000cm^3 of 10% ether/ pet.ether;1000cm^3 30% ether/pet.ether;1000cm^3 50% ether/pet.ether;and finally 750cm^3 of ether, collecting in fractions of 100cm^3. (i.e. 45 fractions).

The initial 15 fractions contained mainly unchanged 4-tert-butyl-cyclohexanone with a small amount of the cis-isomer. Fractions 20-30 gave 0.72g. of the cis-isomer as a colourless liquid. Fractions 30-33 gave a mixture of the two isomers. Fractions 35-40 gave the trans-isomer as a solid which after recrystallisation from pentane gave 0.55g. of m.p.= 82^{o}C. The final fractions gave some trans-isomer together with some 4-tert-butyl cyclohexanol.

1-phenylcyclohexanol

This was prepared by the standard Grignard reaction using cyclohexanone (9.7g), magnesium (3.7g) and bromobenzene (23.4g). The product was distilled under reduced pressure (b.p.152^{o}C/20mm) to give a solid which on recrystallisation from hexane gave white crystals (m.p.61^o) Yield = 5.4g.

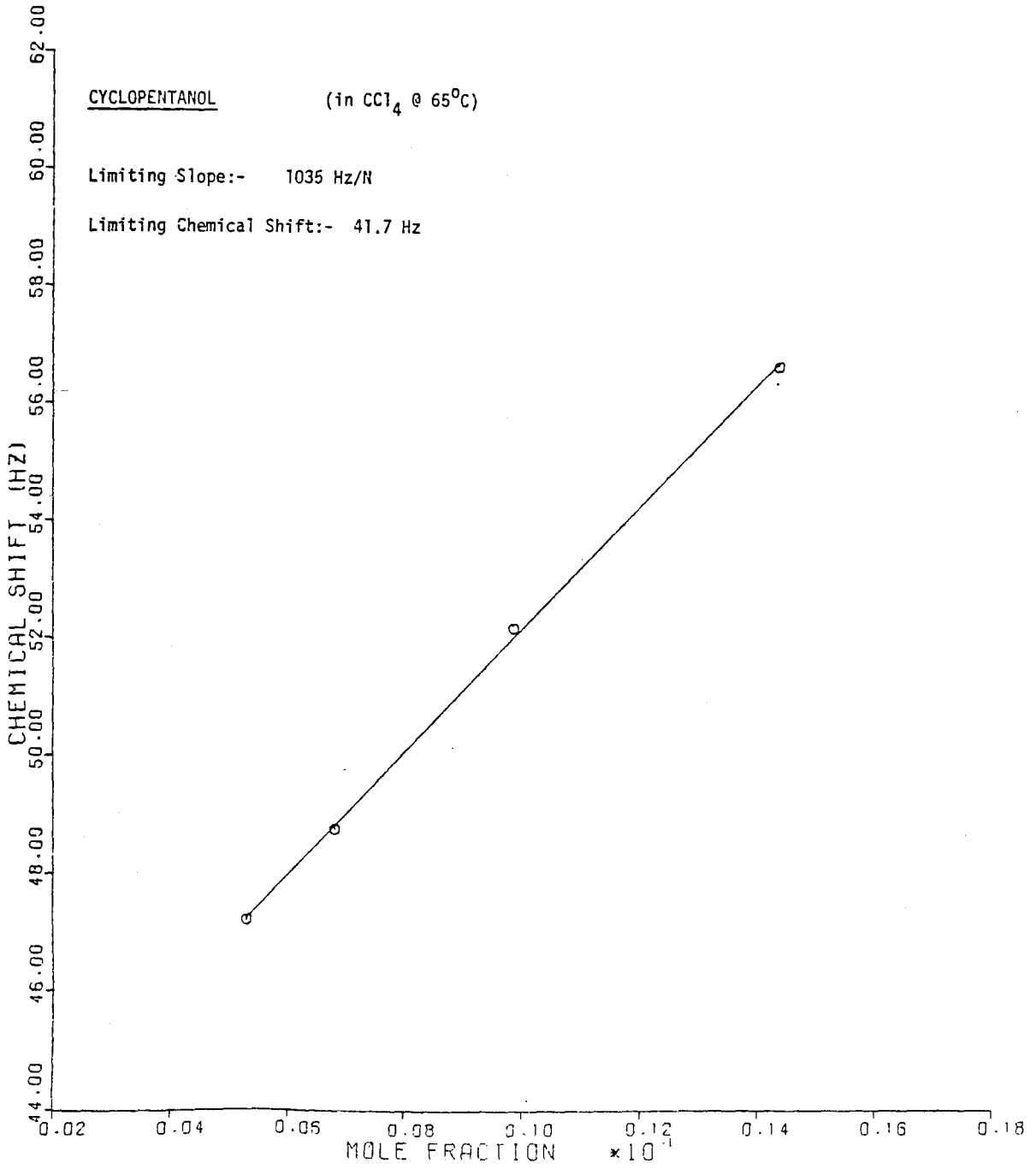
1-ethyl cyclohexanol

This was prepared using the standard Grignard reaction except in the hydrolysis stage, cold aqueous ammonium chloride was utilised because the hydrolysis using hydrochloric acid gave rise to a substantial amount of the dehydrated compound (1-ethyl cyclohex-1-ene).

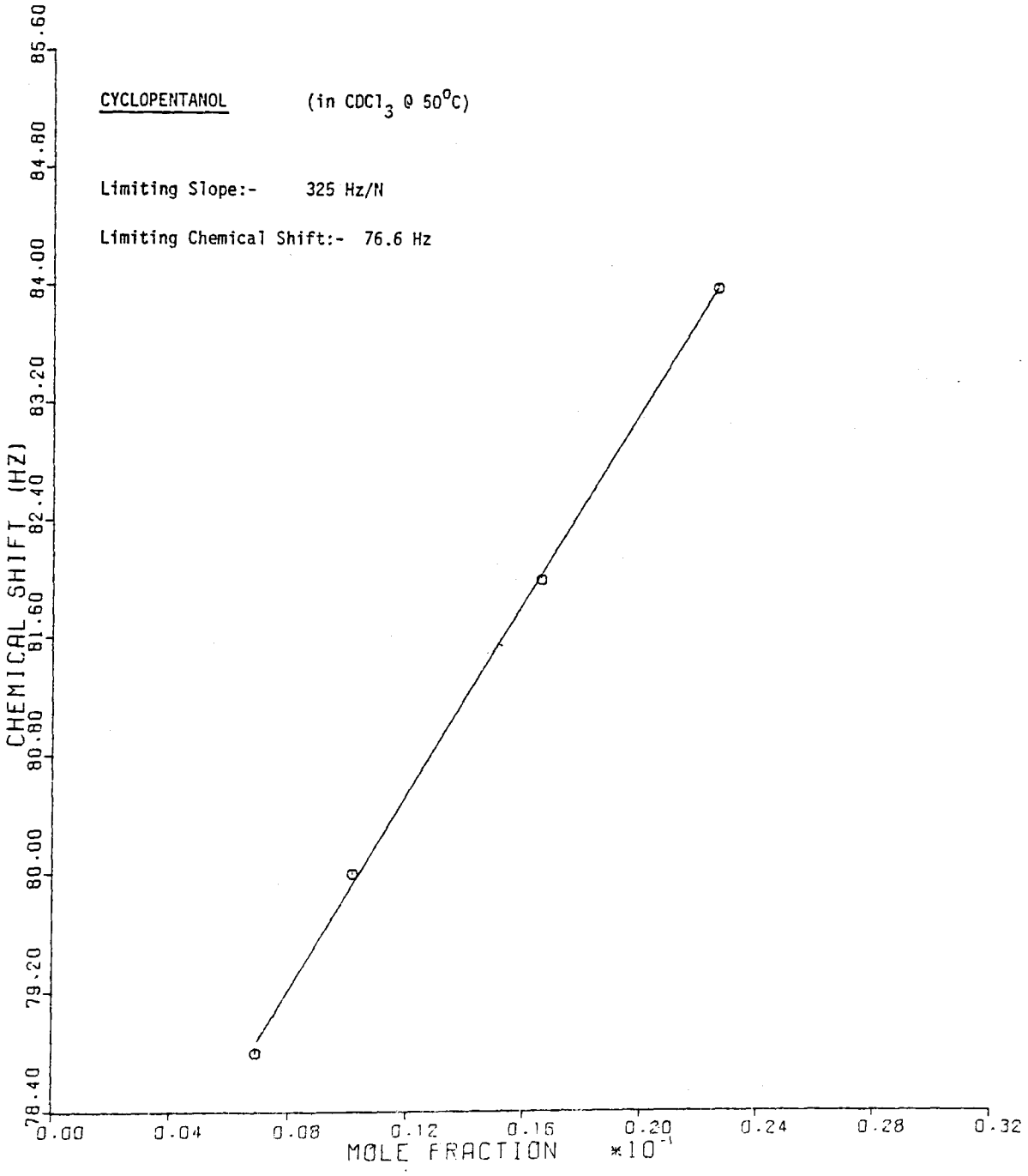
The quantities of reactants used were cyclohexanone (9.7g), magnesium (3.7g) and bromoethane (15.4g). However, even after distillation under reduced pressure ($60^{o}C$/10mm) the product still contained impurities of starting material (cyclohexanone) and some cyclohexanol. Most of the cyclohexanone was removed by shaking an ethereal solution of the product with a saturated solution of sodium metabisulphite and the white gelatinous precipitate (metabisulphite derivative of cyclohexanone) was filtered off. The remaining pale yellow liquid was again distilled under reduced pressure ($58^{o}C$/10mm) which solidified on cooling in ice. This was then further purified using a Pye Unicam 105 preparative V.P.C.(which had a trapping efficiency of approximately 30%) to give 1.8g of 1-ethylcyclohexanol (m.p.= $35.5^{o}C$).

RESULTS

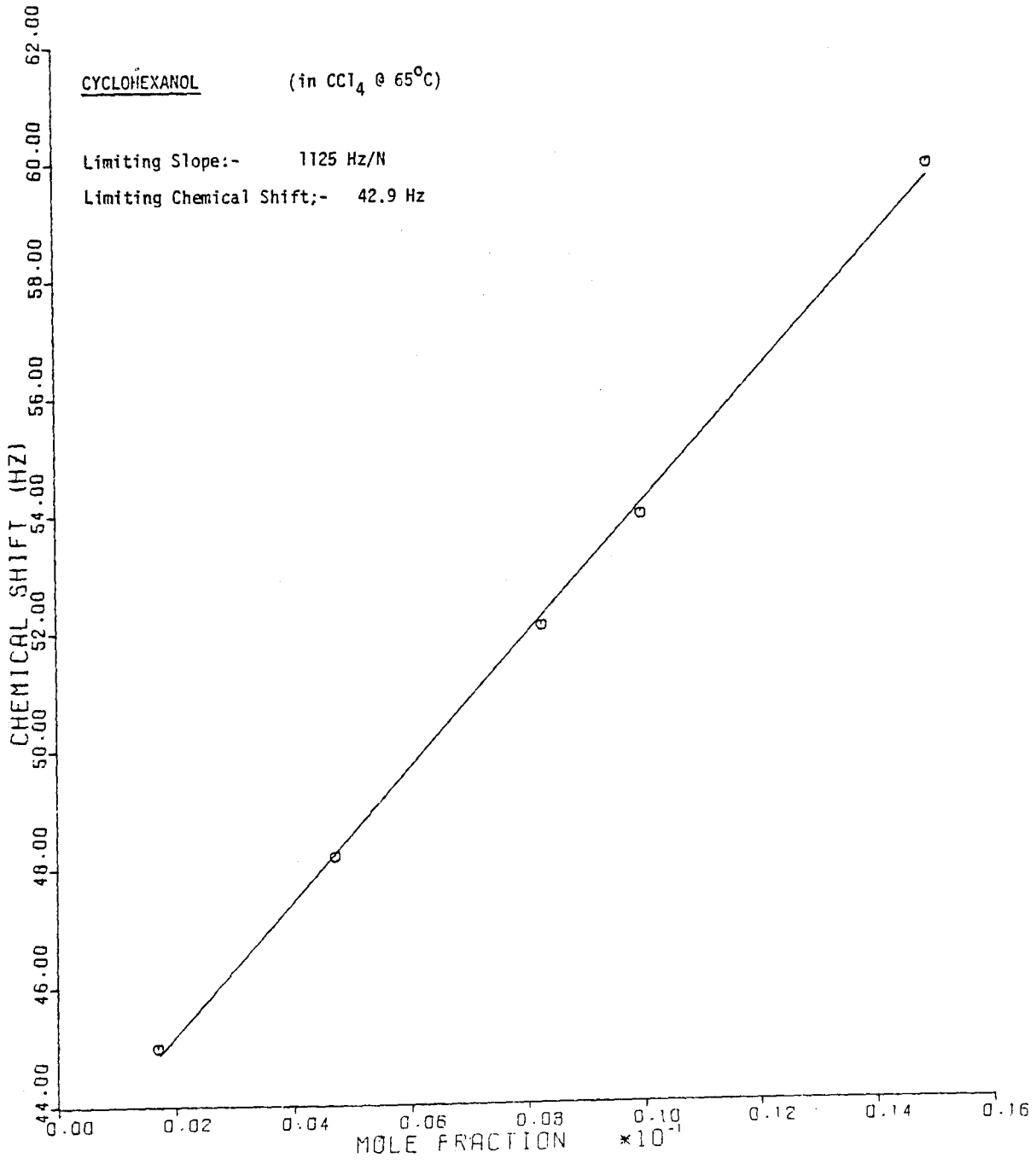
Wt. of alcohol (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
4.40	1.4722	0.005337	47.3
5.95	1.5553	0.006831	48.8
8.80	1.5863	0.009906	52.2
12.85	1.5869	0.014460	56.7



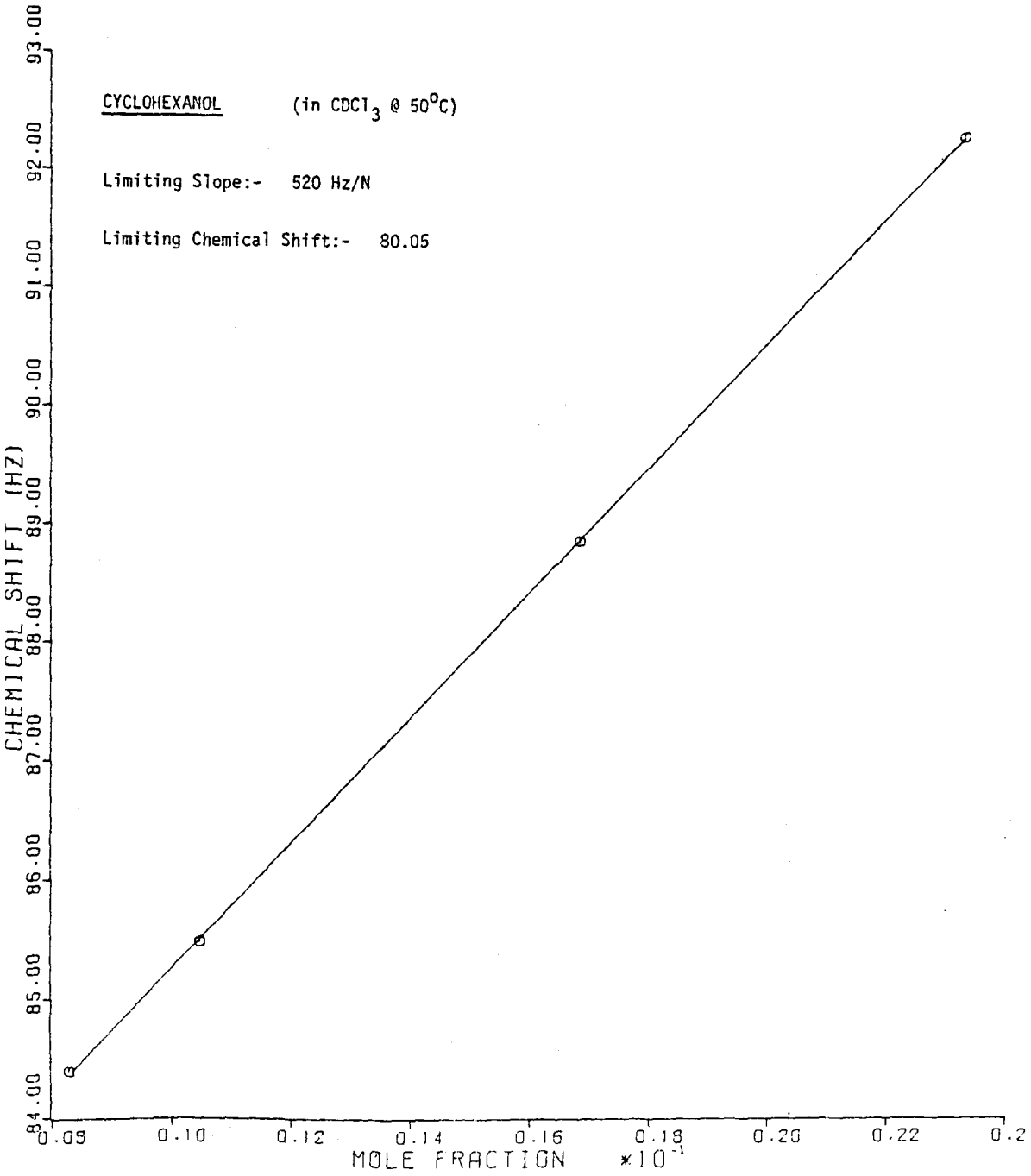
Wt. of alcohol (mg)	Wt. of $CDCl_3$ (g.)	Mole Fraction (N)	Chemical Shift (Hz)
5.20	1.0517	0.006910	78.00
9.45	1.2948	0.010200	80.00
16.70	1.3976	0.016700	82.00
20.20	1.2410	0.022750	84.00



