N.m.r. assay of enantiomeric excess

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N.M.R. ASSAY OF ENANTIOMERIC EXCESS

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DECLARATION

I declare that this is my own work, unless otherwise acknowledged by reference, and that it has not been submitted in any application for a higher degree in this or any other university. The thesis describes the results of research carried out in the Chemistry Department of the University of Durham and at Glaxo Group Research, Greenford between October 1984 and September 1987.

---------- Richard J Taylor

MEMORANDUM

Sections of this work have formed the basis of the following publications:

D. Parker, R.J. Taylor, A.P. Tonge and G. Ferguson, Tetrahedron, 1986, 42, 617.

D. Parker, M. Hodgson and R.J. Taylor, J.Chem.Soc.,Chem.Commun., Commun. 457, in press.

D. Parker and R.J. Taylor, J.Chem.Soc.,Chem.Commun., in press.

D. Parker and R.J. Taylor, Tetrahedron, in press.

Parts of this work were presented as posters at the Royal Society of Chemistry Newcastle and North East coast section General Poster Meeting at the University of Newcastle-upon-Tyne 11th December 1985 and at The Royal Society of Chemistry 8th International Meeting on N.M.R. Spectroscopy at the University of Kent at Canterbury 6th-10th July 1987.
The author also attended the 18th Sheffield Symposium on Modern Aspects of Stereochemistry at the University of Sheffield 19th December 1984 and the 23rd EUCHEM Conference on Stereochemistry on the Bürgenstock, Central Switzerland 3rd-9th May 1987.

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Finally, I thank my parents for their understanding, encouragement and love.

ABBREVIATIONS

G.C.	Gas Chromatography
G.L.C.	Gas Liquid Chromatography
H.P.L.C.	High Performance Liquid Chromatography
C.S.P.	Chiral Stationary Phase
C.M.P.A.	Chiral Mobile-phase Additive
N.M.R.	Nuclear Magnetic Resonance
C.S.A.	Chiral Solvating Agent
C.D.A.	Chiral Derivatising Agent
L.S.R.	Lanthanide Shift Reagent
C.L.S.R.	Chiral Lanthanide Shift Reagent
U.V.	Ultra-violet
T.F.A.	Trifluoroacetic acid
M.T.P.A	α-Methoxy-α-trifluoromethylphenylacetic acid
M.M.P.A.	α-Methyl-α-methoxypentafluorophenylacetic acid
T.P.E.	2,2,2-trifluoromethyl-1-phenylethanol
D.M.S.O.	Dimethyl sulphoxide
e.e.	Enantiomeric Excess
thd	2,2,6,6-tetramethylheptane-3,5-dionato
fod	1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato
dpm	dipivoylmethanato
tfc	3-trifluoromethylhydroxymethylene-(1R)-camphorato
hfc	3-heptafluorobutyryl-(1R)-camphorato

ABSTRACT

Title:	N.M.R. Assay of Enantiomeric Excess
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The use of (S)-methylmandelate as a Chiral Derivatising Agent for chiral acids is described. The diastereoisomers obtained by esterification are studied by ^{1}H N.M.R. Assignment of absolute configuration in these systems is made using models proposed to explain the origin of diastereotopic methylene proton non-equivalence in camphanamides.

The development and application of chiral phosphine platinum(0) and palladium(0) ethene complexes as Chiral Derivatising Agents for chiral alkenes and allenes is reported. The ^{31}P N.M.R. spectra recorded for the mixtures of diastereoisomers obtained when the ethene ligand is displaced "in situ" by alkene or allene enantiomers are fully described.

Efforts to produce a chiral sulphoxide solvating agent for amines, amides and alcohols proved inconclusive. Enantiomerically enriched 2-Naphthyl- and 9-Anthrylmethyl-sulphoxides were synthesised but neither induced non-equivalence in racemic solvates.

O-Acetylmandelic acid has been used as a Chiral Solvating Agent for amines and β-aminoalcohols. Diastereomeric salts formed "in situ" are studied by ^{1}H N.M.R. The accuracy of the integrated enantiomeric composition measurement is ±2% and the sense of chemical shift non-equivalence is consistent with configuration within related series of compounds.

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INTRODUCTION

CHAPTER ONE

Assay of Enantiomeric Excess

General Introduction

"Assay of Enantiomeric Excess defines the efficiency of asymmetric synthesis".[1]

American pharmaceutical companies are legally obliged to market only the physiologically beneficial enantiomer of a chiral drug. The experience with the antidepressant thalidamide prescribed to pregnant women in the early 1960s illustrates the dangers in selling drugs in unresolved form.

Attempts to reproduce in the laboratory the stereo-selectivities of reaction encountered in nature have resulted in the development of highly enantioselective reactions. With such reactions capable of returning enantiomeric excesses greater than 97% there is increased emphasis on reliable analytical techniques for the precise determination of enantiomeric composition; the ability to measure accurately large enantiomeric excesses being particularly important.

Usually enantiomeric excess is estimated indirectly using chiroptical methods:

1. Polarimetry: Measurement of optical rotation at a single wavelength.
2. Optical Rotatory Dispersion: Variation of optical rotation with wavelength.
3. Circular dichroism: The difference in the absorption of left and right circularly polarised light.

Classically the optical purity of a sample is derived by expressing the observed specific optical rotation at a certain wavelength, λ, (usually that of the sodium-D line), $[\alpha]_\lambda$, as a percentage of the optical rotation of the pure enantiomer at the same wavelength, $[\alpha]_\lambda$ max, known as the absolute optical rotation.

i.e. Optical purity = $[\alpha]$ /$[\alpha]$ max * 100

In general optical purity and enantiomeric excess can be equated, but Horeau[2] has shown with α-methyl-α-ethyl-succinic acid, Table 1, (Figure 1), that if optical rotation does not vary linearly with concentration then an alternative method for measuring enantiomeric excess must be sought. The advantage of determining optical rotations is that the data obtained can be compared directly with those in the literature. The disadvantage is that many reported literature rotations are not correct. For example Parker and Hodgson[3] have shown that the optical rotation for exo-2-norbornane carboxylic acid is $[\alpha]^{20}$ = -27.8 (conc. = 1, ethanol) and <u>not</u> $[\alpha]^{20}$ = -10.7 as had been originally surmised. Based on this revised figure the efficiency of catalytic hydrocyanation using transition metals has been redefined. Independent conformation of the enantiomeric purity of the exo-acid was obtained using an N.M.R. method.