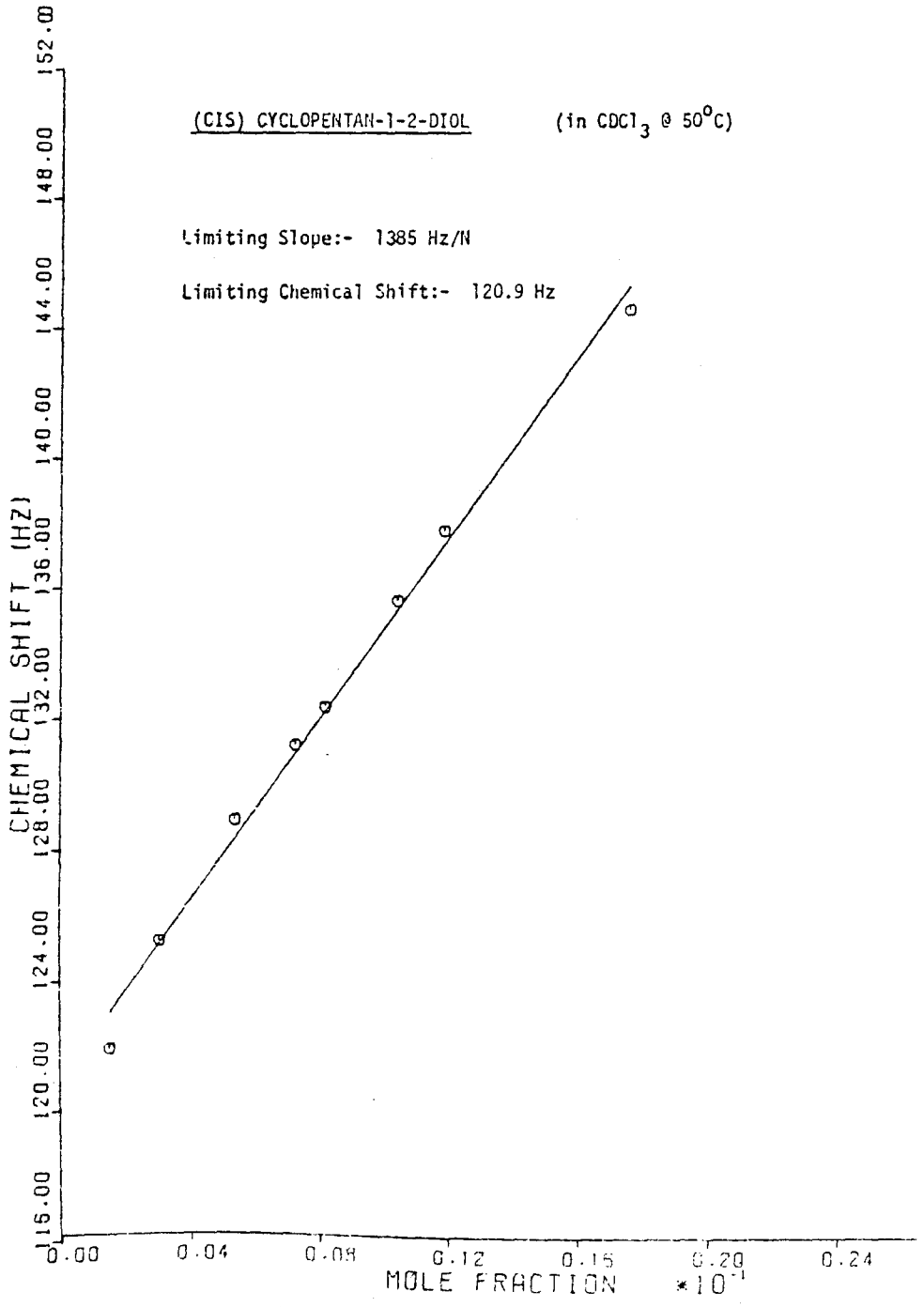
Wt. of alcohol (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
2.70	2.4363	0.001702	45.00
5.35	1.7404	0.004721	48.20
8.75	1.6167	0.008312	52.10
10.20	1.5618	0.010030	54.00
15.95	1.6308	0.015020	60.00



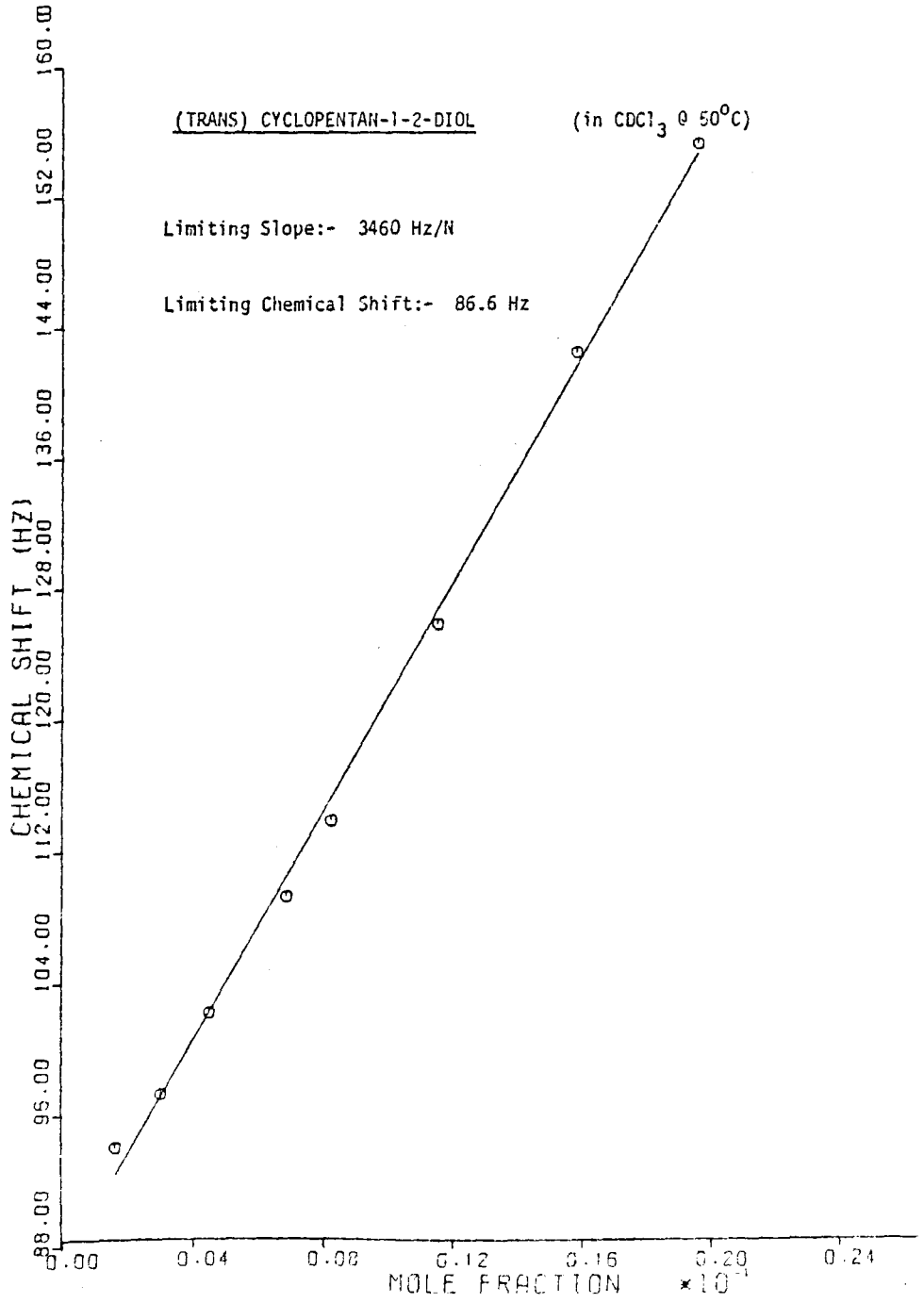
Wt. of alcohol (mg)	Wt. of $CDCl_3$ (g)	Mole Fraction (N)	Chemical Shift (Hz)
8.85	1.2789	0.008318	84.40
10.25	1.1722	0.010510	85.50
15.30	1.0869	0.016920	88.90
23.70	1.2117	0.023510	92.30



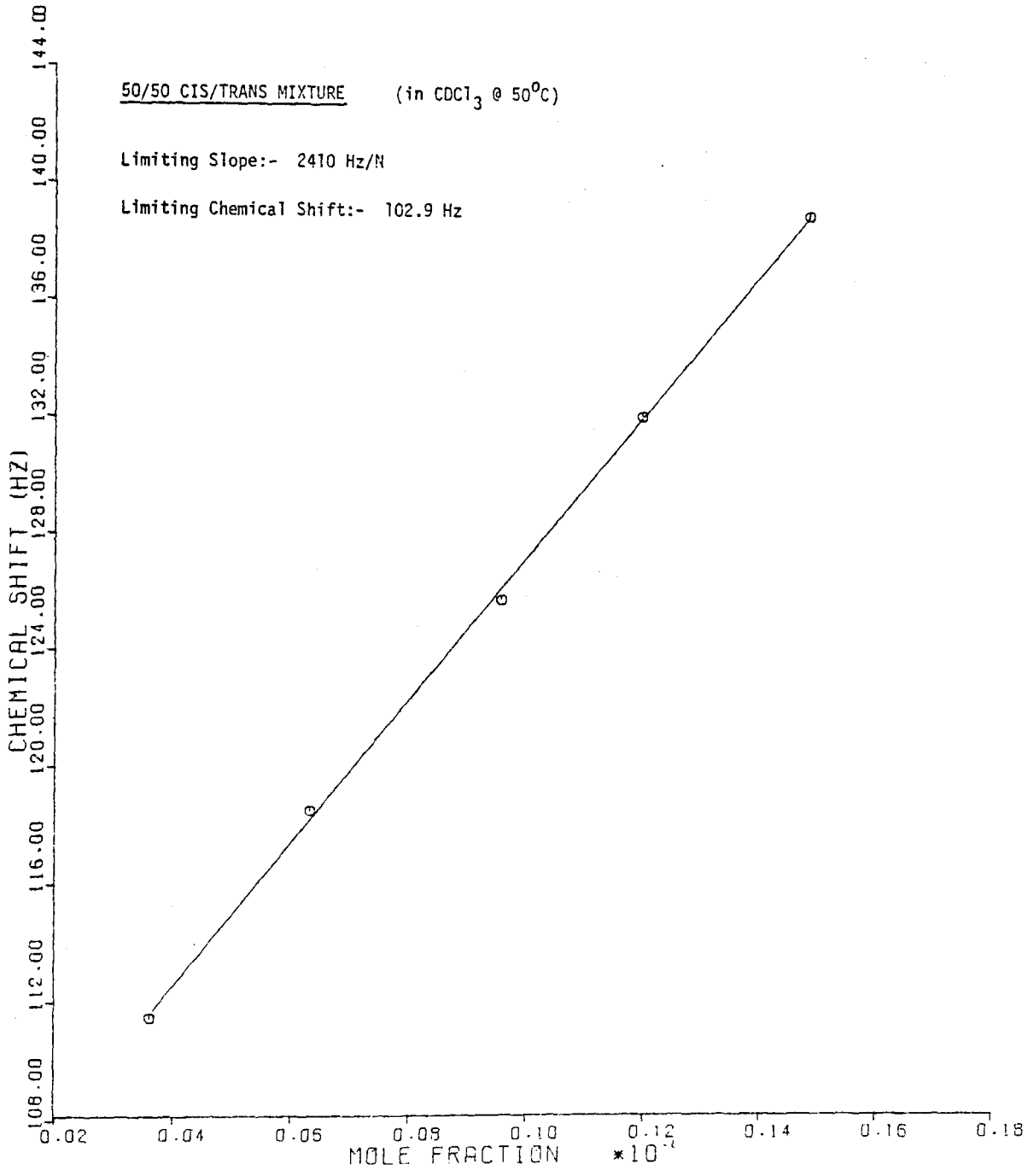
Wt. of diol (mg)	Wt. of $CDCl_3$ (g)	Mole Fraction (N)	Chemical Shift (Hz)
1.90	1.4712	0.001522	121.9
3.90	1.4904	0.003085	125.3
6.85	1.4937	0.005406	129.0
9.05	1.4701	0.007257	131.3
10.30	1.4845	0.008179	132.4
13.30	1.5054	0.010420	135.7
15.00	1.4884	0.011880	137.8
22.65	1.5079	0.017710	144.7



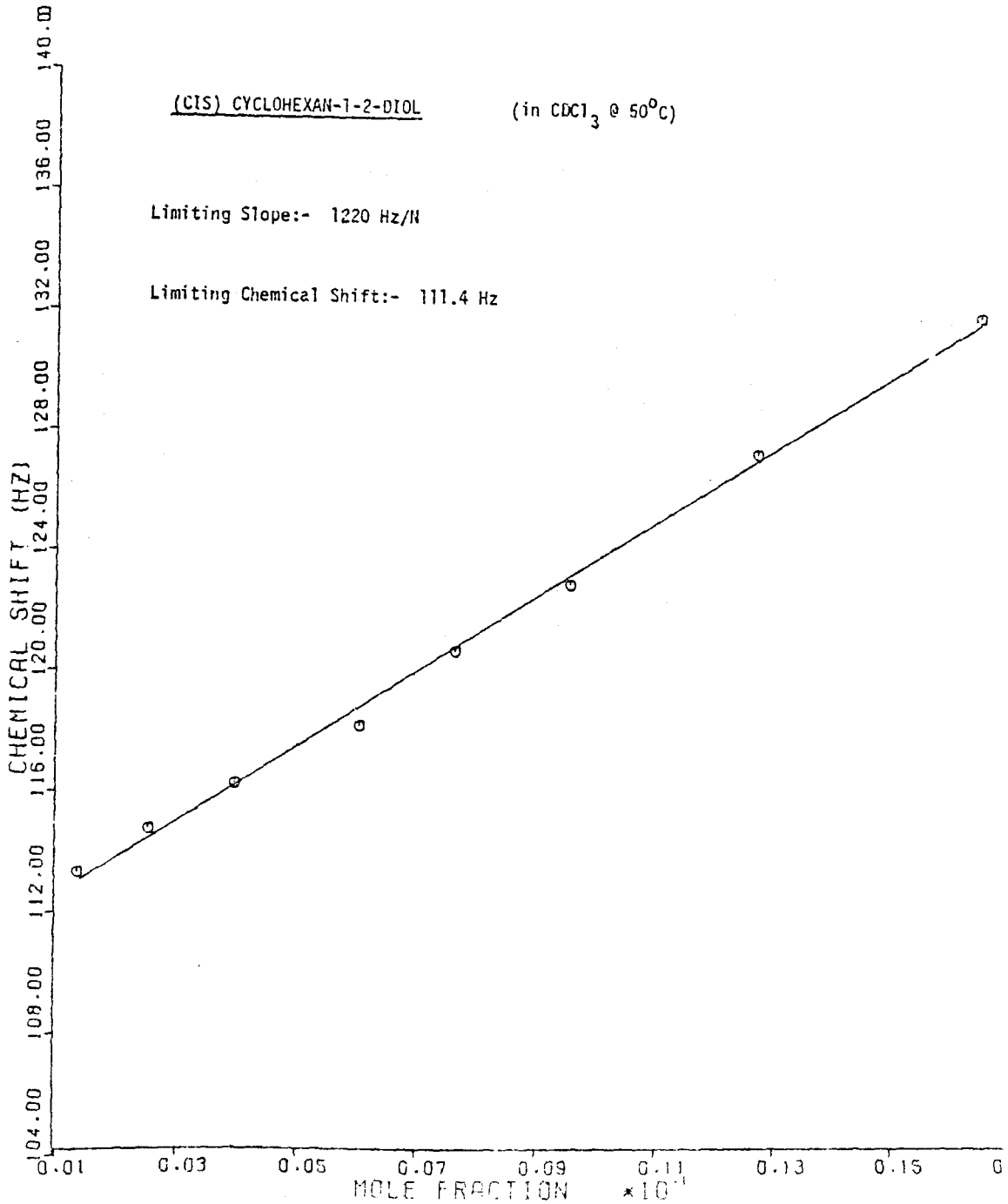
Wt. of diol (mg)	Wt. of $CDCl_3$ (g)	Mole Fraction (N)	Chemical Shift (Hz)
2.10	1.4965	0.001654	94.1
3.90	1.5028	0.003059	97.4
5.75	1.4879	0.004556	102.4
8.80	1.5012	0.006910	109.4
10.50	1.4932	0.008289	114.0
14.90	1.5150	0.011590	125.9
20.50	1.5159	0.015940	142.7
25.10	1.4980	0.019750	155.6



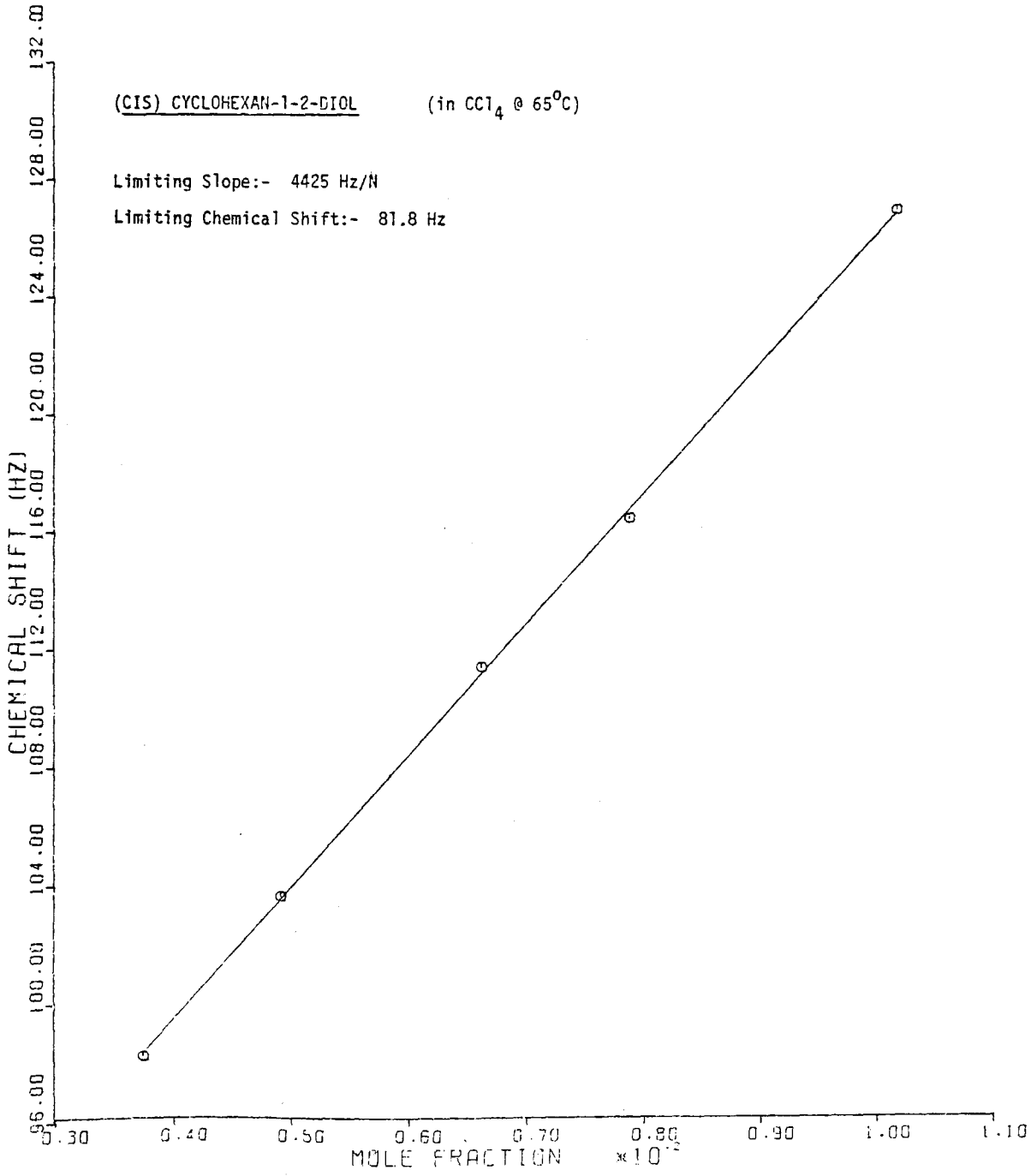
Wts. of diols (mg)	Wt. of $CDCl_3$ (g)	Mole Fraction (N)	Chemical Shift (Hz)
3.90c/3.90t	2.5350	0.003627	111.5
5.65c/5.65t	2.1033	0.006333	118.5
7.70c/7.70t	1.8884	0.009613	125.7
9.70c/9.70t	1.8994	0.012040	132.0
12.00c/12.00t	1.8962	0.014920	138.9



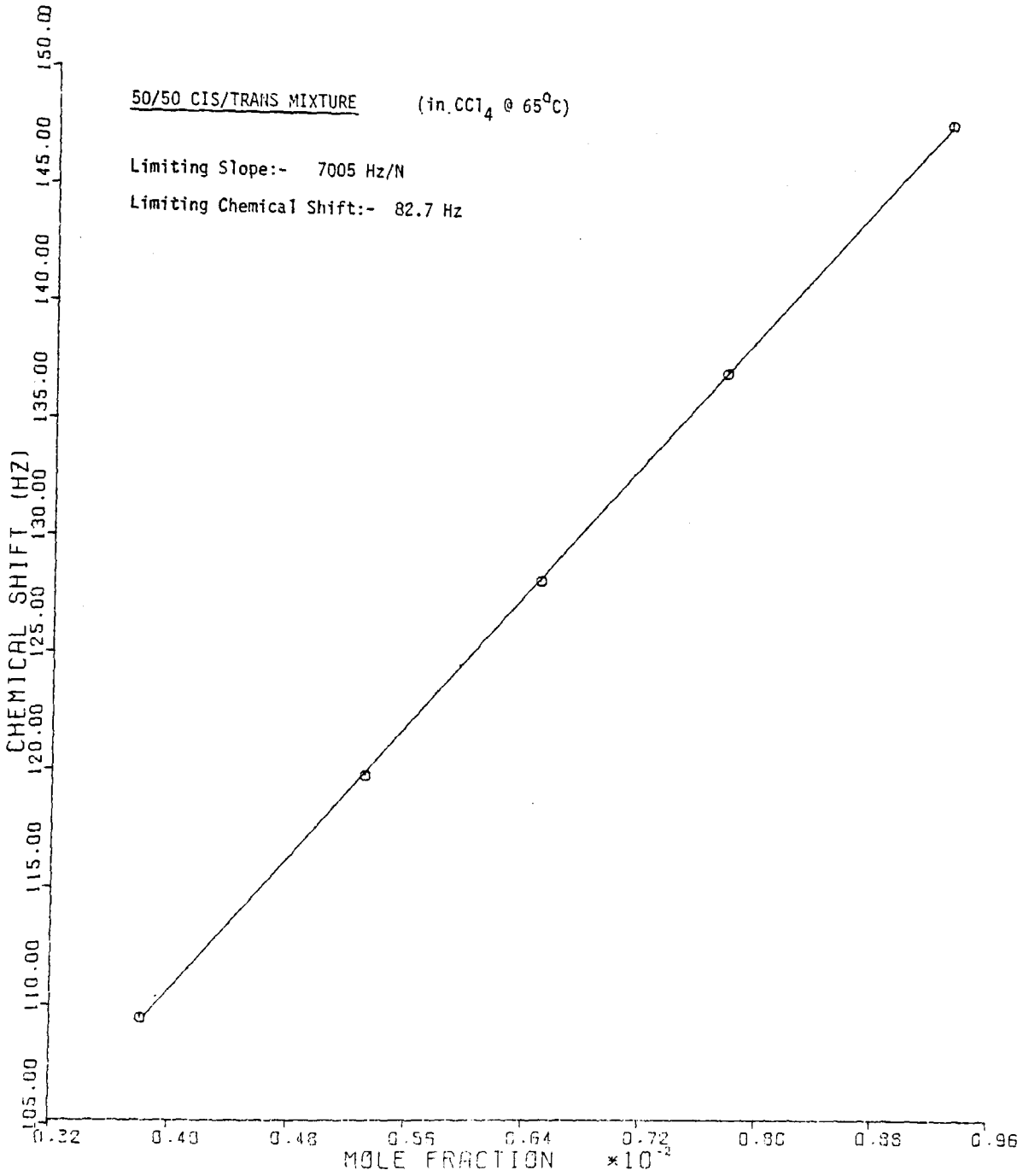
Wt. of diol (mg)	Wt. of $CDCl_3$ (g)	Mole Fraction (N)	Chemical Shift (Hz)
2.00	1.4900	0.001391	113.4
3.70	1.4953	0.002565	114.8
5.80	1.5072	0.003988	116.3
8.80	1.5048	0.006061	118.2
11.10	1.4999	0.007670	120.6
13.80	1.4881	0.009611	122.8
18.45	1.4975	0.012770	127.2
23.90	1.4965	0.016550	131.8



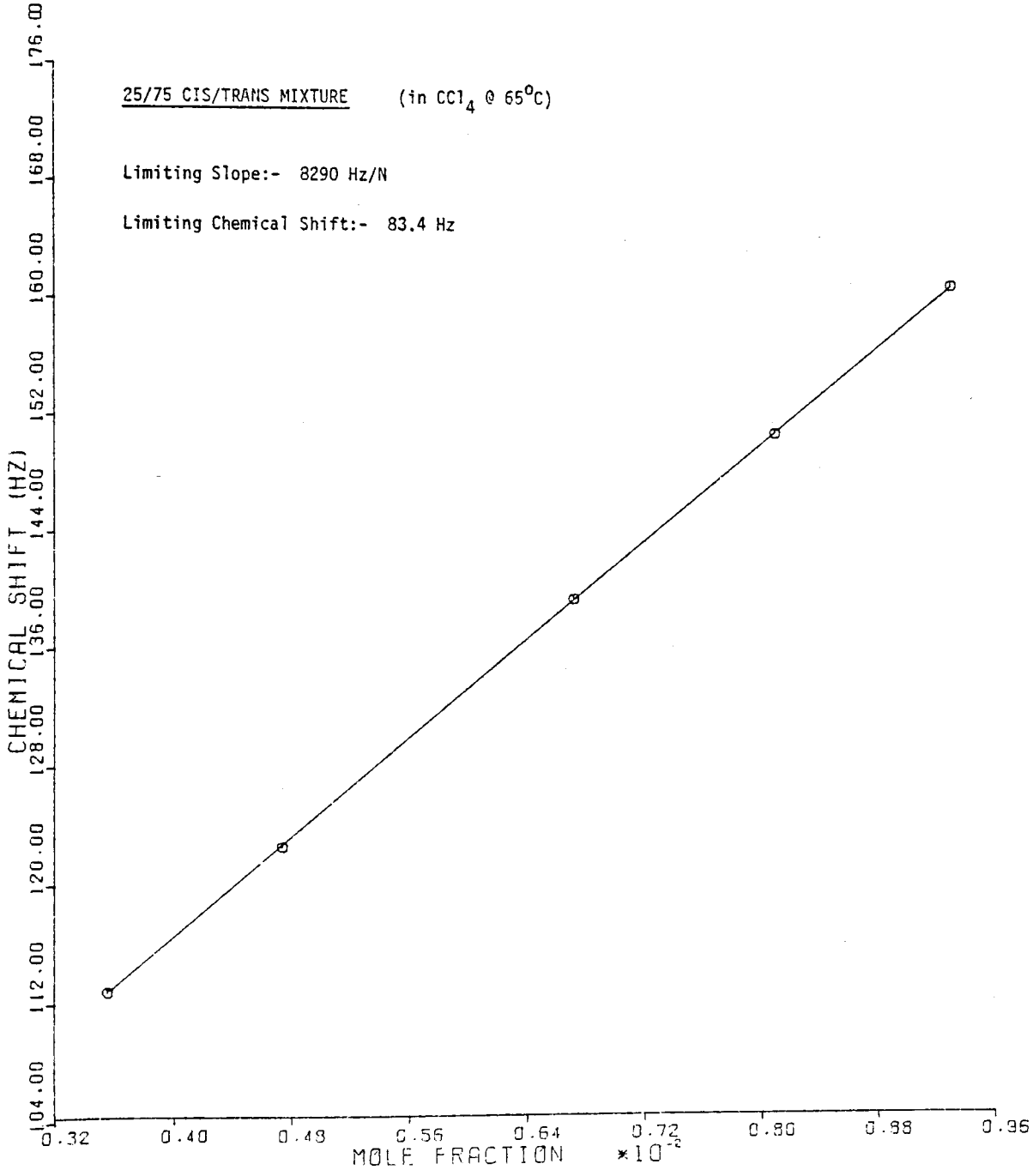
Wt. of diol (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
5.00	1.7642	0.003753	98.3
6.40	1.7218	0.004922	103.7
8.00	1.5964	0.006636	111.4
10.15	1.6986	0.007913	116.5
11.85	1.5354	0.010220	127.1



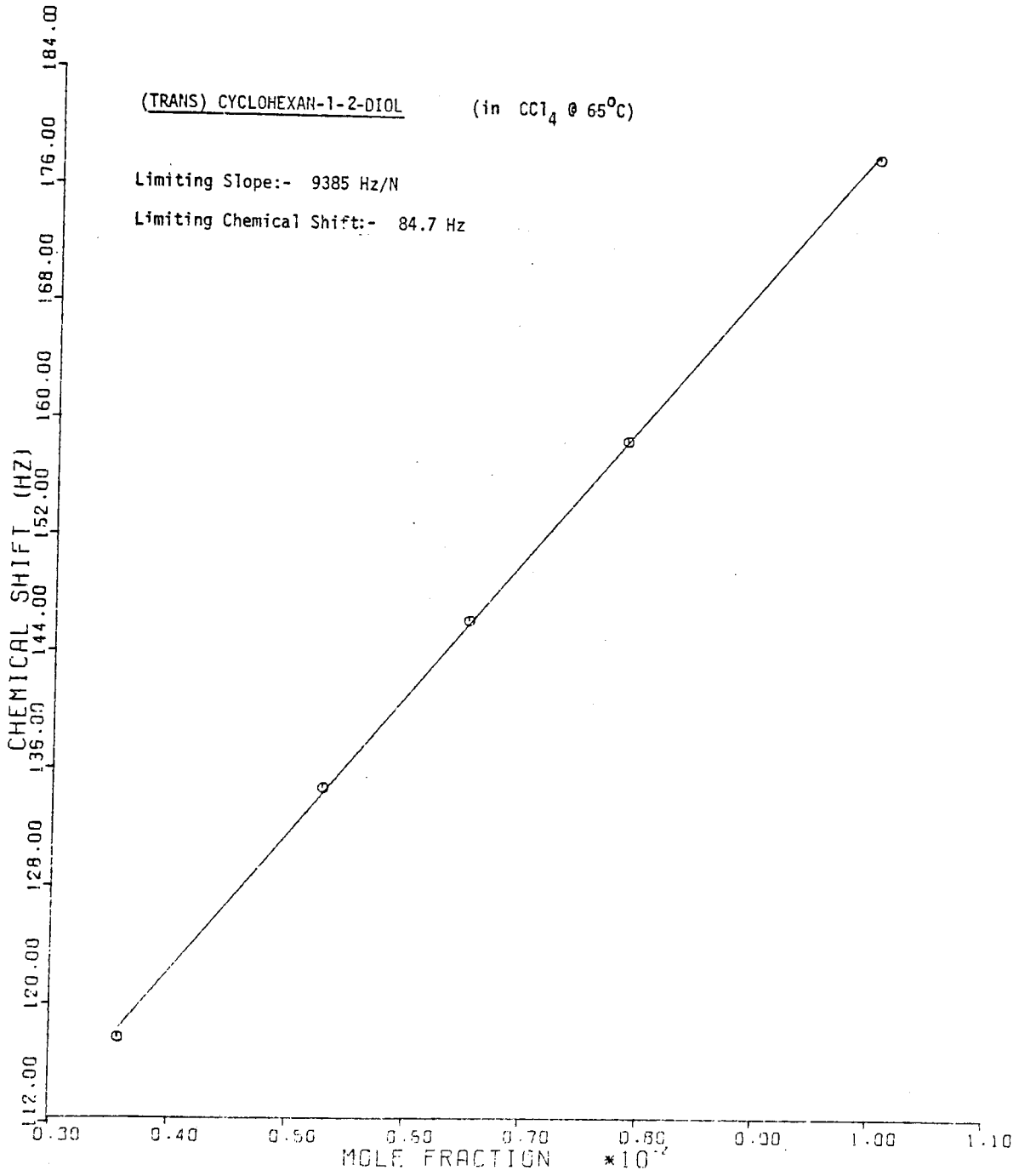
Wts. of diols (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
2.00t/2.00c	1.3895	0.003812	109.5
3.00t/3.00c	1.4935	0.005320	119.8
4.00t/4.00c	1.6255	0.006513	128.2
5.00t/5.00c	1.7016	0.007782	137.2
6.00t/6.00c	1.7055	0.009317	148.0



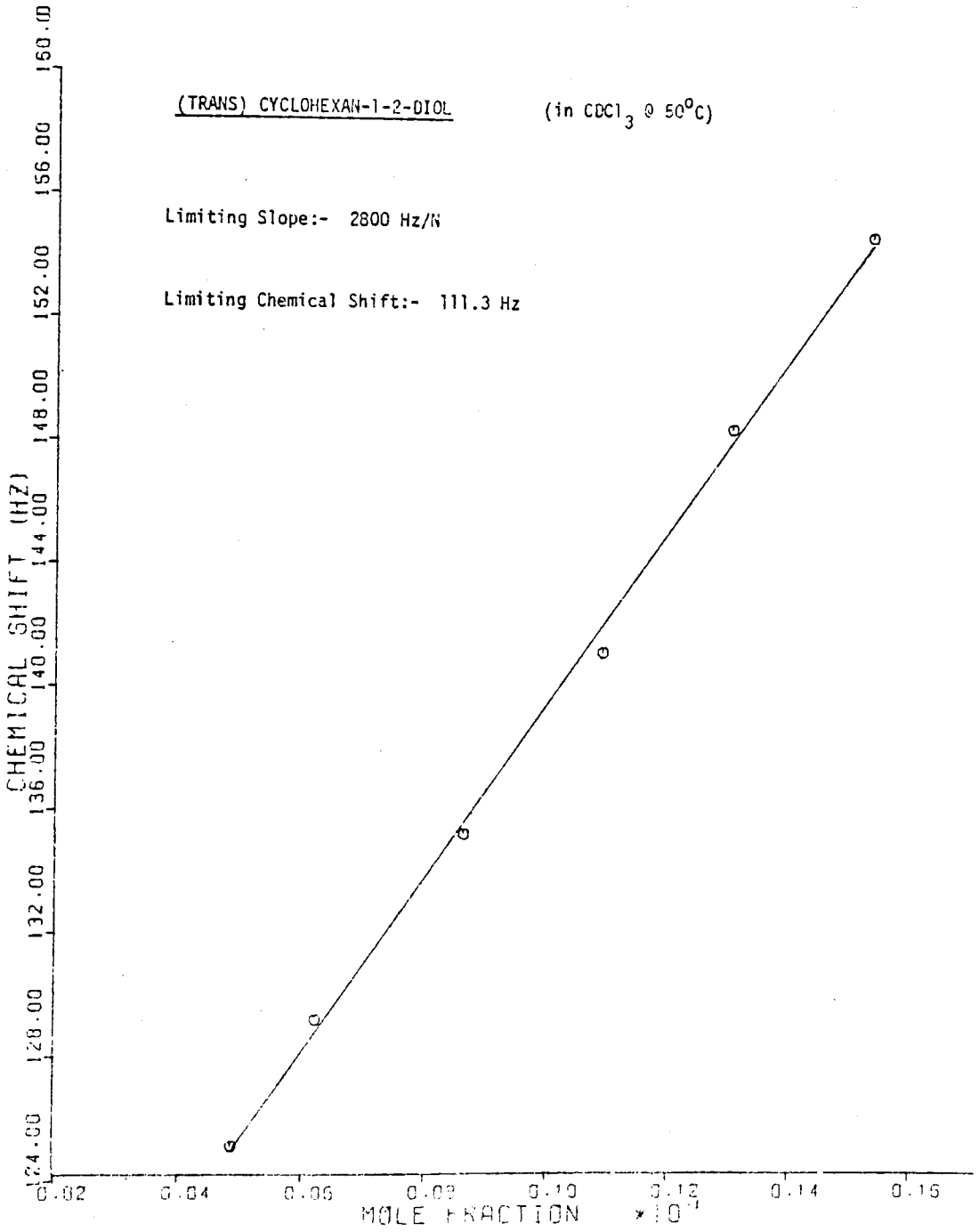
Wts. of diols (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
3.00t/1.00c	1.4900	0.003555	112.9
4.50t/1.50c	1.6773	0.004737	122.6
6.00t/2.00c	1.5725	0.006737	139.3
7.50t/2.50c	1.6314	0.008117	150.6
9.00t/3.00c	1.7050	0.009320	160.7



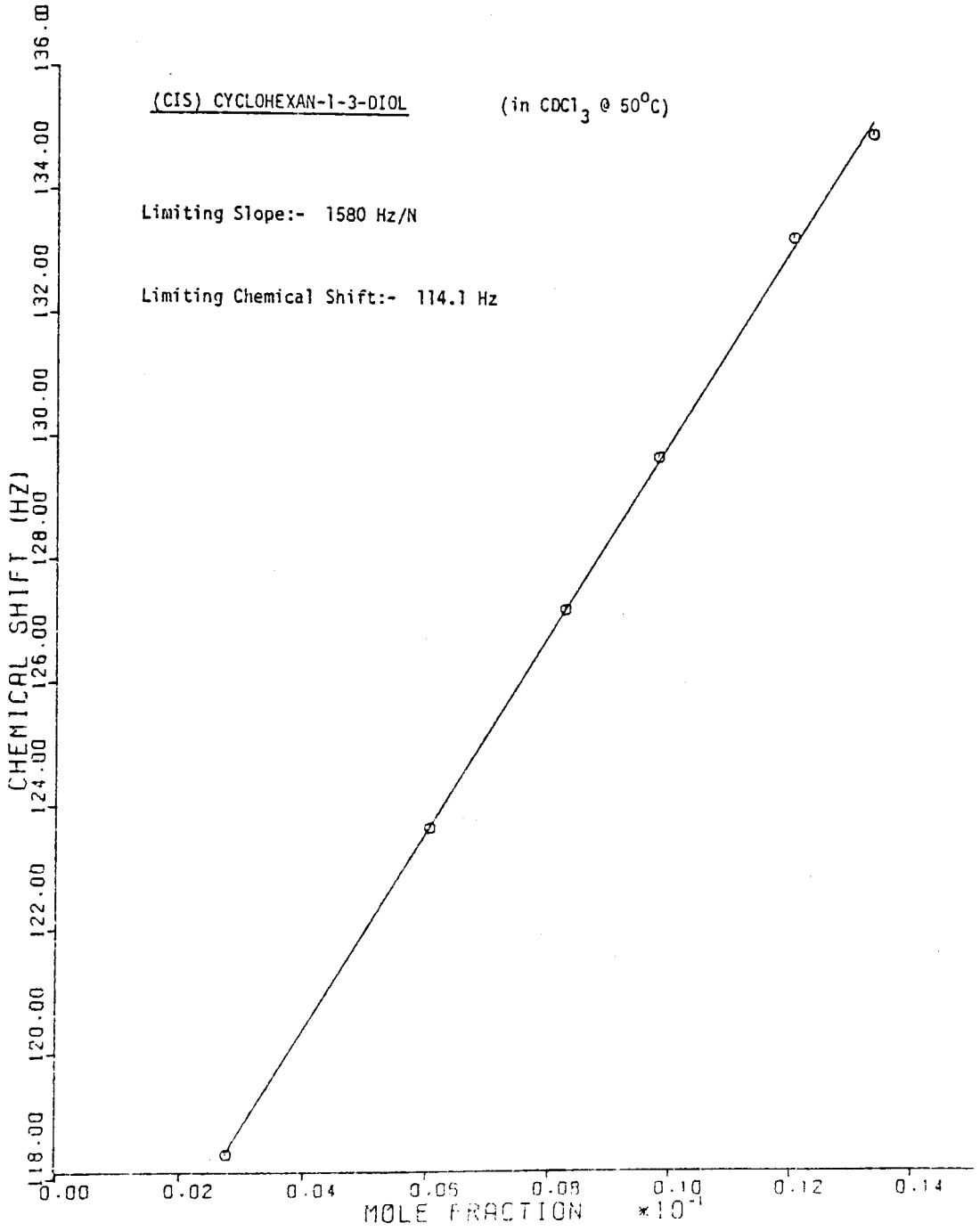
Wt. of diol (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
4.35	1.6072	0.003584	117.8
6.55	1.6396	0.005290	134.8
8.85	1.7950	0.006529	146.3
10.40	1.7470	0.007883	158.8
11.65	1.5380	0.010030	178.5