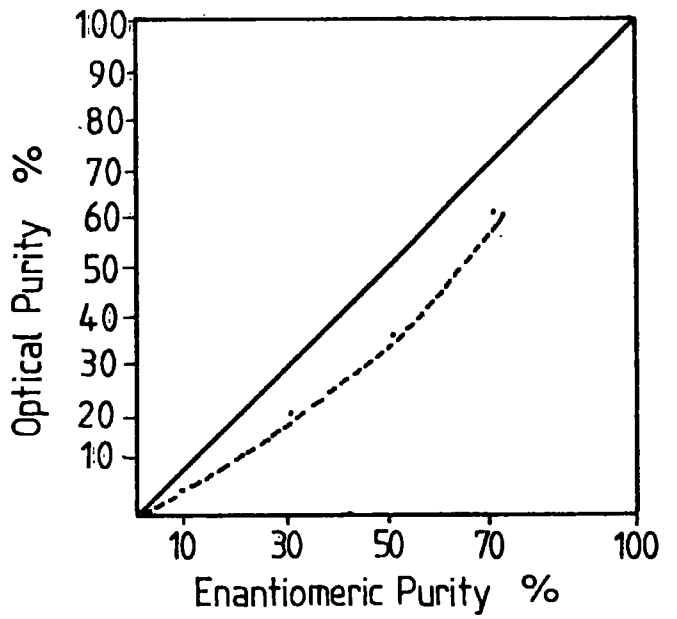
Table 1

Non-linear Relationship Between Optical and Enantiomeric Purity

Observed Rotation*	$[\alpha]_{589}$**	Enantiomeric Purity	Optical Purity***
0.660°	4.4°	100%	100%
0.401°	2.7°	70%	61%
0.236°	1.6°	50%	35.5%
0.139°	0.93°	30%	21%
0.052°	0.35°	10%	8%

*$[\alpha]_{obs}$, l=1, λ=589 **$[\alpha]_{589}=[\alpha]_{obs}*100/15$ ***$[\alpha]_{589}*100/4.4°$

Figure 1



Non-linear Optical Purity / Enantiomeric Purity Relation

ref. 2

The most commonly used non-chiroptical methods for direct determination of enantiomeric excess are:

1. Chromatographic Analysis by gas or liquid chromatography either of the diastereoisomers obtained by reaction of the enantiomeric mixture with a secondary chiral reagent or direct separation of enantiomers on a chiral column or by using a chiral eluent additive.
2. Nuclear Magnetic Resonance. As an assay method for a mixture of diastereoisomers, like gas chromatography, (G.C.), and High Performance Liquid Chromatography, (H.P.L.C.), Nuclear Magnetic Resonance, (N.M.R.), requires the intervention of a chiral auxiliary agent in order to detect enantiomers. In contrast to the chromatographic methods, however, N.M.R. provides the enantiomeric composition information without separation of the diastereoisomers. Resonances in pairs of enantiomers can be rendered chemical shift non-equivalent by conversion to diastereoisomers using a Chiral Derivatising Agent, (C.D.A.). Alternatively, chiral solvents, Chiral Solvating Agents, (C.S.A.), or Chiral Lanthanide Shift Reagents, (C.L.S.R.), form diastereomeric solvates or complexes "in situ" facilitating direct N.M.R. study.

1.1 Assay of Enantiomeric Excess by Chiroptical Methods

Measurement of optical rotation is a straightforward procedure requiring relatively inexpensive equipment. The sample, if solid, is dissolved or, if liquid, is mixed with an achiral solvent to give a solution of known concentration, which is placed in a cell of known optical path length within the polarimeter. Plane polarised light from a sodium-vapour lamp passes through the solution and the extent and sense of rotation of the polarisation is read directly from the rotation of the analysing polaroid. The standard form for reporting the specific rotation of a sample was defined by Elsenbaumer and Mosher[4] and indicates the temperature of measurement, the wavelength (sodium-D line), solvent and concentration in grammes per 100cm^3

e.g. for (R)-(-)-Mandelic Acid $[\alpha]_D^{20°} = -155.4°$ (c=2.913, 95%EtOH)

A sample can be measured neat, as a solution, as a solid film or even as a gas. The observed rotation $[\alpha]_{obs}$ is a function of the number of molecules through which the plane polarised light (wavelength λ) passes and is related to the specific optical rotation at temperature t by the expression:

$$[\alpha]^t = [\alpha]^{obs}/l*\rho$$

where l is the optical path length in decimeters and ρ is the sample density at temperature t in g/dm^3.

Determination of optical purities by polarimetry suffers from the following drawbacks:

1. The maximum rotation of the pure enantiomer (the absolute optical rotation, $[\alpha]^t max$) must be known with certainty.
2. Relatively large samples are often required to produce measurable rotations. This is particularly true for compounds which are chiral by virtue of isotopic substitution.
3. The sample must exhibit medium to high optical rotatory power if small differences in optical purity are to be detected.
4. The chiral product must be isolated and freed from chemical contaminants, such as starting material, without accidental enantiomeric enrichment.
5. Optical rotation varies with temperature and concentration. Temperature variation results from at least three effects; the volume of neat liquid or solution changes with temperature causing a direct change in the number of molecules in the optical path. The interaction of solute molecules with each other and solvent molecules is affected by temperature and the relative populations of stereochemically important conformations alters, particularly during low temperature work.[5]

   In solution: $[\alpha]^t = 100[\alpha]_{obs}/l*c$ where c is the concentration in grammes per $100cm^3$. The specific optical rotation, $[\alpha]^t$, is not always linearly proportional to concentration; for example interactions between solute molecules may cause non-linear rotations in concentrated

solutions whilst even in dilute solutions $[\alpha]^t$ may not be truly constant. It is therefore essential to use the same concentration of solution when comparing solutions' rotations on an absolute basis and to report the concentration of solution when recording optical purity data for new compounds. If possible at least two determinations should be made at different concentrations to indicate whether the $[\alpha]$/concentration dependence is linear. Plattner and Heusser[6] suggested that the errors in measurement of optical rotation owing to temperature and concentration effects combined are at least ±4%.

6. Optical rotation measurements can be adversely affected by the presence of small quantities of contaminants having high optical rotatory power. The enhancement of optical rotation by addition of racemic compounds to the solution of an optically active compound is called the Pfeiffer effect[7], although the precise mechanism is unknown.
7. Interaction between a certain solvent and solute can cause specific conformational changes and variations in ionic species leading to changes in optical rotation dependent on the nature of the solvent. For example many amphoteric substances such as amino acids show a change in sense of optical rotation when the pH of solution is adjusted. The choice of solvent for an unknown, potentially chiral, molecule is based on the observed solubility during isolation and scope for interactions indicated by spectral data. Ideally the preferred solvent is the most non-polar one in which the product is soluble. It is vital to quote the solvent used in determination of optical purities.