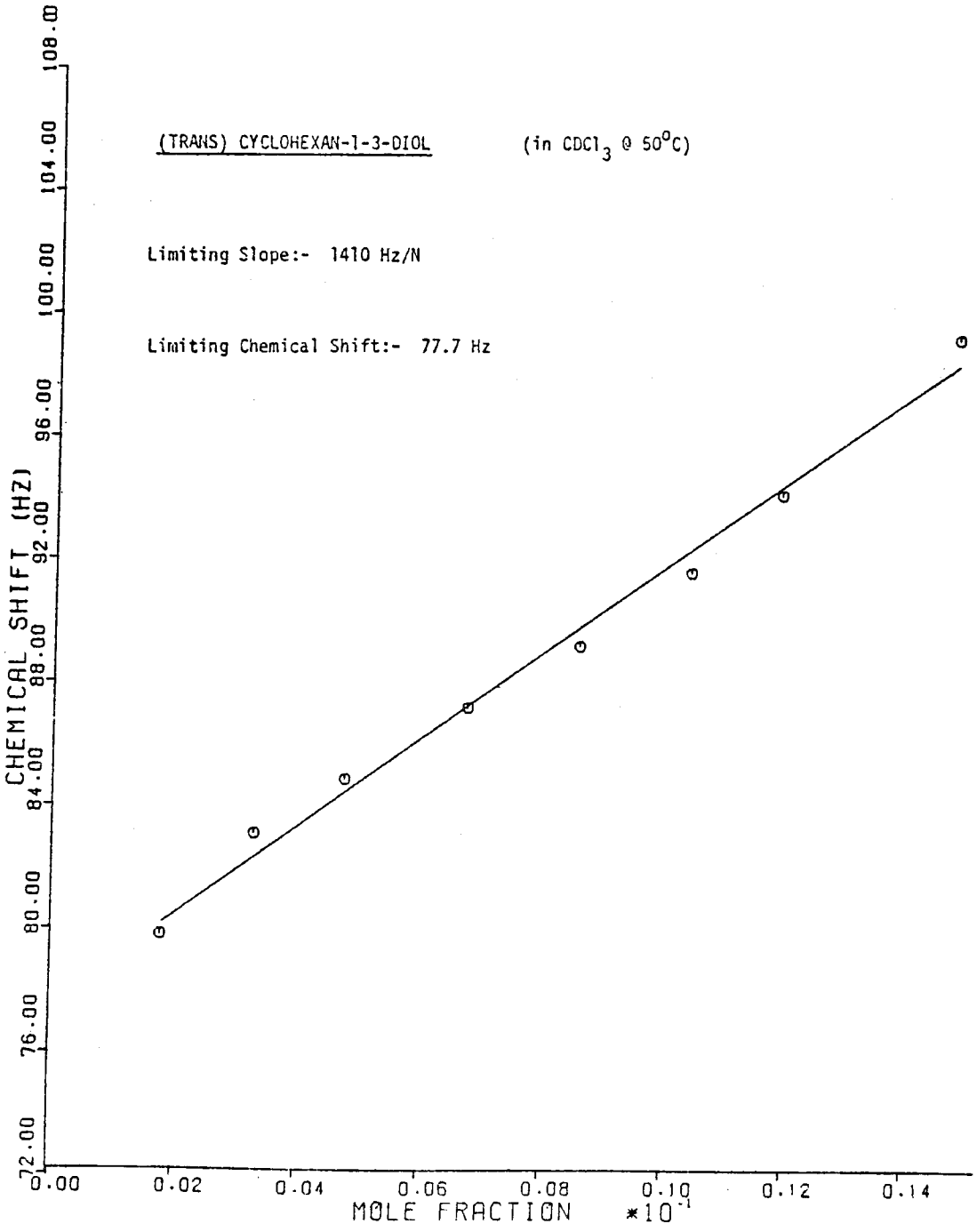
Wt. of diol (mg)	Wt. of $CDCl_3$ (g)	Mole Fraction (N)	Chemical Shift (Hz)
7.00	1.4843	0.004888	125.2
9.00	1.4964	0.006234	129.2
12.25	1.4654	0.008664	135.2
15.90	1.5048	0.010950	141.1
18.85	1.4920	0.013090	148.4
22.35	1.5030	0.015410	154.7



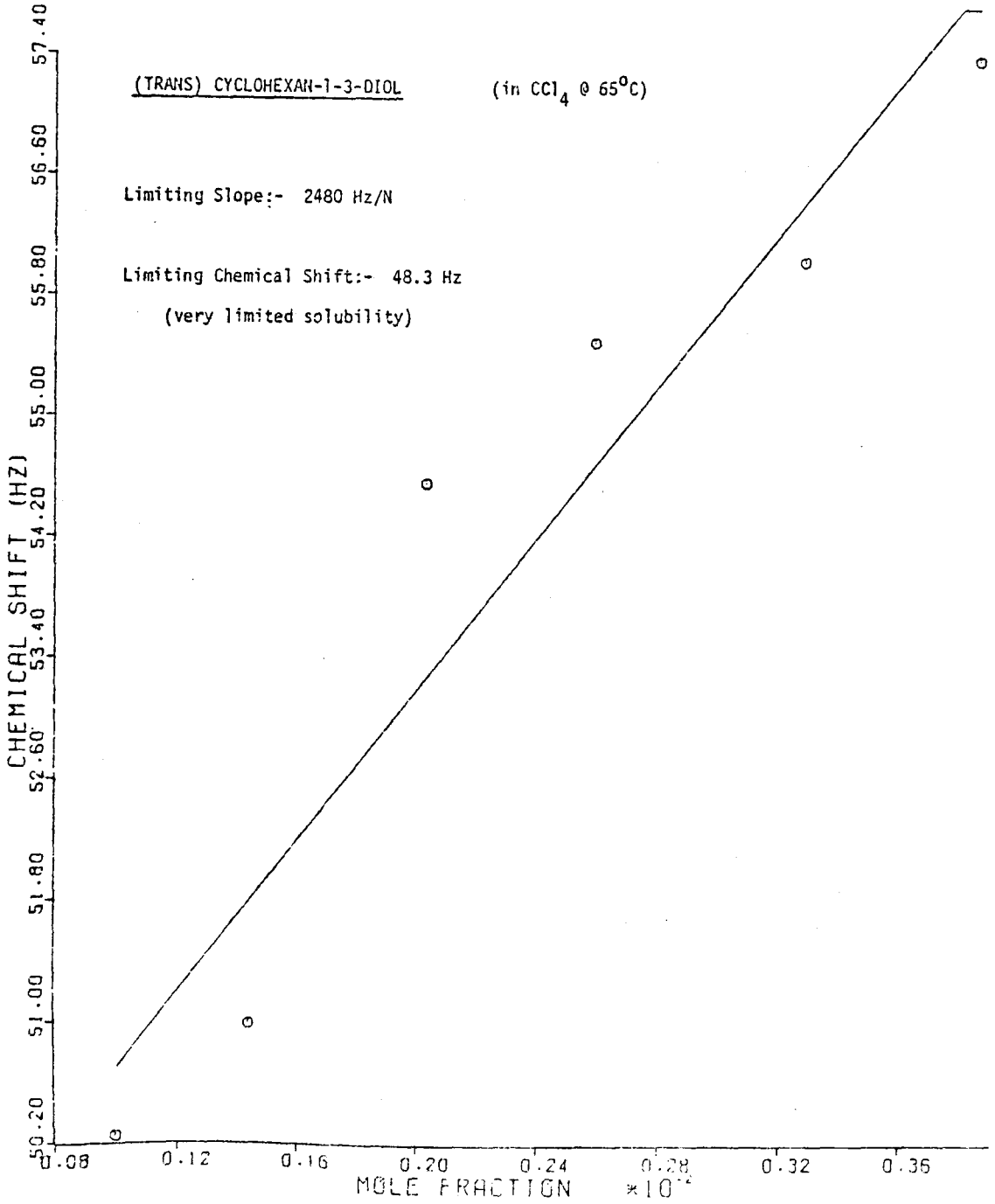
Wt. of diol (mg)	Wt. of $CDCl_3$ (g)	Mole Fraction (N)	Chemical Shift (Hz)
4.00	1.4903	0.002782	118.4
8.80	1.4985	0.006086	123.7
12.05	1.5023	0.008313	127.2
14.25	1.4983	0.009857	129.7
17.40	1.4413	0.012090	133.3
19.30	1.4930	0.013400	135.0



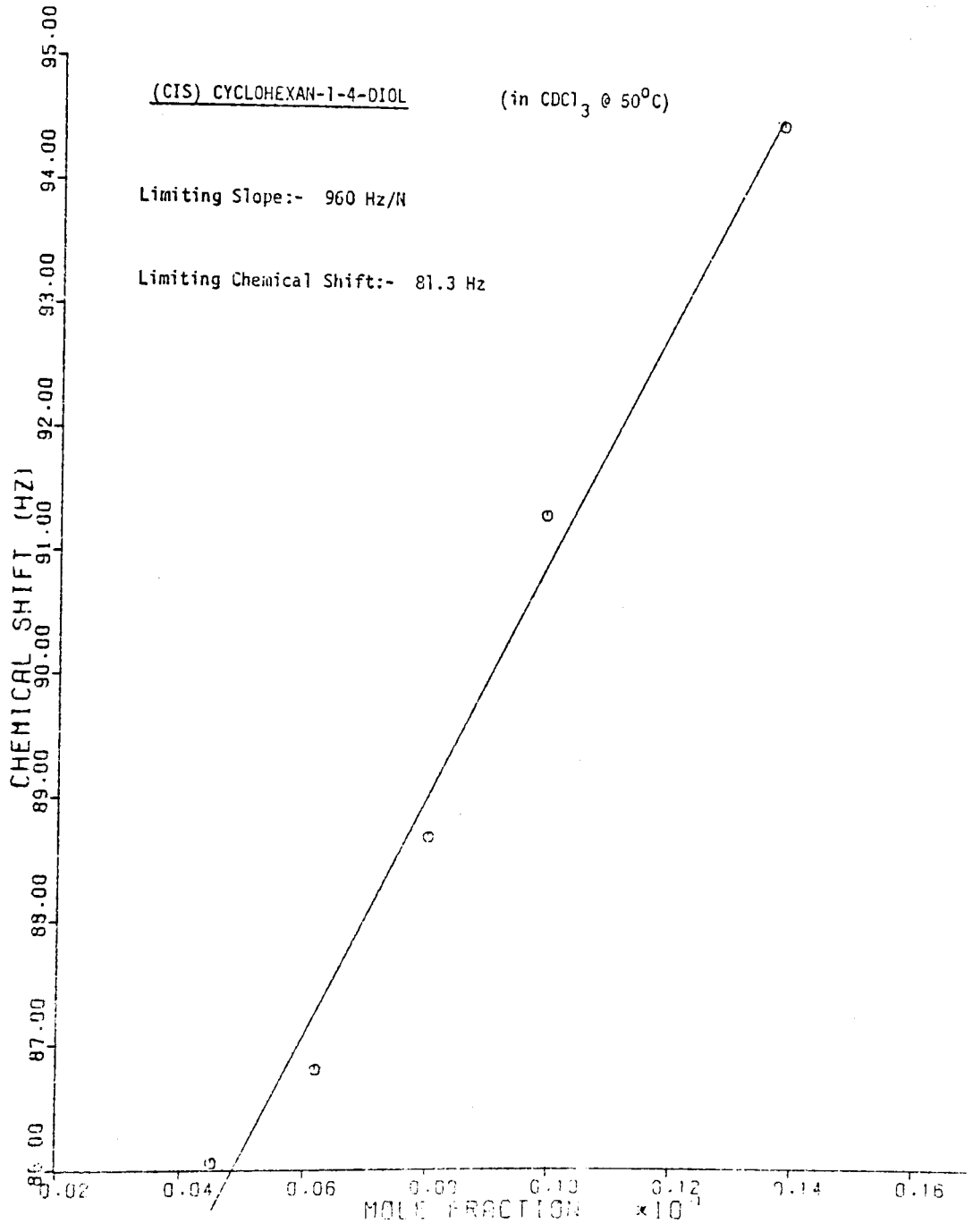
Wt.of diol (mg)	Wt. of $CDCl_3$ (g.)	Mole Fraction (N)	Chemical Shift (Hz)
2.55	1.4803	0.001785	79.9
4.75	1.4970	0.003289	83.1
6.80	1.4780	0.004768	84.9
9.75	1.4889	0.006787	87.2
12.40	1.4910	0.008619	89.3
15.10	1.4957	0.010460	91.7
16.95	1.4702	0.011950	94.3
21.25	1.4835	0.014850	99.5



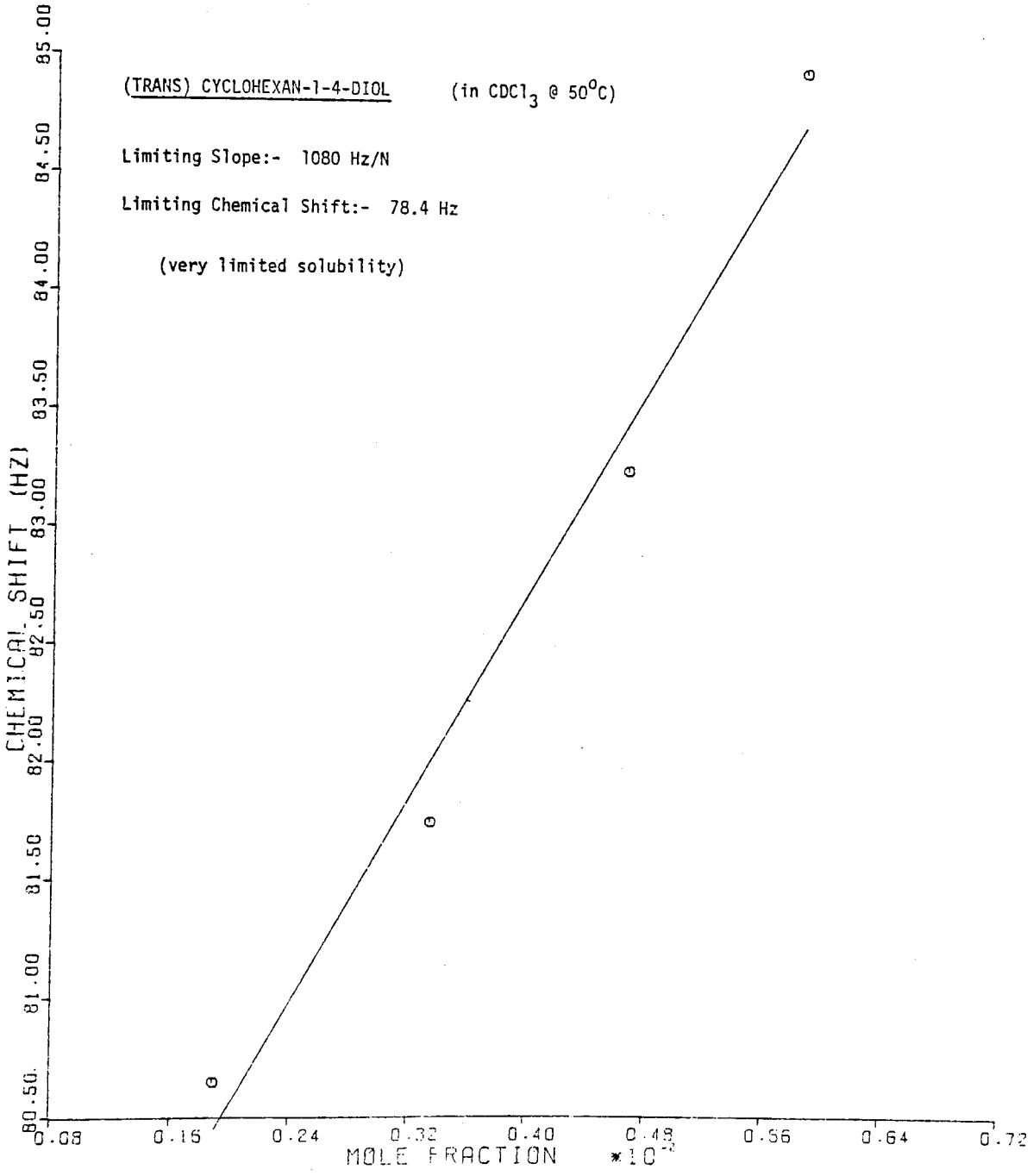
Wt. of diol (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
1.20	1.5867	0.001001	50.3
1.75	1.6012	0.001447	51.0
2.45	1.5939	0.002036	54.6
3.10	1.5727	0.002610	55.5
4.00	1.5956	0.003320	56.1
4.70	1.5933	0.003906	57.4