8. It is not possible to correlate absolute configuration with the sense of optical rotation. A closely related reactant and product with the same configuration may rotate the plane of polarised light in opposite directions. This inconsistency rules out predictions concerning molecular configuration based on the sign of optical rotation.
9. Many compounds containing chromophores absorb light in the U.V.-Visible region of the electromagnetic spectrum and produce anomalous optical rotatory dispersion curves, in such cases the Cotton effect gives rise to very large rotations at specific wavelengths. The usual wavelengths of light used for measuring rotations are 589.0nm and 589.6nm.

Variation of specific optical rotation with temperature, solvent, concentration, wavelength and contaminants will all distort the observed optical purity figure and give an erroneous estimate of the enantiomeric excess.

1.2 Assay of Enantiomeric Excess by Gas Chromatography

Gas Chromatography is a quick and simple technique for separation of organic compounds, offering high resolution and excellent reproducibility of results. An auxiliary chiral reagent is necessary for the resolution of enantiomers by G.C. Enantiomers can be converted into diastereoisomers by chemical reaction with an enantiomerically pure chiral resolving agent, the diastereoisomers can then be separated on an achiral stationary phase.[8,9] This method is restricted to substrates that possess at least one reactive function for quantitative reaction with the resolving agent. Difficulties in the

reaction step involving racemisation or kinetic resolution of enantiomers reacting via energetically different diastereomeric transition states may result in the diastereoisomer ratio differing from that of the original enantiomers. Further, systematic errors may arise from incomplete optical purity of the resolving agent which will affect the accuracy of enantiomeric excess determination, especially for highly enriched mixtures.

Direct resolution of enantiomers on a Chiral Stationary Phase, (C.S.P.), is potentially less problematic[10] and has proved to be more reliable. Resolution is effected via rapid and reversible diastereomeric interaction between the sample enantiomers and the optically active stationary phase. The approach requires an efficient solute-solvent system which is capable of chiral recognition through molecular association rather than resorting to more clumsy chemical reaction. Since this technique involves enantiomers rather than diastereomers, the enantiomeric ratio of the sample will not be altered by chemical, physical or analytical manipulations prior to resolution. The only possible source of error is partial diastereoselective decomposition of the racemate on the chiral stationary phase during elution. The observed enantiomeric ratio is independent of the enantiomeric purity of the column packing material, although lower enantiomeric purity will result in poorer resolution (i.e. the separation factor, α, is reduced). In addition an achiral detection device will respond equally to eluted enantiomers but diastereoisomers may produce differing responses.

The inherent advantages of direct enantiomer resolution favour its application even in cases where derivatisation is necessary to reduce molecular polarity or enhance volatility, with α-amino acids, for example. In principle a chiral resolving agent could be selected to give diastereoisomers separable on a standard G.C. column, but it is preferable to choose an achiral derivatising agent and resolve on a chiral column. In both cases, the absence of racemisation accompanying derivatisation must be rigorously established.

Once a quantitative enantiomer resolution on a chiral stationary phase has been achieved then Table 2[11] shows that inspection of the chromatogram can yield much useful information. The peak parameters (c), (d) and (e) are most relevant for analytical applications to asymmetric synthesis.

Table 2

Gas Chromatographic Parameters of Enantiomer Resolution[11]

Parameter	Definition
a) Peak Retention	A thermodynamic measure of the selective association between sample and column.
b) Peak Separation	A thermodynamic measure of chiral recognition between racemic sample and optically active column.
c) Peak Ratio	A precise quantitative measure of the enantiomeric composition of the sample.
d) Peak Assignment	A correlation of sample retention and molecular configuration (assignment of absolute configuration).
e) Peak Coalescence	A kinetic measure of sample racemisation during resolution.

A comparison of relative peak areas provides an unambiguous measurement of the enantiomeric excess and since peak integration can be performed electronically with a high degree of accuracy, (± 0.01%), precise data can be obtained. This is a particularly important feature in two significant borderline situations; first, in producing evidence of very small enantiomeric excess (i.e. close to the racemic limit), and second in analysis of highly enantiomerically enriched mixtures, (i.e. close to the 100% e.e. limit). Gil-Av has estimated[9] that as little as 0.1% of an enantiomeric impurity (i.e. 99.8% e.e.) can be detected by G.C. In terms of the difference in Gibbs Free Energy of activation, $\Delta\Delta G^{\#}$, for the separation of diastereomeric intermediates this corresponds to an energy difference of 16.7 kJmole^{-1} at 298K.

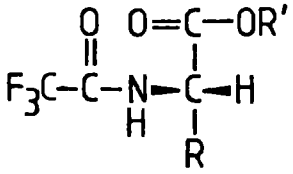
$\Delta G^{\#}_S = -RT\ln K_S$ $\Delta G^{\#}_R = -RT\ln K_R$ hence $\Delta\Delta G^{\#} = RT\ln(K_S/K_R)$.

Resolution of enantiomers by chromatography depends solely on the disparity between the stability constants of the diastereomeric intermediates formed during the elution event, consequently assignment of absolute configuration involves the correlation of molecular configuration with order of enantiomer elution. In many instances absolute configuration <u>can</u> be assigned simply by observing the order of peak emergence. There are however, notable exceptions which demonstrate the limitations of this approach.

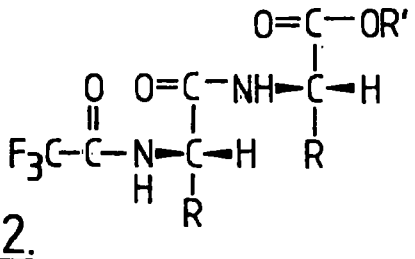
1.2.1 <u>Enantiomer Resolution using Chiral Stationary Phases</u>

The first successful resolution of racemic N-trifluoro-acetyl-amino acid esters on glass capillary columns coated with N-trifluoroacetyl-L-isoleucine lauryl ester, (1), was performed

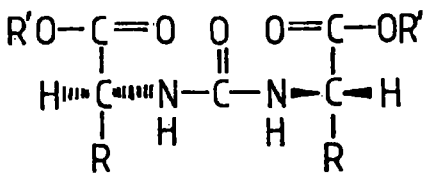
by Gil-Av.[12] The separation factor, α, was small and the column efficiency low. Rapid development of superior chiral stationary phases followed, most of which included additional NH groups capable of participating in chiral recognition via hydrogen bond formation; for example the dipeptide phase, (2), the carbonyl bis amino acid phase, (3), and the diamide phase,(4).[13-20] In addition to α amino acids; β and γ amino acids and amines have also been resolved.[21] A novel type of C.S.P., N-lauroyl-(S)-α-(1-naphthyl)-ethylamine, (5), permitted resolution of aromatic and aliphatic N-trifluoroacetyl amines as well as α-methyl and α-phenyl carboxylic acid amines.[22]



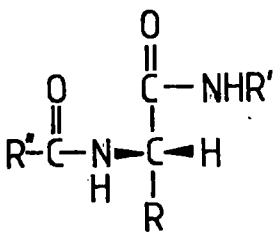
1. R=sec-butyl
R'=dodecyl



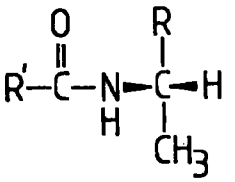
2. R=isopropyl, R=cyclohexyl



3. R=R'=isopropyl

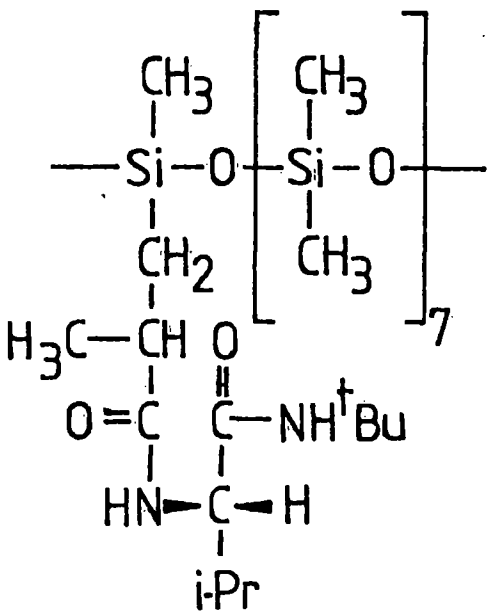


4. R=isopropyl
R'=tert-butyl
R=undecyl



5. R=1-naphthyl
R'=undecyl

Early C.S.P.s suffered from low thermal stability. This was a problem when undertaking the study of a series of naturally occurring amino acids, for example, when it is usual to make use of temperature programming. This technique increases the G.C. oven temperature over a selected time interval in order to elute the components from the column within a reasonable experimental time. Improved thermal stability (up to 190°C) has been achieved by careful purification of N-docasanoyl-L-valine-tert-butylamide[23] and related diamide phases.[24,25] The fluid polymeric phase, (6), known as Chirasil-Val is commercially available as both (L) and (D) coatings, it was developed by Frank[26] by coupling the versatile diamide phase, (4), via the amino function to a copolymer of methyl siloxane and (2-carboxypropyl)-methyl siloxane.



6. Chirasil-Val

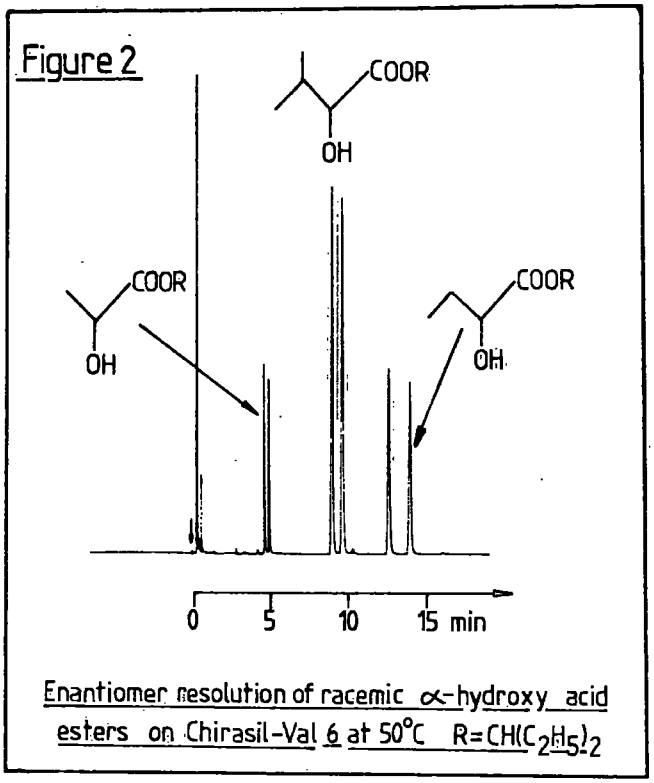
Chirasil-Val is thermally stable up to 240°C and has been used to resolve enantiomers of a number of different compound classes.[27,28] The highest resolution and thermal stability are observed when the chiral side chains are separated by seven dimethyl siloxane units.[29] Further developments in C.S.P. technology utilise Frank's methodology, coupling diamide phases to polysiloxanes, most effort being aimed towards improved resolution of amino acids.[30-32] In all cases, however, amines and amino acids must be converted to N-trifluoromethyl or N-pentafluoropropanoyl derivatives to reduce molecular polarity.

1.2.2 Applications of C.S.P.s to Enantiomer Resolution

The first enantiomer resolution by G.C. involved amino acid derivatives, consequently this class of compounds has been widely studied.

1. The configuration of amino acids in biological polymers (proteins), biological fluids, extraterrestrial material, sediments, and soils have been determined.[33,9,34]
2. α-Amino acids and α-hydroxy acids are versatile starting materials for conversion to optically active building blocks for other chiral syntheses.[35] Hence knowledge of the enantiomeric purity of these starting materials is essential. For example commercial (S)-ethyl lactate was found to contain 1.67±0.06% of the (R) enantiomer by G.C. analysis of its tert-butyl isocyanate derivative.[36]
3. G.C. analysis on (4) of N-acetylphenylalanine as its diazomethane derivative not only established the correct enantiomeric yield for asymmetric homogeneous hydrogenation of the dehydroamino acid using a chiral

Rhodium(I) catalyst, but also permitted the correct value of the absolute optical rotation, $[\alpha]^{t}max$, to be determined by extrapolation.[37,38]



Enantiomer resolution of racemic α-hydroxy acid esters on Chirasil-Val 6 at 50°C R=$CH(C_2H_5)_2$