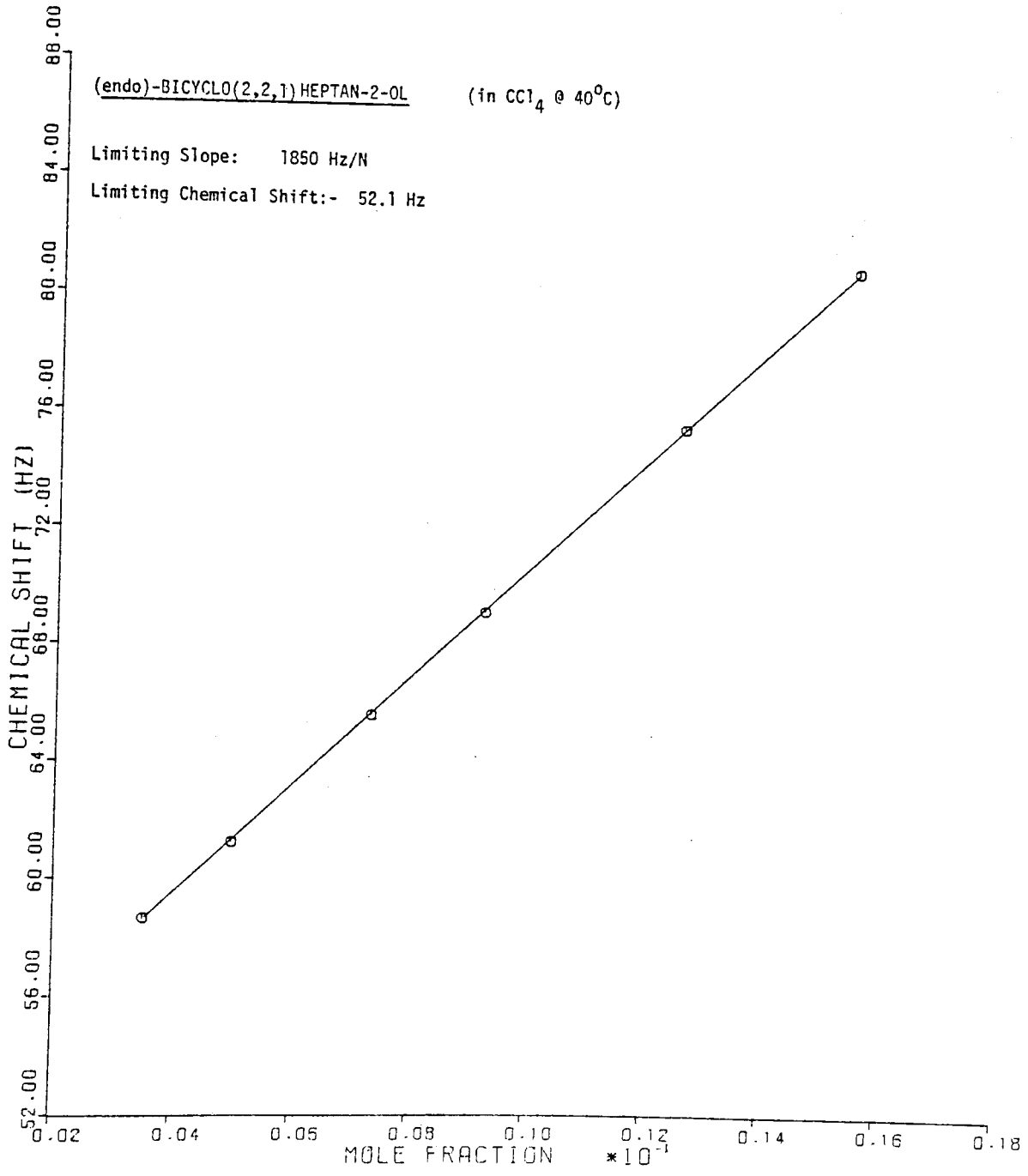
Wt. of diol (mg)	Wt. of $CDCl_3$ (g)	Mole Fraction (N)	Chemical Shift (Hz)
6.65	1.5234	0.004524	86.1
9.00	1.5046	0.006199	86.8
11.70	1.5120	0.008020	88.7
15.15	1.5816	0.009928	91.3
20.25	1.5246	0.013770	94.5



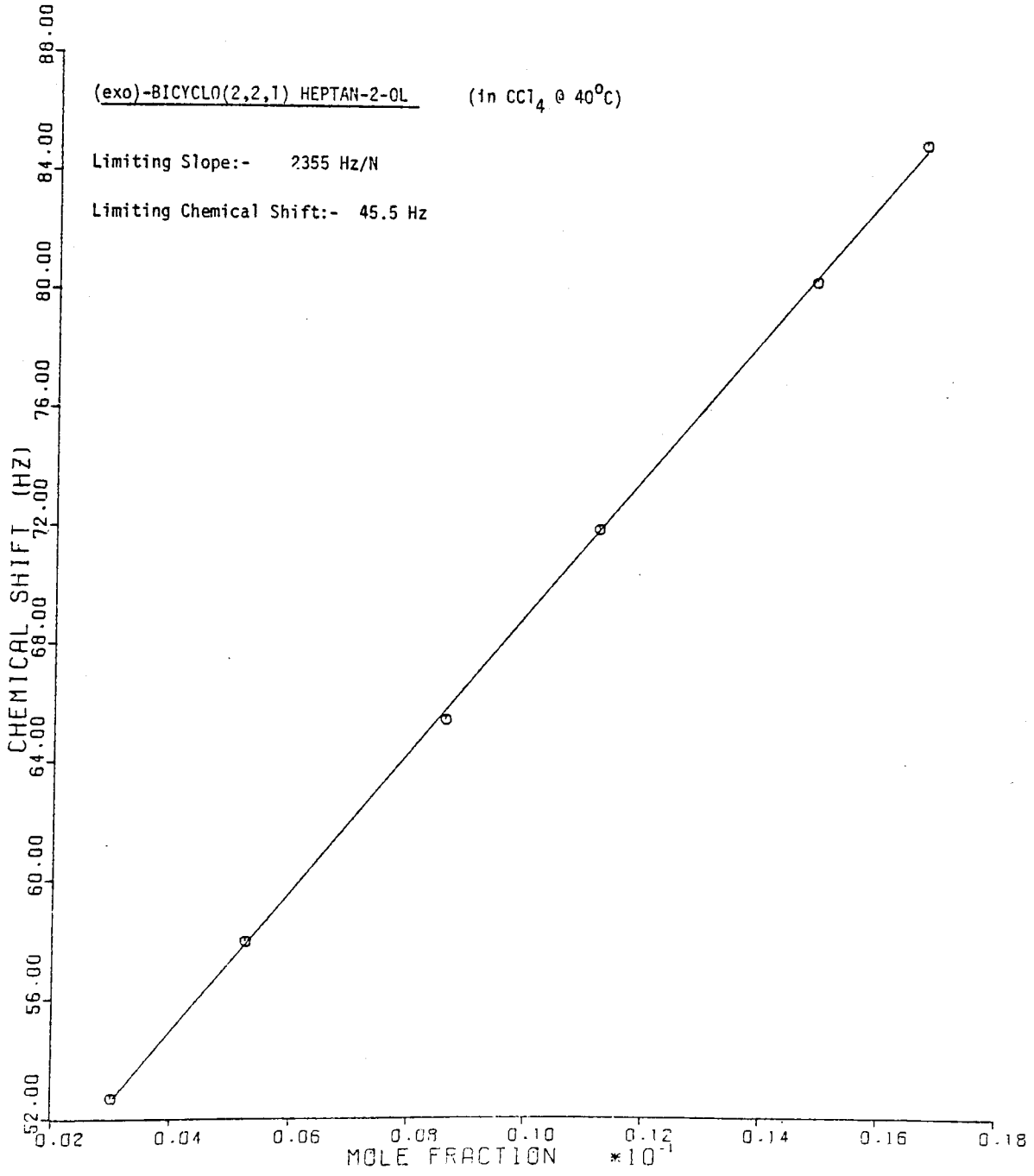
Wt.of diol (mg)	Wt. of $CDCl_3$ (g)	Mole Fraction (N)	Chemical Shift (Hz)
2.65	1.4487	0.001896	80.7
4.95	1.5315	0.003350	81.8
6.70	1.4833	0.004681	83.3
8.25	1.4595	0.005858	85.0



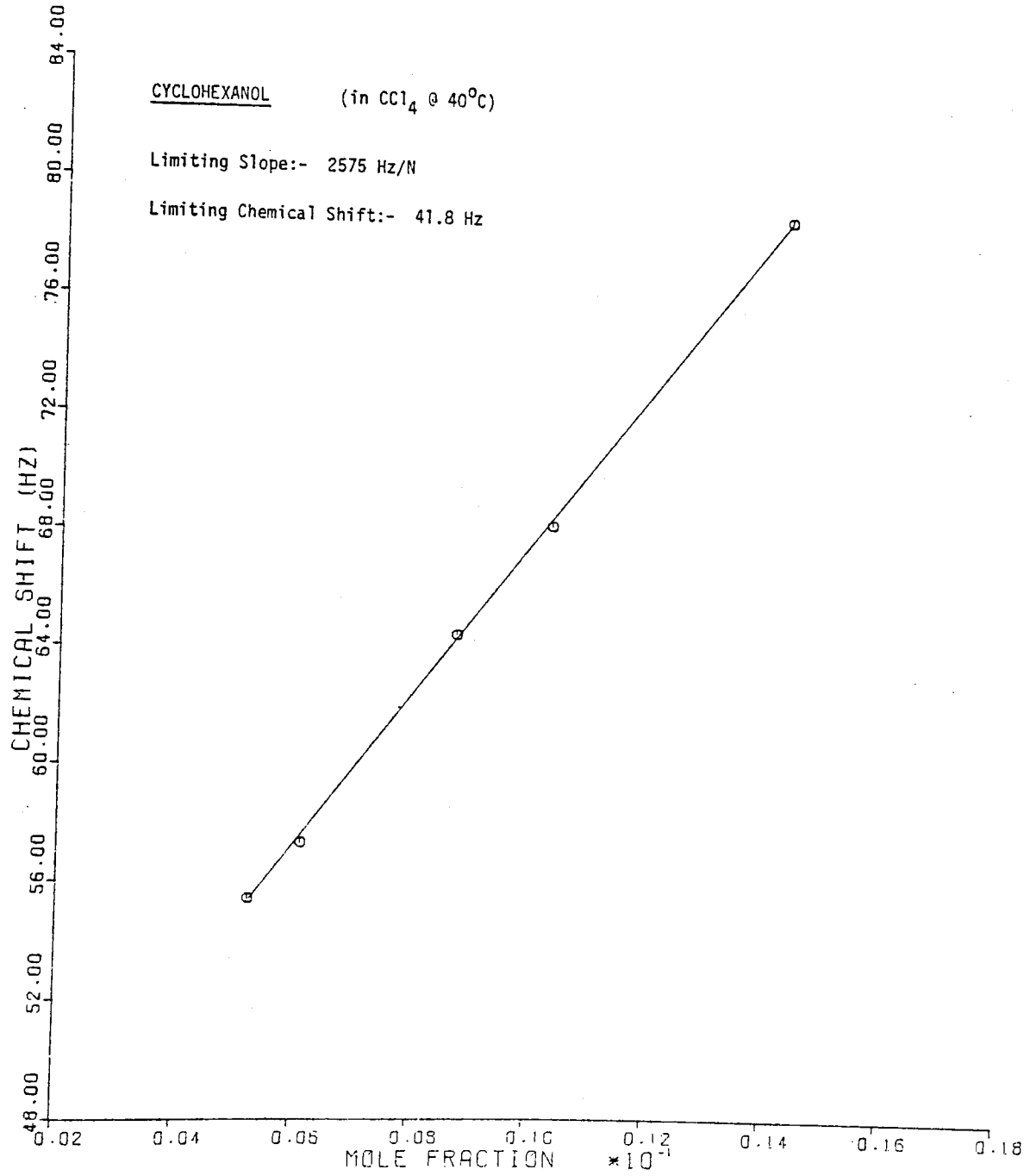
Wt. of alcohol (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
3.30	1.2874	0.003515	58.7
5.65	1.5577	0.004974	61.3
8.60	1.6118	0.007317	65.7
10.25	1.5207	0.009243	69.2
14.00	1.5201	0.012630	75.6
17.40	1.5325	0.015570	81.0



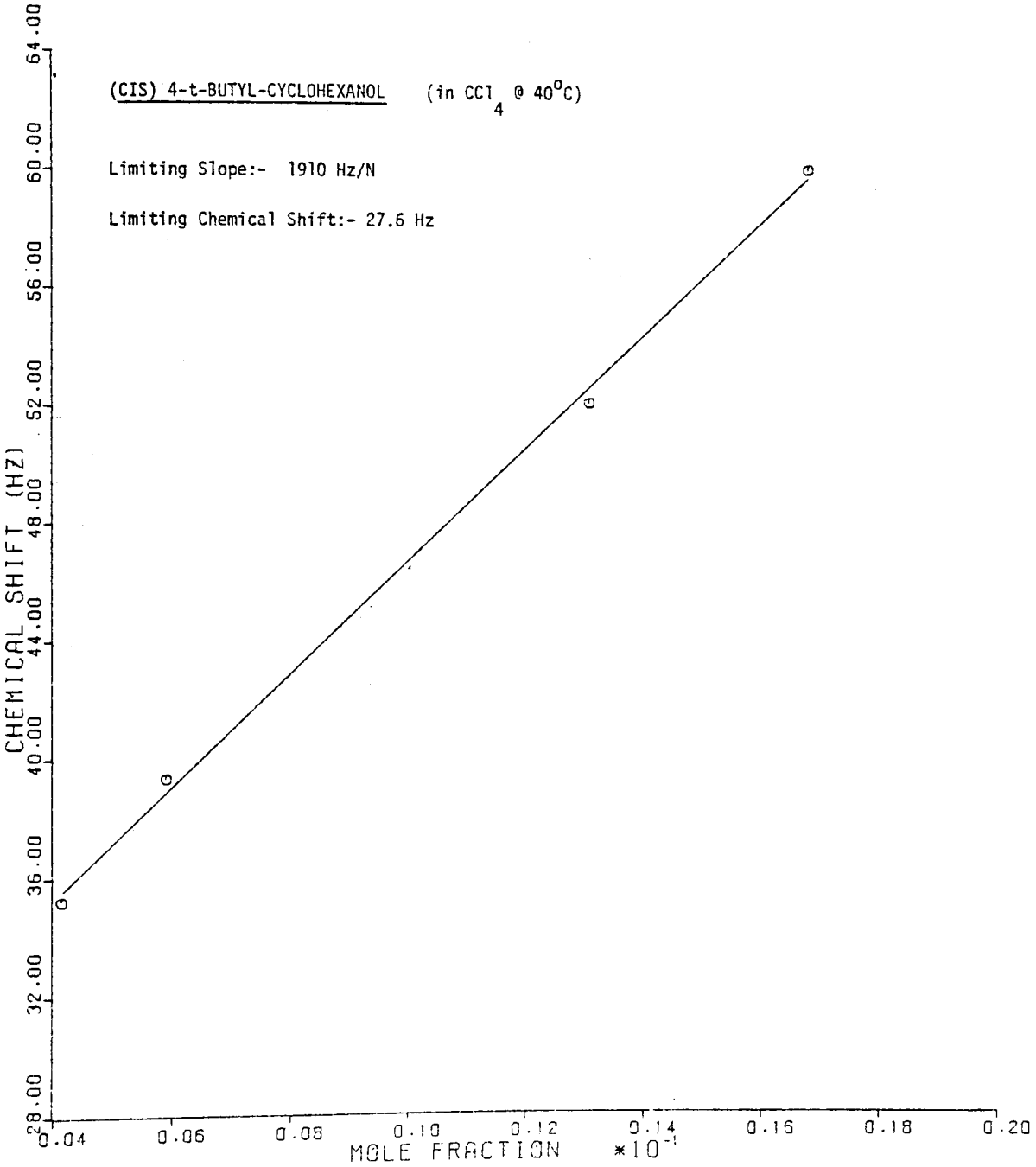
Wt. of alcohol (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
3.20	1.4564	0.003013	52.7
6.10	1.5927	0.005252	58.0
8.75	1.3912	0.008625	65.5
11.20	1.3689	0.011220	72.0
16.00	1.4725	0.014900	80.5
18.20	1.4900	0.016750	85.2



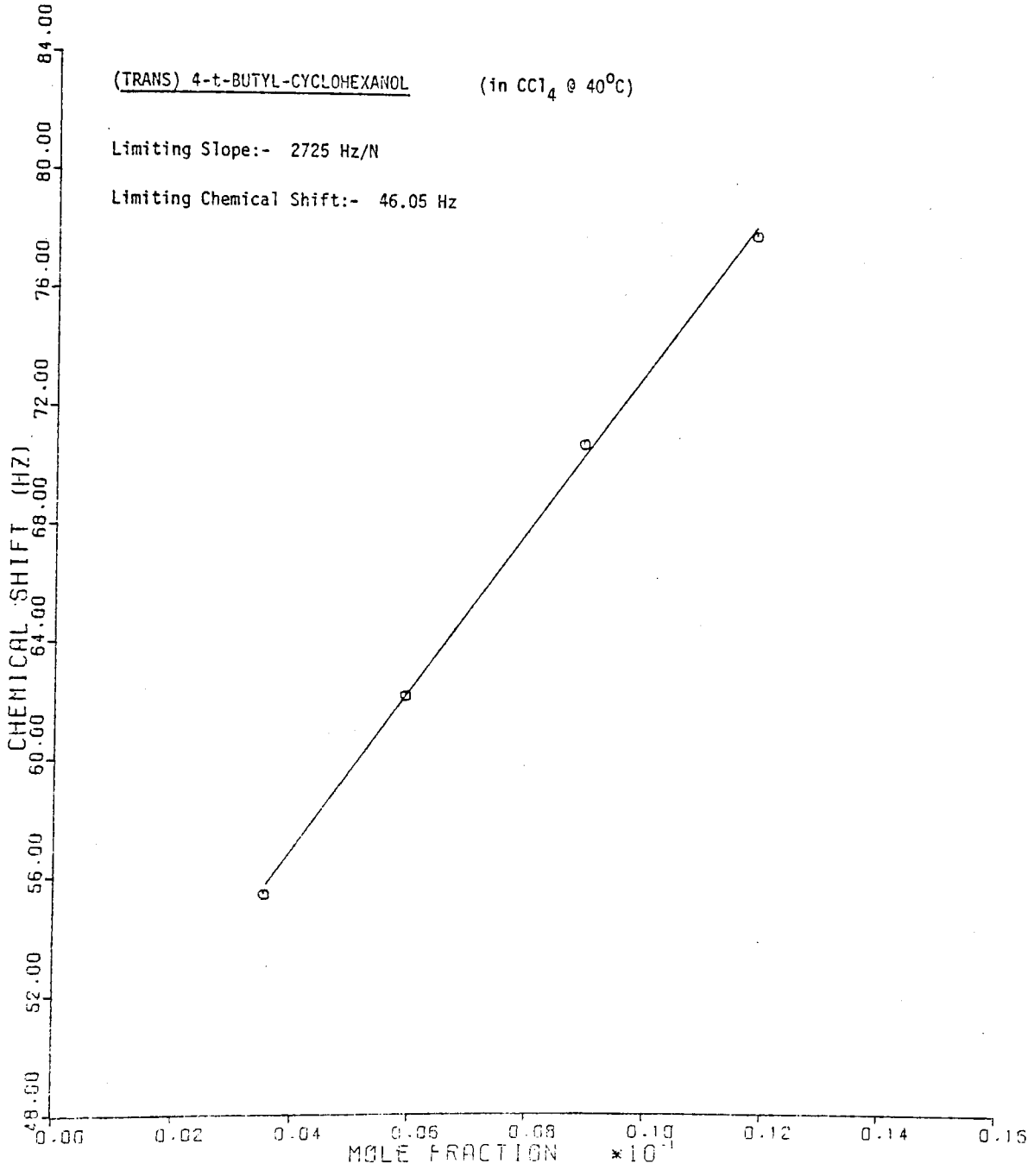
Wt. of alcohol (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
5.40	1.5805	0.005247	55.5
6.70	1.6802	0.006124	57.4
12.35	2.1736	0.008726	64.5
14.20	2.1131	0.010320	68.3
18.35	1.9679	0.014320	78.8