1.2.3 Assignment of Absolute Configuration

The direct identification of absolute configuration by G.C. involves co-injection of the sample and reference compound and inspection of the order of elution from the resolving C.S.P. An indirect assignment of absolute configuration involves comparison of the order of peak emergence between the sample and a structurally related reference compound of known chirality. Gil-Av noted in his early work with α-amino acids[12] using C.S.P. (1) that D-amino acids eluted before L-amino acids. This elution order was confirmed for C.S.P.s (4) and (6) derived from L-valine.[26,30] It has been found, however, that β and γ amino acids emerge in reverse order from the diamide phase N-lauroyl-L-valine-6-undecylamide.[20] A systematic study

of N-trifluoroacetylated α,β, and γ amino acid esters showed[21] that elution from the C.S.P. (3) was in an order related to the steric requirements of the ligands surrounding the chiral carbon. Viewing the molecule from the chiral carbon in the direction of the trifluoroacetylated nitrogen the remaining substituents at carbon 1 are arranged in order of decreasing size either anti-clockwise or clockwise. Enantiomers with an anti-clockwise arrangement elute first from L-valine derived C.S.P.s. It was observed, coincidentally, that as the effective size of the substituents becomes similar there is a lowering in resolvability of the enantiomers.

1.2.4 Accuracy and Precision of C.S.P. G.C.

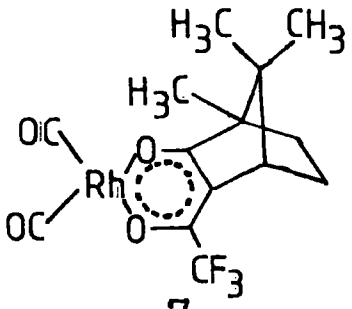
The accuracy and precision of G.C. for determination of enantiomeric excess of leucine was reported by Bonner[39]: Accuracy (absolute error) 0.03-0.70%, Reproducibility (standard deviation) 0.03-0.60%. Digital electronic integration of a 50:50 racemic mixture gave standard deviation of 50±0.03% (4 determinations) and 50±0.17% (3 determinations).

Reversal of elution pattern for enantiomerically enriched samples by inversion of the chirality of the C.S.P. has been used to differentiate between true enantiomer resolution and accidental peak splitting due to accompanying chemical impurities.[40,41] It has been suggested[42] that this technique could be used in the measurement of minute amounts of enantiomeric impurities if the deficient enantiomer elutes after the main component and is lost in the tail of the abundant enantiomer.

1.2.5 Complexation Gas Chromatography[43]

Complexation gas chromatography involves the direct resolution of enantiomers (i.e. without derivatisation) on a metal containing chiral stationary phase. An attempt to resolve chiral olefins by G.C. in 1971 using a dicarbonyl rhodium(I)-β-ketonate (7) containing a 3-trifluoroacetyl-(1R)-camphorate failed.[44] In 1977, however, a racemic mixture of 3-methylcyclopentene was resolved on this C.S.P.[40,41] Golding[45] has reported the use of the chelate (8), known to be a powerful N.M.R. shift reagent,[46] for semi-quantitative resolution of methyloxiranes. Subsequent reports of resolutions include tertiary butylmethyl carbinol, spiroketals and pheromones but are mainly limited to small heterocycles. Short packed columns have been used for the resolution of alkyl oxiranes. Oi[47,48] resolved α-hydroxy acid esters and amino alcohols on a chiral copper(III) Schiff base chelate.

Generally complexation gas chromatogaphy does not require derivatisation of samples prior to analysis and the sample size required is very small, (10^{-8}g or less). Since peak resolution is usually rapid and no chemical or physical manipulation of samples is necessary before injection, the enantiomeric yield can be monitored during the course of a reaction. This permits the relationship between enantiomeric excess and extent of conversion in kinetic resolutions, for example, to be established quantitatively. To date most work with complexation gas chromatography has been concerned with analysis of enantioselective epoxidation reactions, the molybdenum(IV)oxodiperoxo-(S)-dimethyllactamide complex,(9), proving a particularly effective C.S.P. in this application.



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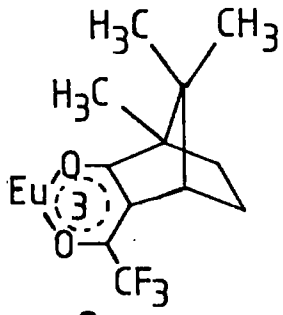
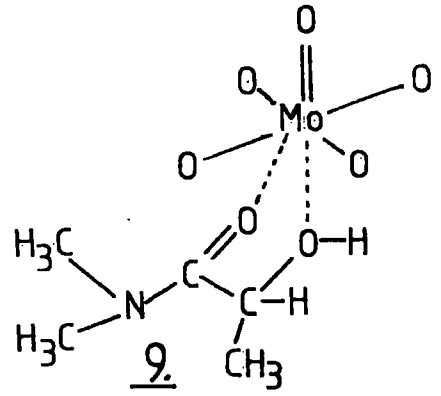
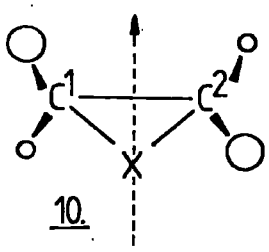


8.

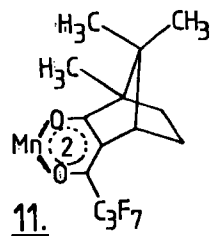


9.

Schurig[1,49] has proposed a model for assigning absolute configuration based on the elution sequence for three membered heterocycles. When the molecule is viewed from the heteroatom towards the horizontal carbon-carbon bond, (10), the absolute configuration of the enantiomer eluting as the second peak (i.e. that corresponding to the stronger interaction) is that in which the bulkier groups are situated upper at C-1 and/or lower at C-2. This model works well in predicting elution order for methyl, ethyl, isopropyl, sec-butyl, and tert-butyl oxiranes[11] but fails with (2S,3S)-trans-dimethyl oxirane.



10.



11.

The C.S.P.(11) has been used to measure the e.e. of (R)-isopropyl oxirane obtained from (S)-valine,[50] (e.e.>99.5%). Digital electronic integration revealed 1.12 ±0.04% of the (S) enantiomer, e.e. = 97.76 ±0.08%, whilst the unconventional "cut-out-and-weigh" approach gave e.e. = 97.2 ±0.5%. Complexation G.C. is limited in scope by the availability of

C.S.P.s which must be "tailored" to a specific class of compounds.

In conclusion: Gas chromatography is a highly efficient and precise technique for determining the enantiomeric purity of chiral samples. The method is especially suitable for determinations of small, (i.e. e.e. ≈0%), and large (i.e. e.e. >95%) enantiomeric purities. The accuracy of the method when measured by digital peak integration is typically ±0.3% and may even be as good as ±0.1%. The limitations of this approach are that the sample should have sufficient volatility and exhibit good thermal stability.

1.3 Assay of Enantiomeric Excess by Liquid Chromatography

It is opportune to define a few chromatographic terms which are conceptually easier to comprehend in the context of liquid rather than gas chromatography. The volume of solvent required to elute a non-retained sample is equal to the void volume of the column, in order to elute a retained sample an additional volume of solvent is required. The ratio of this additional volume to the void volume is the capacity ratio, denoted by kappa, K. The separability factor, α, for two components is K_2/K_1, a value that corresponds to the ratio of the two partition coefficients being related to the energy difference between the retention mechanism for the two components. The separation obtained in a chromatogram depends on the band shape and is directly related to the column efficiency i.e. sample size, particle size, quality of packing and flow rate. An increase in α represents an increase in separability. Highly efficient analytical High Performance

Liquid Chromatography, (H.P.L.C.), systems produce reasonably good separations for two components having an $\alpha \geq 1.04$. Slightly less efficient Medium Performance Liquid Chromatography, (M.P.L.C.), systems, used for preparative work, require $\alpha = 1.2$ or more in order to resolve gramme quantities of material.

The separation of enantiomers requires the intervention of a chiral agent. This can take the form of a separate derivatisation of a pair of enantiomers using a Chiral Derivatising Agent, (C.D.A.), to give chromatographically separable diastereoisomers, or it can take the form of short term interaction of enantiomers with the chiral agent affording diastereomeric complexes. As in the G.C. technique the first approach involving a discrete derivatisation step is referred to as the indirect method. The second approach involves direct resolution of enantiomers in one of two modes:

Either using a column packed with a Chiral Stationary Phase, (C.S.P.), in which case the diastereomeric complexes formed between the solute enantiomers and the column will have non-identical stabilities and will elute at different times. Alternatively a Chiral Mobile Phase Additive, (C.M.P.A.), may be added to the achiral eluting solvent; the diastereomeric complexes formed in solution will have differing stabilities and will elute sequentially from an achiral column.

1.3.1 Direct and Indirect Enantiomer Resolutions

The direct approach is more elegant and less problematic than the indirect approach. Since indirect resolution is not an absolute method incomplete enantiomeric purity of the C.D.A.

or differential extents of enantiomer derivatisation will adversely affect the estimate of enantiomeric excess obtained. Direct chromatographic resolution is an absolute method in that no external standard of enantiomeric purity is required to determine the enantiomeric excess of the sample. Like many of the N.M.R. methods, chromatography is a weighted time average view of dynamic processes, hence a less than enantiomerically pure C.S.P. or C.M.P.A. will affect the separation but <u>not</u> the relative size of the bands arising from the solute enantiomers. Reduction in enantiomeric purity of C.S.P. or C.M.P.A. reduces α by increasing K_1 and decreasing K_2 until at the racemic limit $K_1 = K_2$. Occasionally solute derivatisation is necessary to enhance detectability. In general an achiral derivatising agent is employed ruling out problems with selective reaction and C.D.A. purity.

Of the two direct methods, the use of a C.S.P. has two advantages over a C.M.P.A. First, the C.M.P.A. method requires a continuous source of chiral additive; this is a particular problem in preparative work where volumes are naturally larger. This can be alleviated to some extent by recycling recovered C.M.P.A. provided that separation from the eluted solute enantiomers is trivial. Second, detector response to the eluted C.M.P.A./solute diastereomers may be non-identical, in the C.S.P. approach detection is of eluted enantiomers which will produce identical responses

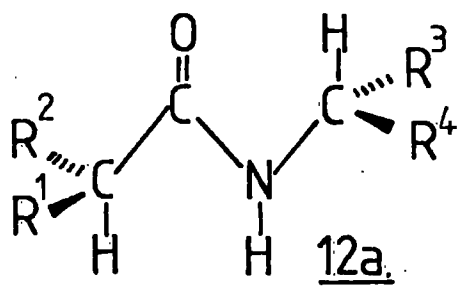
Offsetting the advantages of the direct approach is the lack of commercially available C.S.P.s and C.M.P.A.s. In contrast many chemical catalogues contain chiral molecules with

the appropriate functionality to permit use as C.D.A.s for a range of compounds.

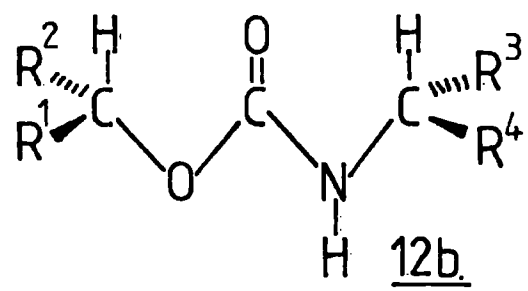
Absolute configuration can be determined by any chromatographic method if a configurationally known sample is available for reference. Failing this, absolute configuration can be assigned on the basis of elution order, provided that the molecular configuration of the chiral agent and the mechanism of chromatographic diastereoisomer separation are known.

1.3.2 Indirect Resolutions

1. Early work by Helmchen[51] focused on diastereomeric amides (12a) derived from chiral acids and amines. Either reaction partner can be used as the C.D.A. if it is available as a pure enantiomer. A wide range of amides have been separated on silica or alumina.[52,53] Typically α=2.5, but unfortunately retrieval of the chiral components by amide hydrolysis is frequently accompanied by racemisation.
2. Pirkle and others[54-57] have synthesised a series of carbamates (12b) from alcohols and isocyanates or from chloroformates and amines. Separability factors for H.P.L.C. analysis are around α=1.5. After resolution the chiral alcohols or amines can be recovered by decomposition of the carbamate using trichlorosilane.[58]

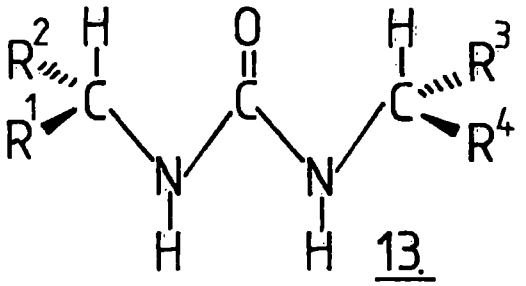


12a.