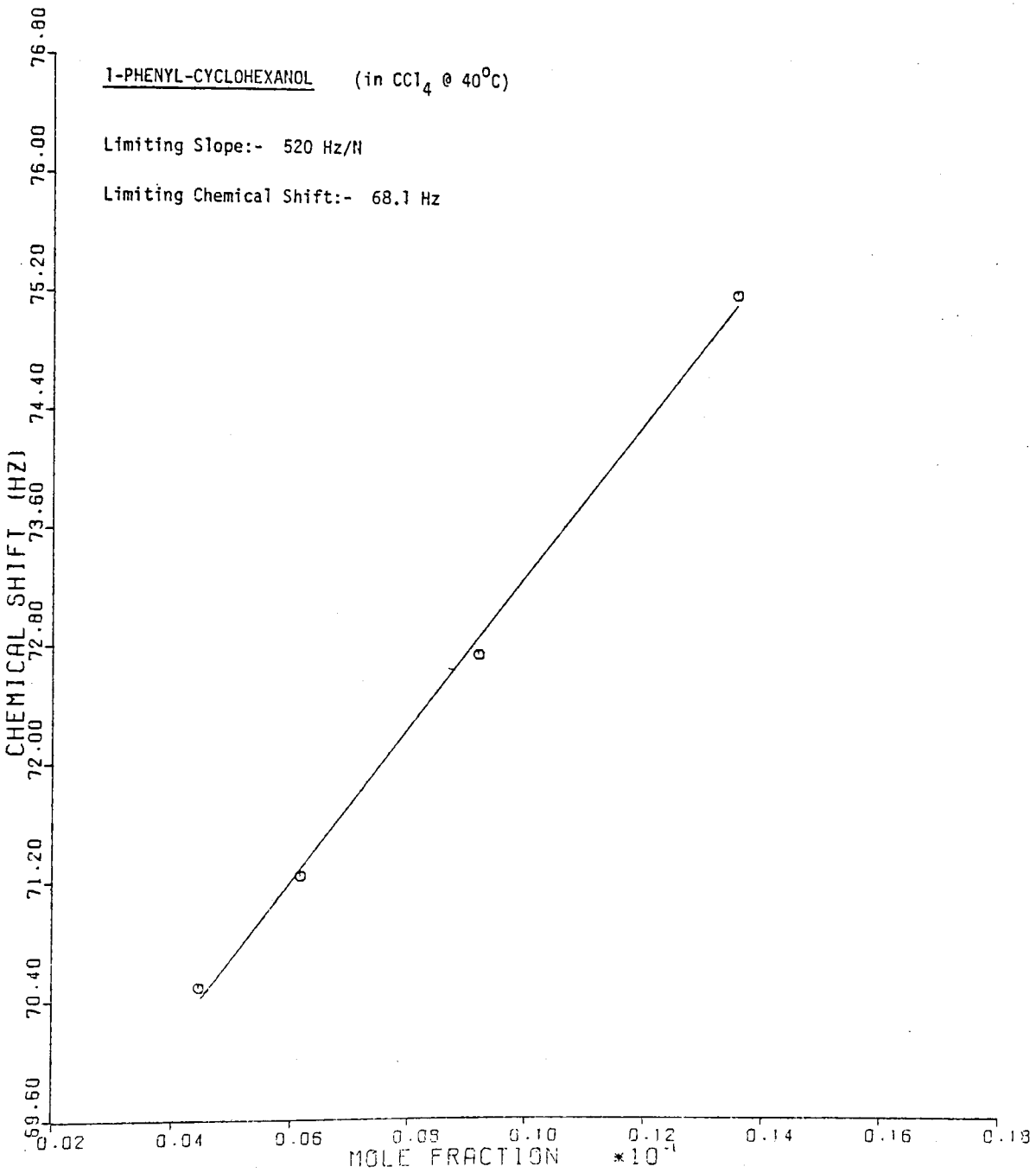
Wt. of alcohol (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
6.70	1.5865	0.004157	35.3
10.35	1.7229	0.005913	39.4
18.20	1.3671	0.013104	52.1
21.70	1.2679	0.016820	60.0



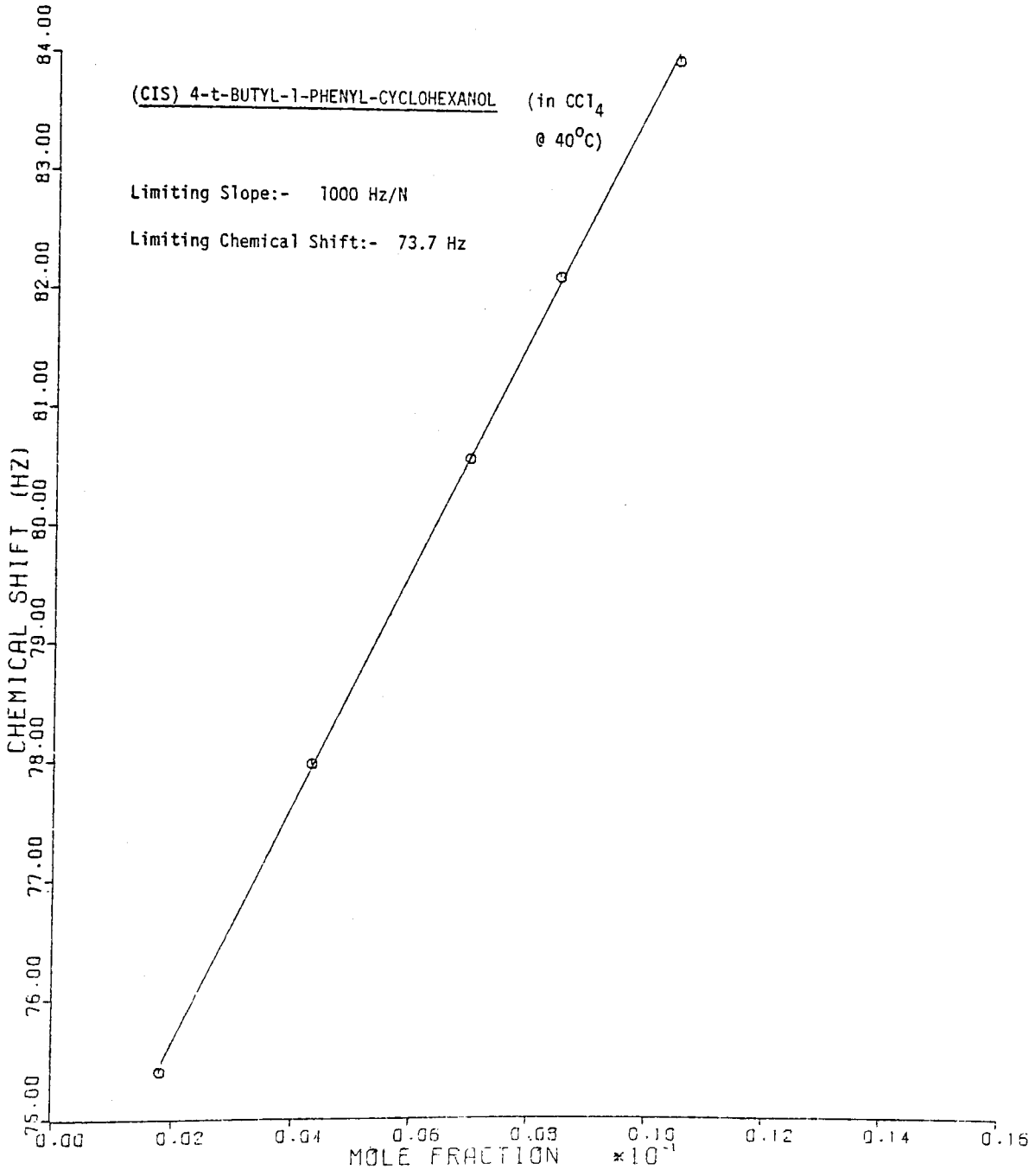
Wt. of alcohol (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
5.90	1.6424	0.003536	55.5
8.65	1.4399	0.005913	62.3
14.10	1.5538	0.008932	71.0
17.60	1.4644	0.011830	78.0



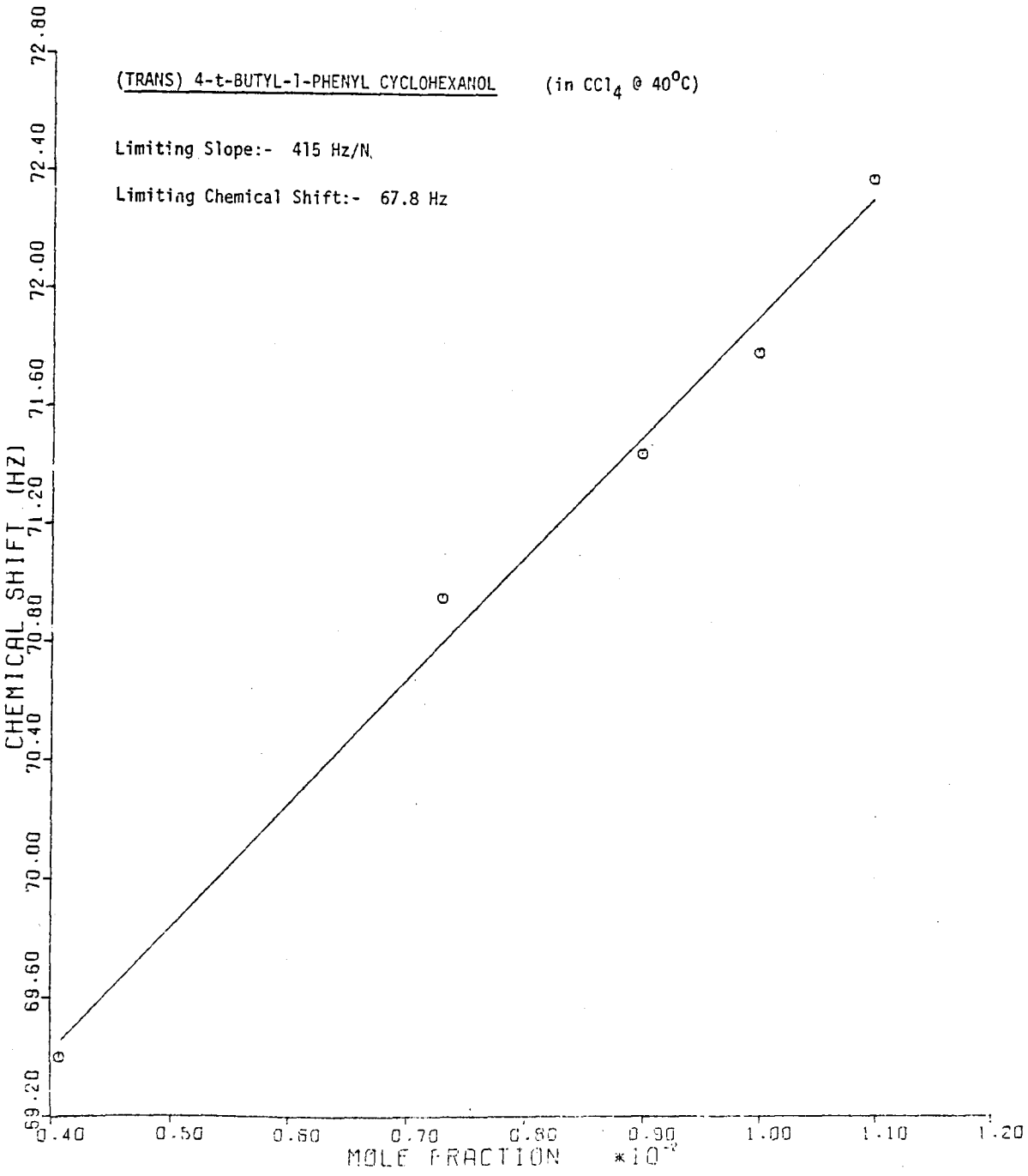
Wt. of alcohol (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
8.00	1.5661	0.004459	70.5
11.00	1.5555	0.006171	71.3
17.85	1.6929	0.009202	72.8
34.65	2.2276	0.013570	75.2



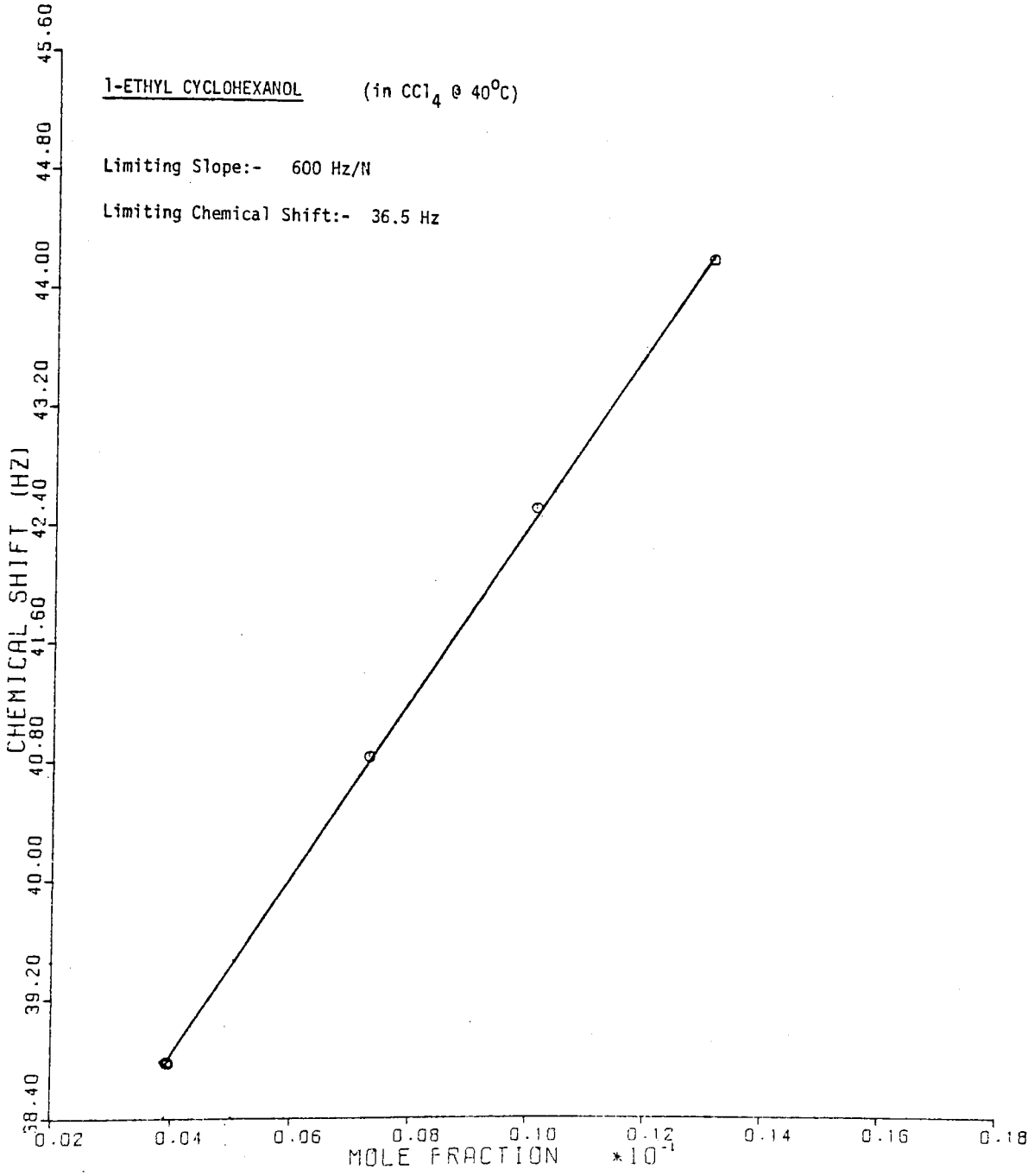
Wt. of alcohol (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
2.95	1.0807	0.001807	75.4
6.40	0.9830	0.004310	78.0
10.55	1.0073	0.006933	80.6
13.25	1.0396	0.008437	82.2
15.70	0.9983	0.010410	84.0



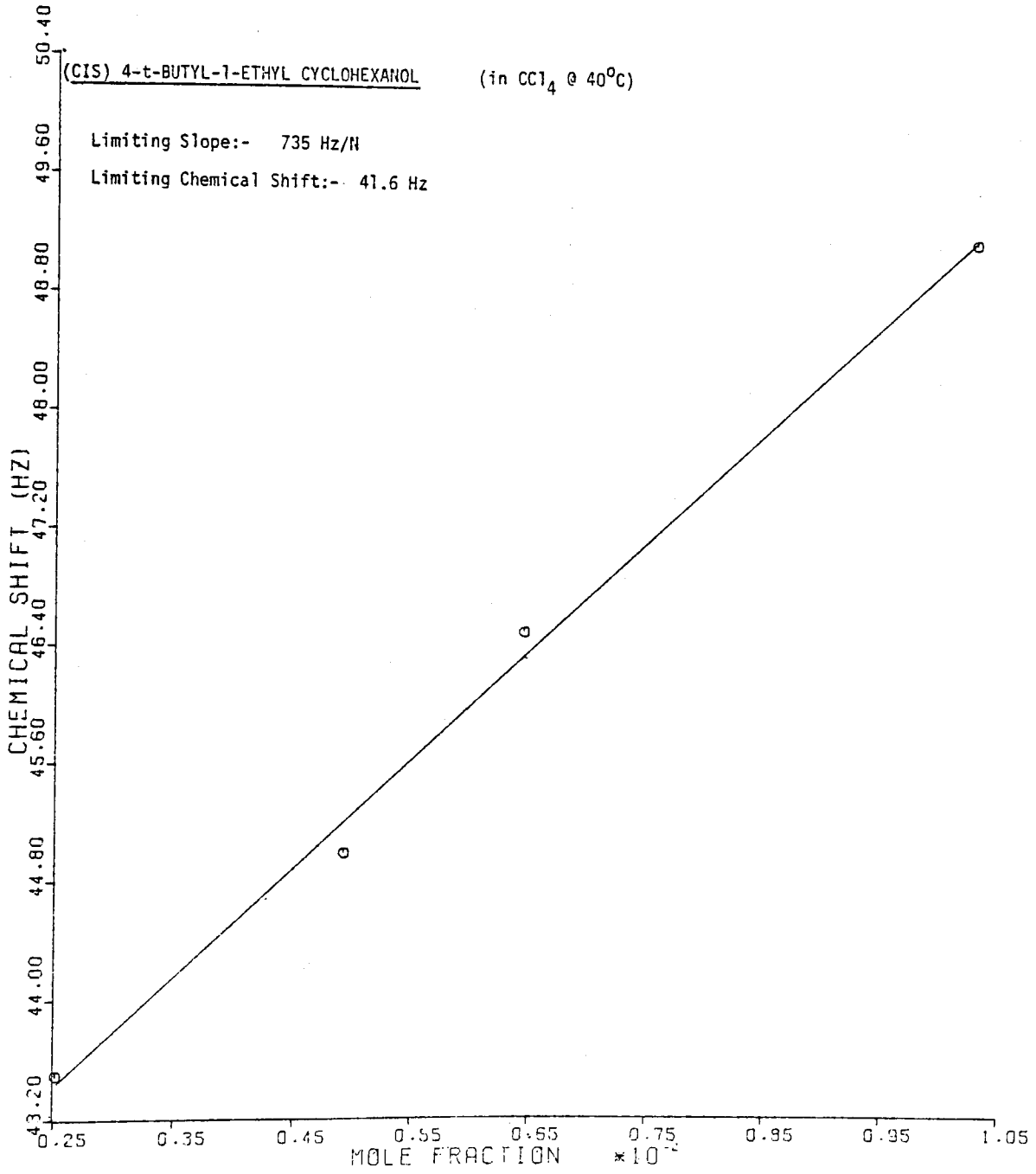
Wt. of alcohol (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
5.15	0.8366	0.004075	69.4
8.10	0.7333	0.007312	71.0
10.90	0.8001	0.009018	71.5
12.55	0.8291	0.010020	71.8
16.30	0.9800	0.011010	72.4