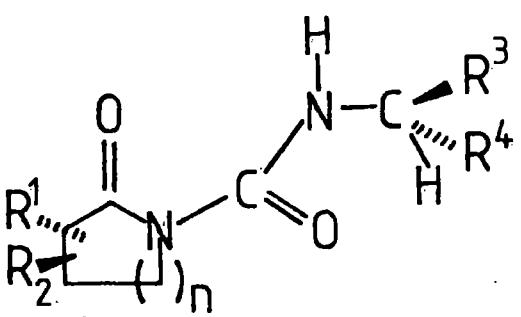


12b.

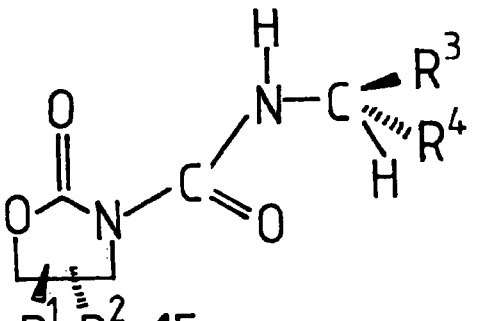
3. Although ureas such as (13), derived from two amine components, are known to separate chromatographically, only the acyl ureas (14) and (15), derived from action of isocyanates on lactones, have been studied in detail; α is usually 2.25 for a range of aromatic ureas.



13.



14.



15.

4. Helmchen's work has been extended to a series of isoprenoid and terpenoid acids[59,60,61] using (R)-1-(p-nitrophenyl)-ethylamine or 1-α-naphthyl-ethylamine as C.D.A.s, whilst diastereomeric hydroxyamides have been used to obtain optically pure acids and amines.[57]
5. A number of amino acids have been indirectly resolved by H.P.L.C. Usually the C.D.A. is used to derivatise the amino group, the acid function having previously been converted to an ester.
6. The diastereoisomers of esters and carbonates separate less well on silica or alumina than those of structurally similar

amides or carbamates. For example the separability factor for the carbamate (14) is 1.36 whilst for the carbamate (15) α is only 1.19. Diastereomeric esters possessing an additional polar site, such as mandalates,[62] offer improved separability.

7. Diastereoisomers chiral at sulphur[63,64] and phosphorus[65] have also been separated.

1.3.3 Direct Resolution on C.S.P.s

Before the advent of synthetic chiral stationary phases numerous attempts were made to separate racemates on columns packed with naturally occurring materials[66] such as quartz, wool, lactose, and potatoe starch. Most failed, but triacetylated cellulose found some success with aromatic solvates.[67] Synthetic Chiral Stationary Phases can be divided into two types:

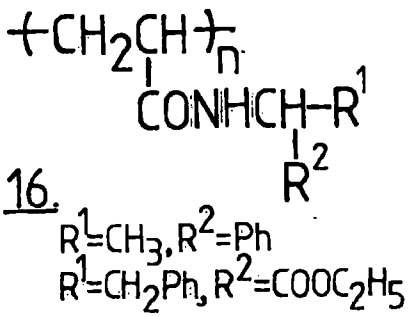
Co-operative which use an assemblage of subunits acting in concert to achieve chiral recognition, such as a polymer with a chiral backbone.

Independent in which molecules each capable of chiral recognition are bound to an achiral polymeric support and operate independently in distinguishing between enantiomers.

1.3.4 Co-operative C.S.P.s

The simplest approach to a chiral polymeric C.S.P. is by polymerisation in the presence of a chiral template molecule which, when removed, leaves a chiral cavity. Schwanghart[68] has prepared several polyacrylamide (16) and polymethyl acrylamide (17) C.S.P.s and has chromatographed a number of racemates on them. Only partial resolution of enantiomers results but

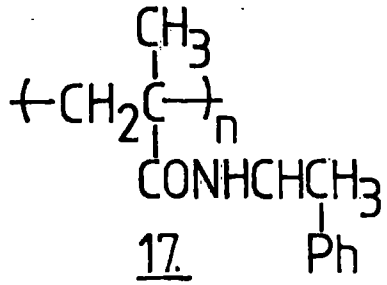
enantiomerically pure material is obtained by repeated passes. Blaschke and Markgraf[69] have succeeded in resolving a number of pharmaceutically interesting compounds on the polyacrylamide (16). Polymerisation of (triphenylmethyl)methyl acrylate,[70] the first C.S.P. in which chirality is due solely to the helicity of the polymer, was initiated by the chiral anionic catalyst {(-)sparteine-n-butyllithium}.



16.

$R^1=CH_3, R^2=Ph$

$R^1=CH_2Ph, R^2=COOC_2H_5$



17.

1.3.5 Independent C.S.P.s

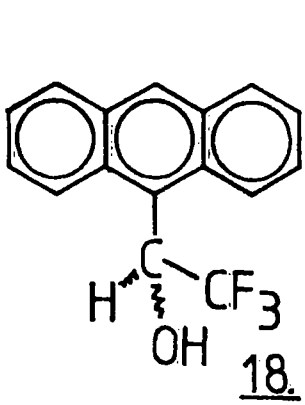
These must have a minimum of three simultaneous interactions with one of the solute enantiomers, one of these interactions being stereochemically dependent. In a simple model the balance between the attractive and repulsive interactions for each enantiomer can be used to understand the elution order. The types of possible interactions include hydrogen bonding, dipole-dipole forces, charge transfer complexes, steric repulsions and hydrophobic attractions. For optimum results three different interaction types should be involved since this avoids the possibility of interchange of sites. Thus an independent C.S.P. consists of chiral molecules each with three sites of interaction bound to a polymer support which is usually silica based. For example L-arginine bound to sephadex will resolve β-3,4-dihydroxyphenyl alanine.[71] Direct

resolution of chiral helicenes has been accomplished on columns packed with 2-(2,4,5,7-tetranitro-9-fluorenylideneaminoxy)-propionic amide,[72] N-(2,4-dinitrophenyl)alanine amide[73] and tri-β-naphthol-diphosphate amide.[74] Chiral recognition in these cases operates via a combination of π-π charge transfer and steric interactions. Amino acids have been resolved as their esters on crown ether C.S.P.s[75,76] and as N-acylated derivatives on amino acid derived C.S.P.s.[77]