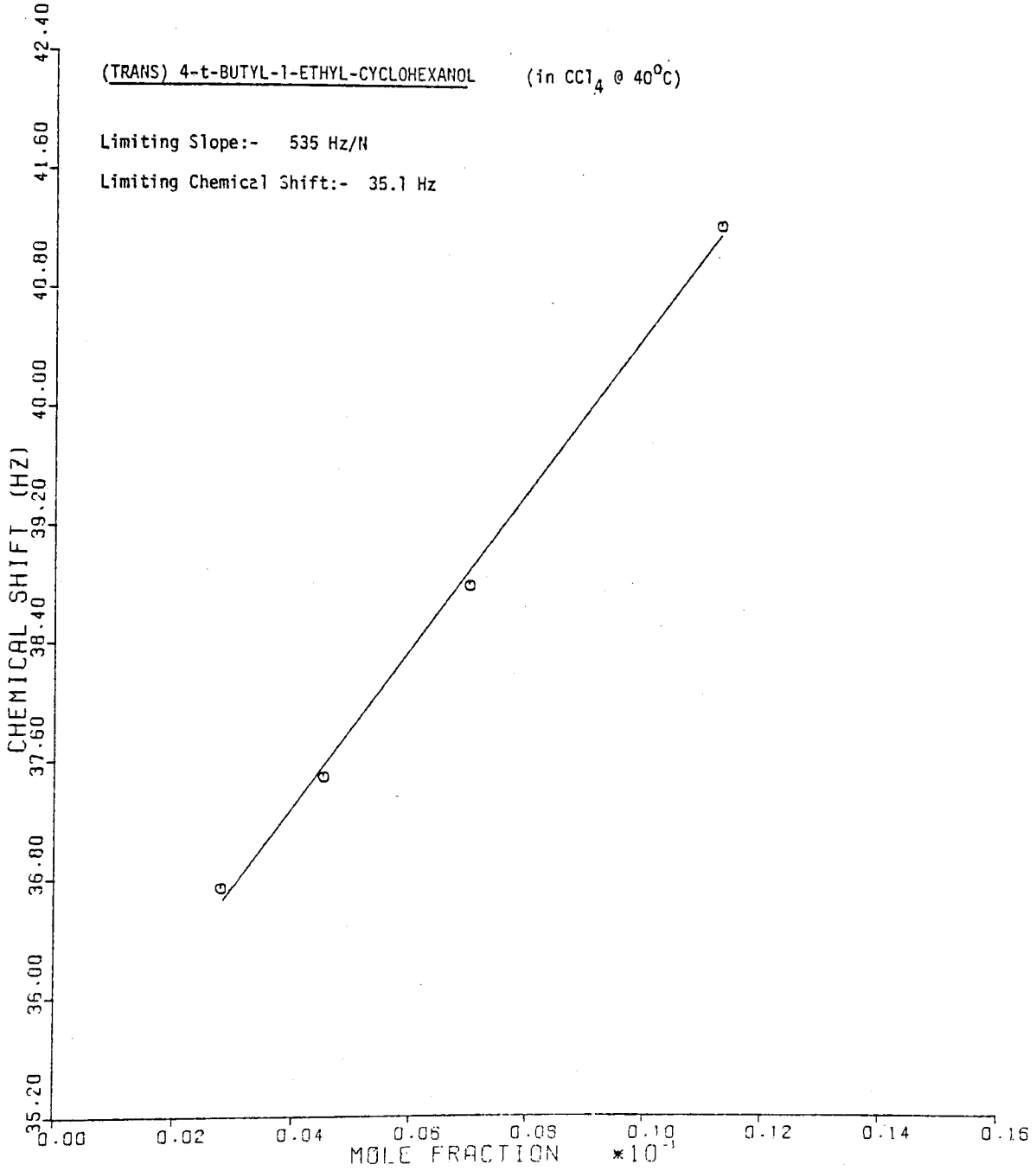
Wt. of alcohol (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
4.55	1.3985	0.003903	38.8
8.65	1.4192	0.007312	40.9
10.30	1.2210	0.010120	42.6
14.35	1.3141	0.013100	44.3

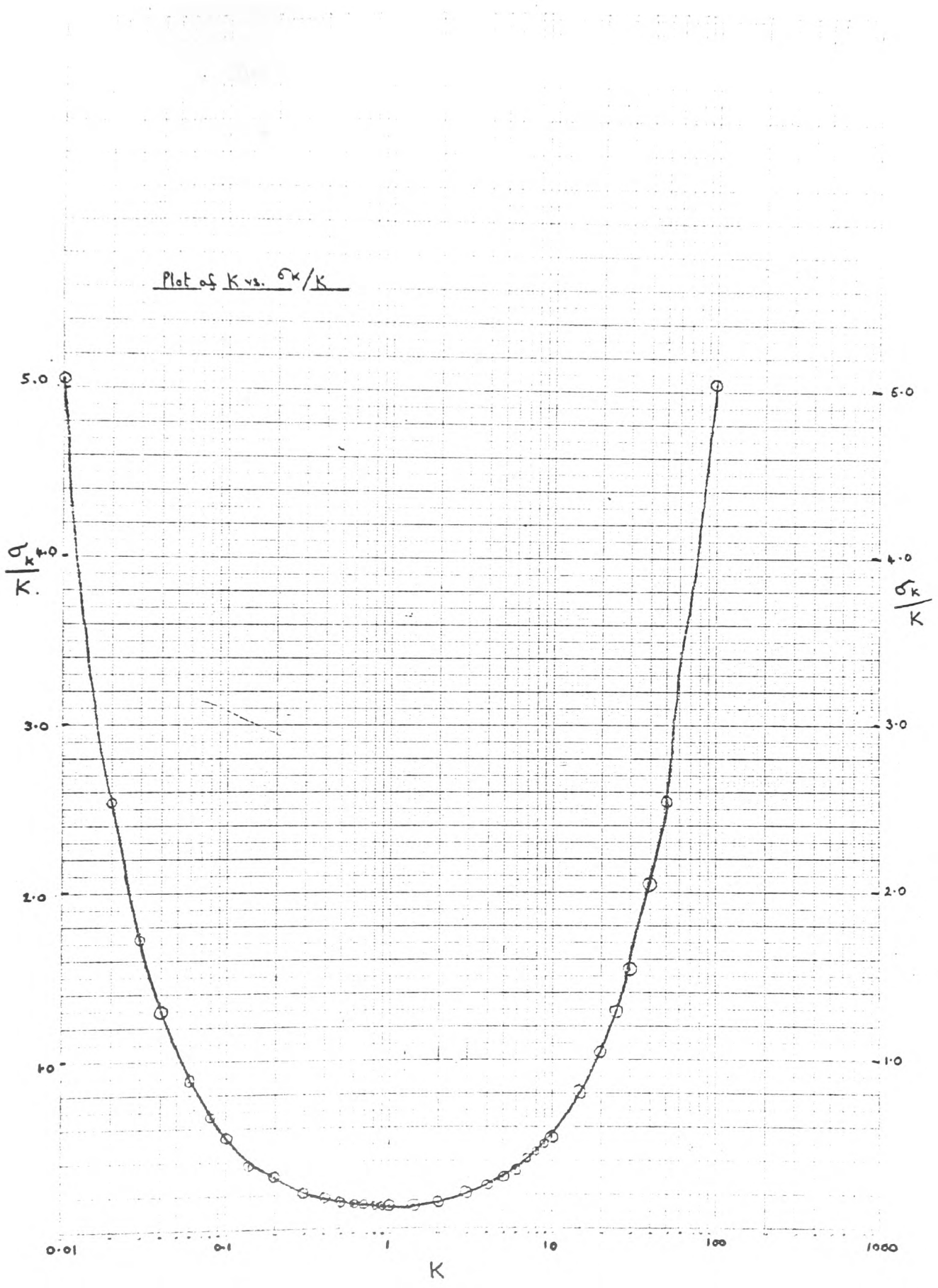


Wt. of alcohol (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
5.55	1.8372	0.002521	43.5
9.35	1.5828	0.004930	45.0
13.50	1.7442	0.006459	46.5
22.25	1.7992	0.010320	49.2



Wt. of alcohol (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
4.75	1.4122	0.002807	36.8
8.20	1.5096	0.004533	37.5
17.05	2.0268	0.007020	38.8
20.00	1.4777	0.011295	41.3




Plot of K vs. σK/K
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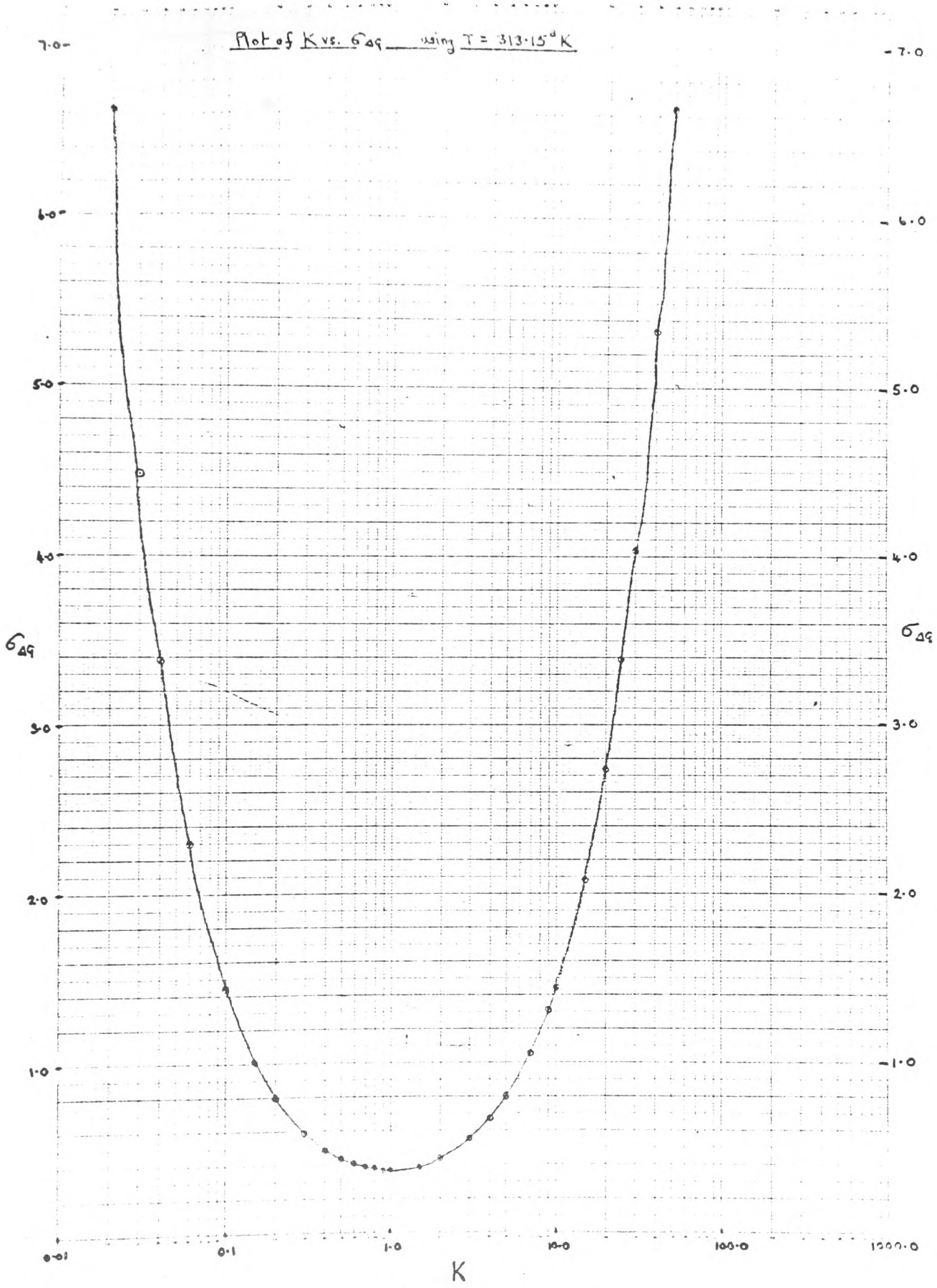
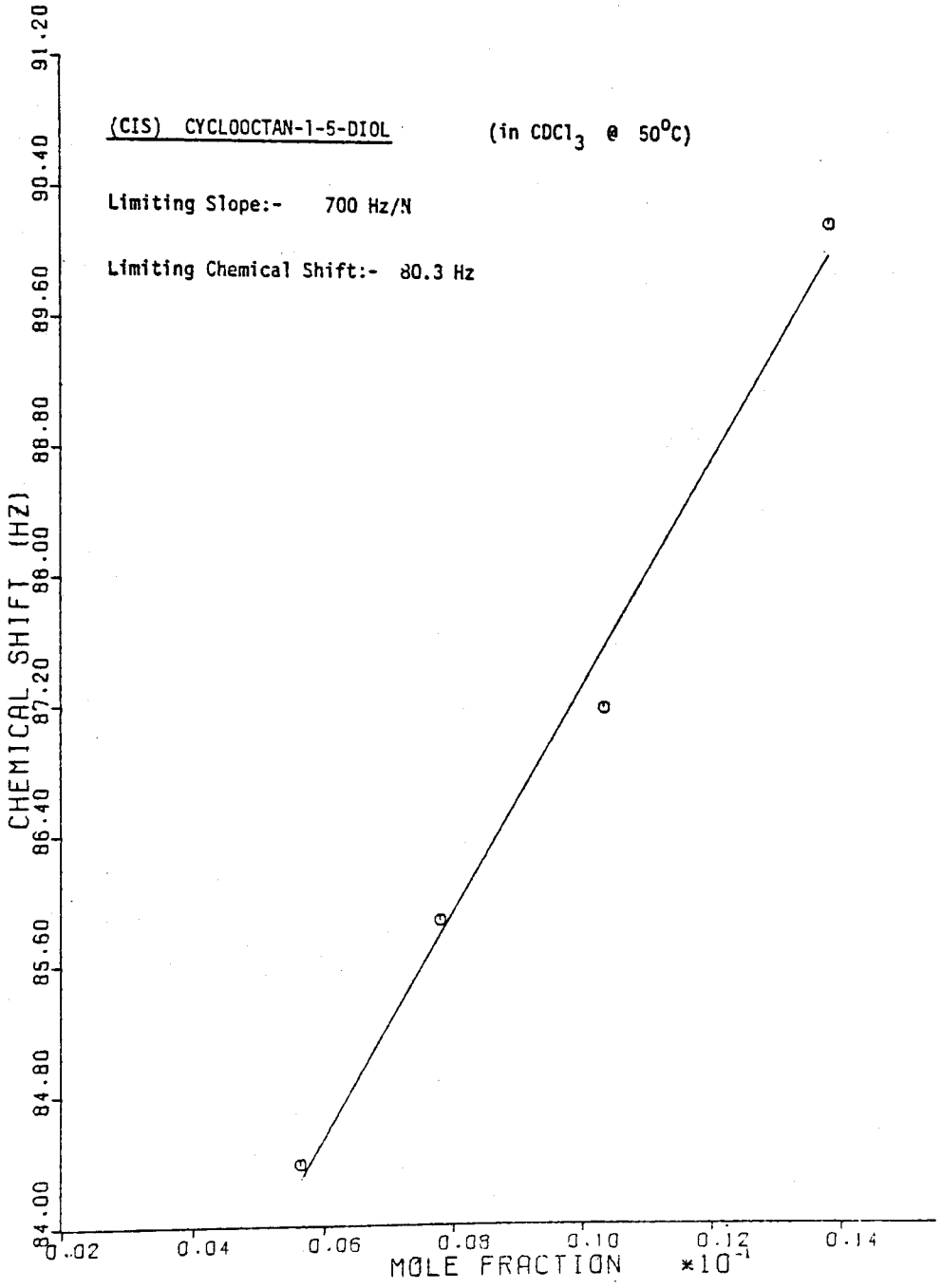
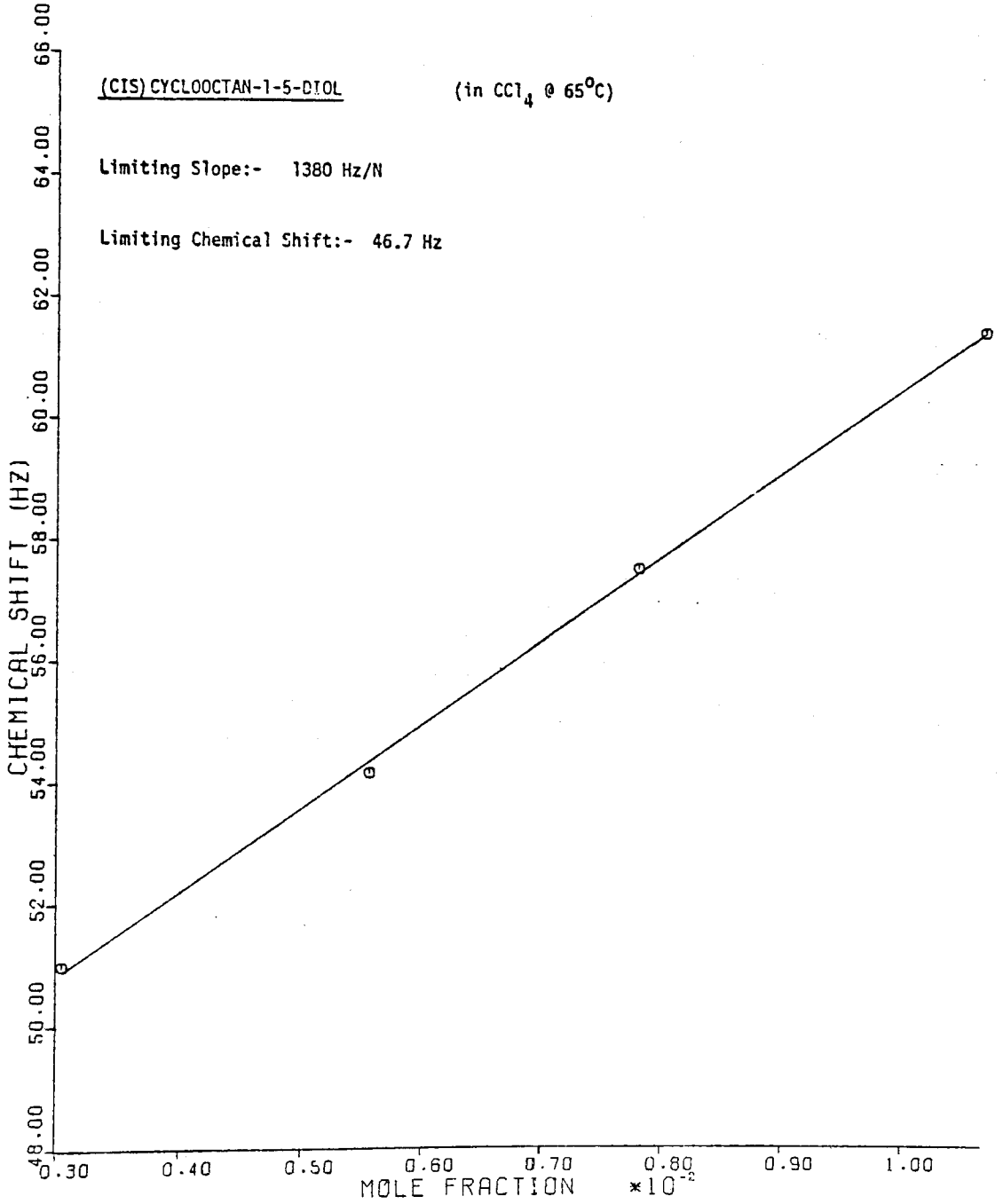
4.0
3.0
2.0
1.0
σK/K
0.01
0.1
1
10
100
1000
K


Plot of K vs. $\sigma_{\Delta G}$ using T = 313·15°K
7·0
6·0
5·0
4·0
3·0
2·0
1·0
$\sigma_{\Delta G}$
0·01
0·1
1·0
10·0
100·0
1000·0
K

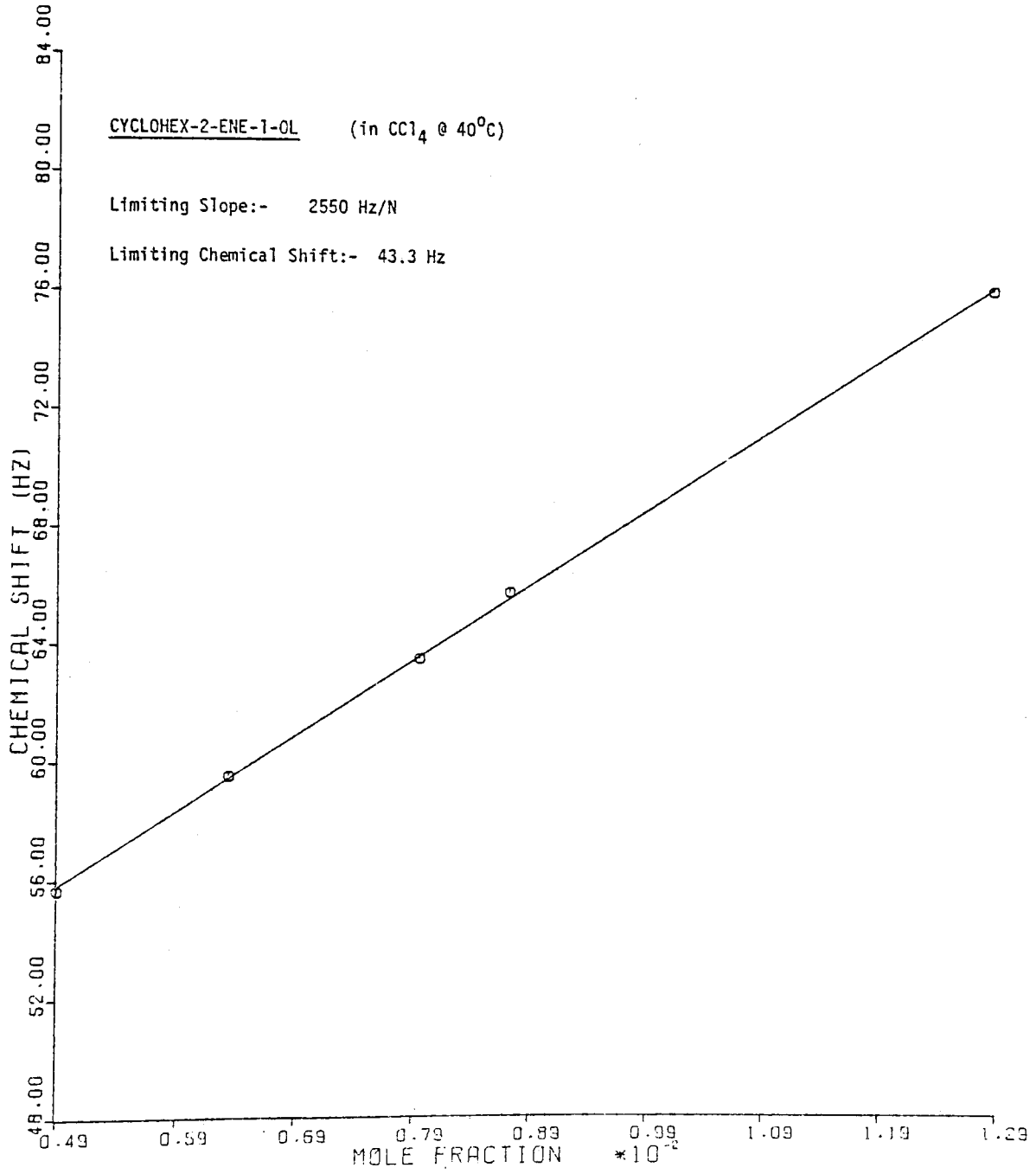
Wt. of diol (mg)	Wt. of $CDCl_3$ (g)	Mole Fraction (N)	Chemical Shift (Hz)
8.95	1.4873	0.005650	84.4
12.40	1.4911	0.007808	85.9
16.50	1.4975	0.010350	87.2
23.85	1.6194	0.013830	90.2



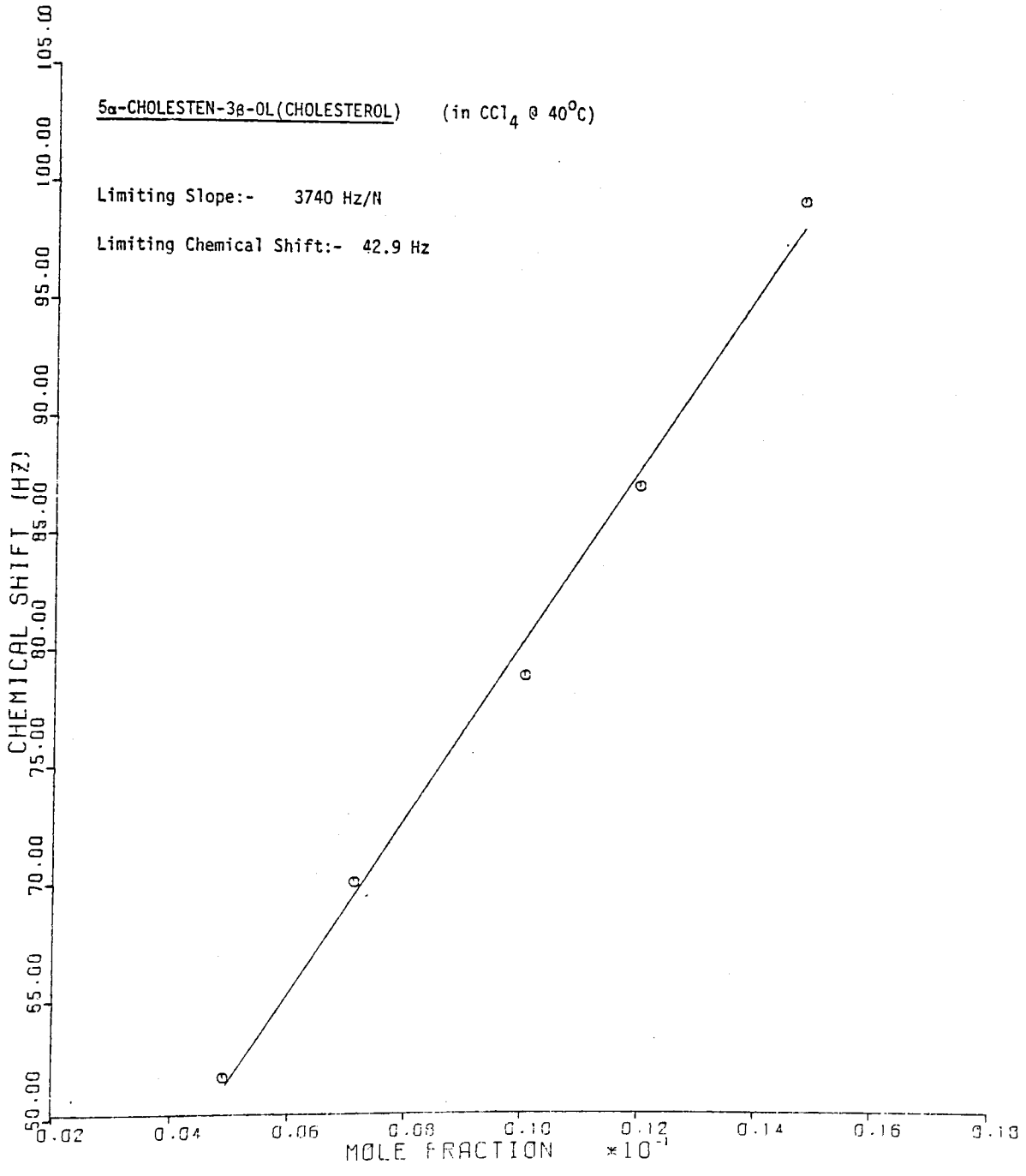
Wt. of diol (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
4.00	1.5734	0.003050	51.0
7.35	1.5848	0.005564	54.2
10.50	1.6124	0.007812	57.6
14.30	1.6022	0.010710	61.5

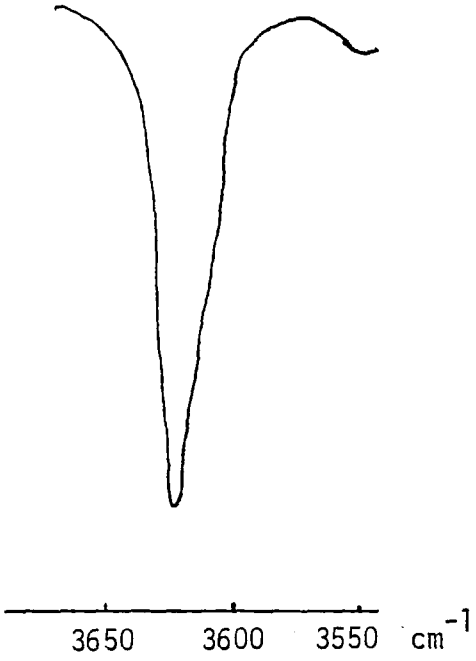


Wt. of alcohol (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
4.80	1.5332	0.004906	55.7
7.25	1.7914	0.006342	59.6
8.50	1.6748	0.007953	63.6
9.85	1.7689	0.008726	65.8
12.70	1.5451	0.012880	76.1

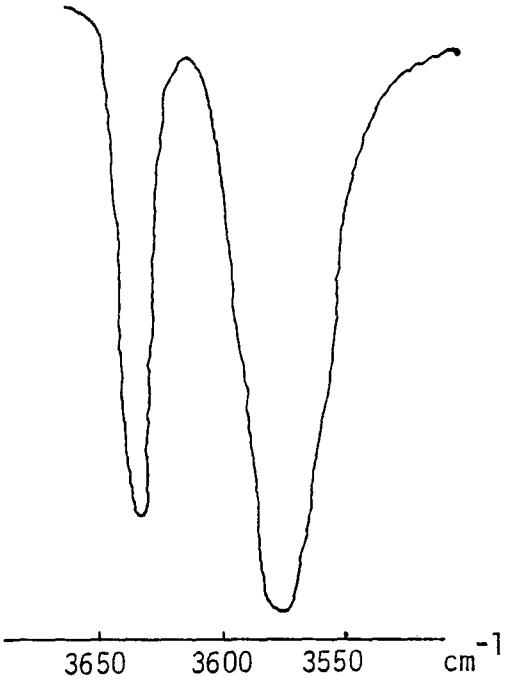


Wt. of steroid (mg)	Wt. of CCl_4 (g)	Mole Fraction (N)	Chemical Shift (Hz)
19.40	1.5696	0.004917	61.8
28.00	1.5644	0.007120	70.2
40.95	1.6210	0.010050	79.0
48.00	1.5900	0.012010	87.2
57.00	1.5308	0.014813	99.5

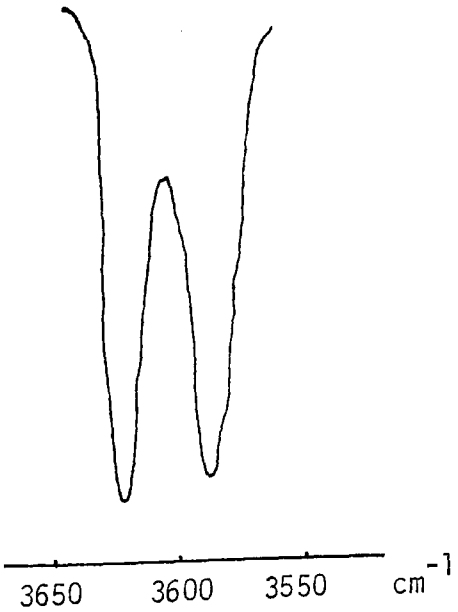




trans-Cyclopentan-1-2-diol



cis-Cyclopentan-1-2-diol



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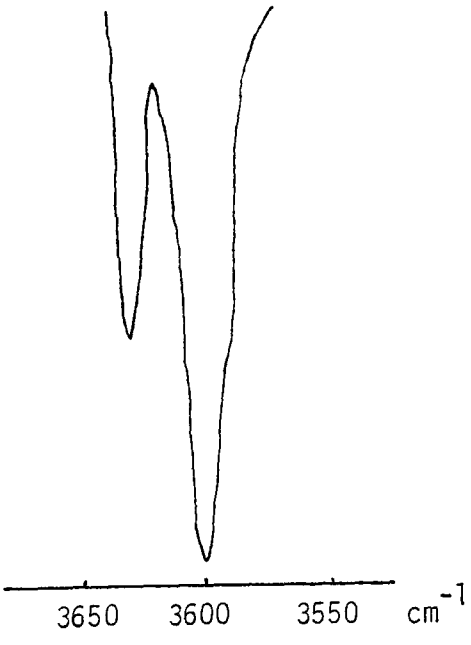
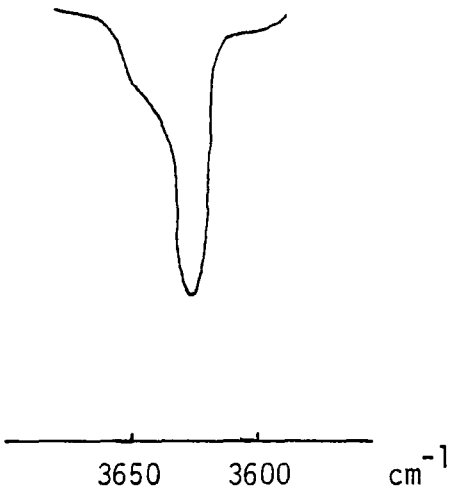


trans-Cyclohexan-1-2-diol



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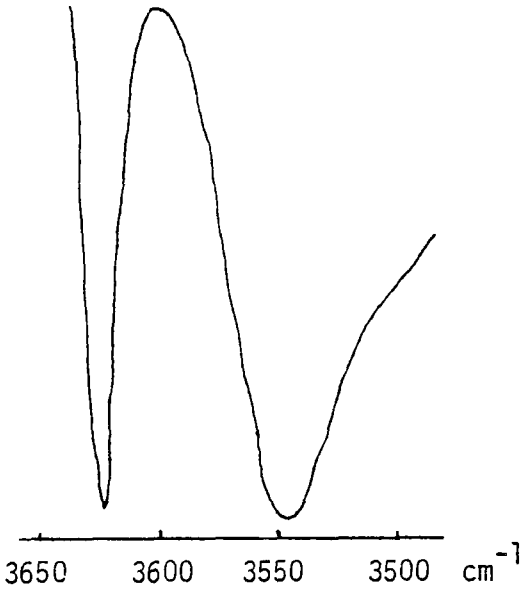
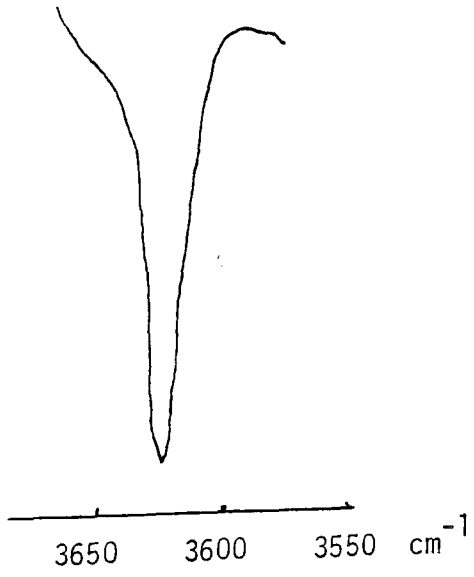
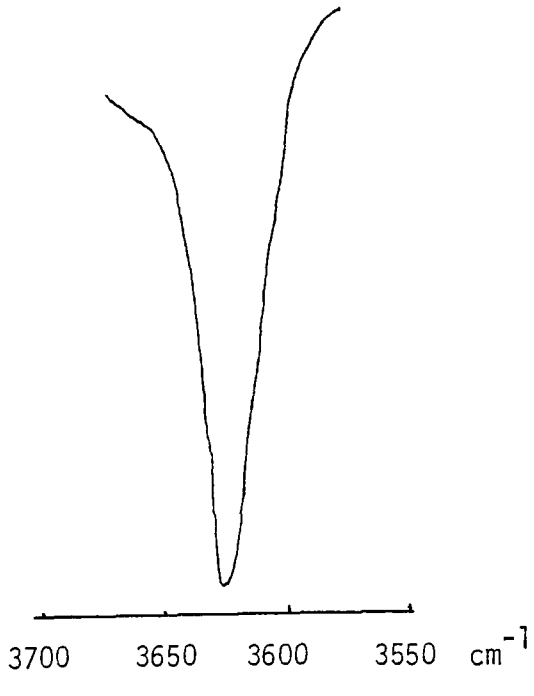


cis-Cyclohexan-1-3-diol



cis-Cyclohexan-1-4-diol



trans-Cyclohexan-1-4-diol

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