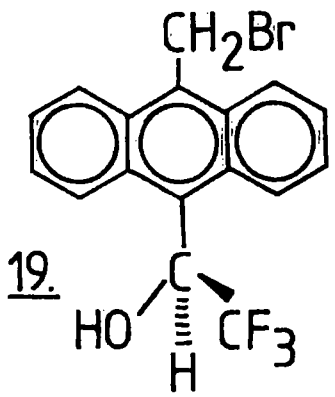
1.3.6 Fluoroalcohol C.S.P.s

Chiral fluoroalcohols such as (18) have proved useful as chiral solvating agents for the N.M.R. determination of absolute configuration and enantiomeric purity. N.M.R. studies have revealed that these fluoroalcohols form "chelate-like" solvates involving two interactions with a variety of dibasic solutes. The first interaction is hydrogen bonding and the second is carbinyl hydrogen bonding. The diastereomeric solvates formed differ in stability only when a third simultaneous interaction is possible for one but not both solute enantiomers. This condition is met when the solute contains a π-acidic substituent capable of interaction with the π-basic anthryl ring of (18). For example Pirkle and Sikkenga[78] have shown that solvates formed with racemic methyl-2,4-dinitrophenyl sulphoxide are of unequal stability and that the sulphoxide can be resolved on a silica column using the fluoroalcohol as a C.M.P.A. House and Pirkle[79] used 9-(10 bromomethylanthryl)-trifluoromethyl carbinol (19) to alkylate mercaptopropyl silanised silica to give the C.S.P. (20). This C.S.P. is capable of resolving the enantiomers of all alkyl-

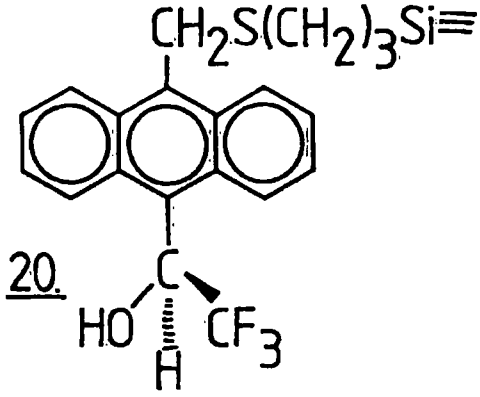
2,4-dinitrophenyl sulphoxides and a variety of 3,5-dinitrobenzoyl derivatives of alcohols and amines provided that these compounds posses the additional basic site required by the chiral recognition model.



18.



19.



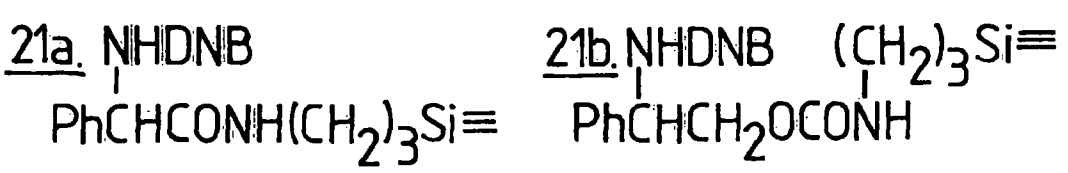
20.

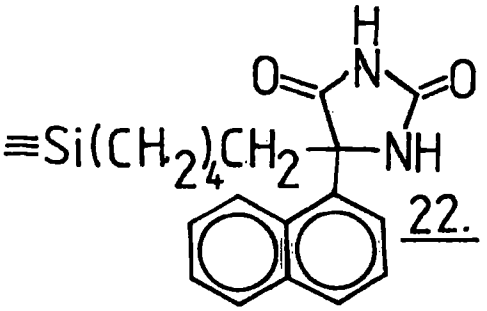
1.3.7 Amino Acid-Dinitrobenzoyl derived C.S.P.s

The diastereomeric interactions that allow a column derived from chiral A to resolve racemic B also allow a column derived from chiral B to resolve racemic A. This "reciprocality" has been used to design new C.S.P.s.[80,81] Thus the observed resolution of 3,5-dinitrobenzoyl-phenyl glycine on fluoroalcohol C.S.P.s has been translated into the C.S.P.s' (21a, 21b) which effectively resolve 9-anthryl carbinol enantiomers. Preparative techniques have been extended to afford other 3,5-dinitrobenzoylamino acid derived C.S.P.s which have resolved a wide range of compound classes. All of these having the necessary functionality to take part in π-π, hydrogen bonding and steric interactions as required for chiral recognition.[82,83]

Since the chirality of the column packing material and the

mechanism of chiral recognition are known, absolute configuration can be assigned on the basis of elution order. In addition to dinitrobenzoyl derivatives of amino acids, dinitrobenzoyl derivatives of amines and amino alcohols have been resolved on a C.S.P.(22) derived from hydantoin.[84]





22.

1.3.8 Chiral Mobile-Phase Additives

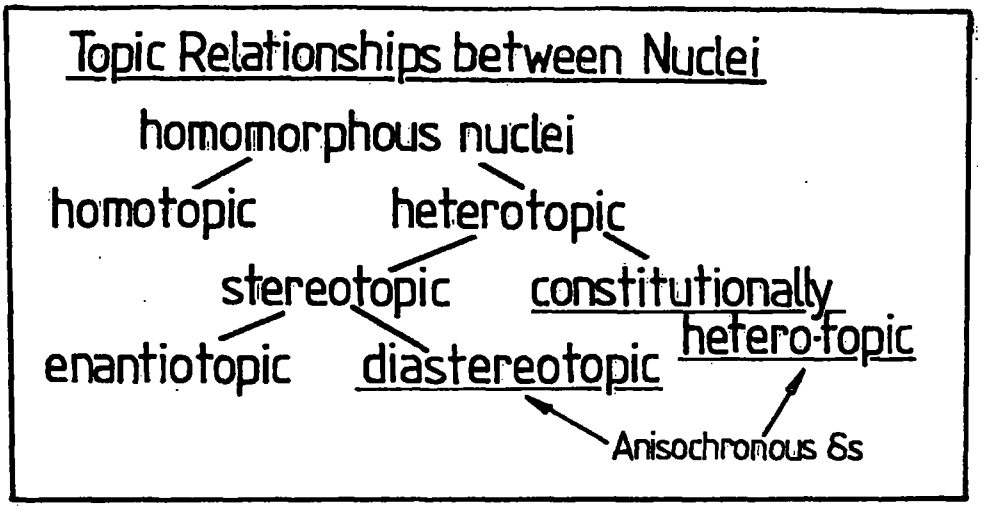
The majority of C.M.P.A. methods developed involve separation of α-amino acid enantiomers using a variation of Ligand Exchange Chromatography. A metal ion (Cu^{2+}, Ni^{2+} or Zn^{2+}) is present in solution capable of forming multidentate diastereomeric complexes containing a chiral ligand (the C.M.P.A.) and one of the solute enantiomers. The C.M.P.A. is usually an amino acid, amino acid derivative or chiral amine. Column requirements are simple but difficulties in detection can necessitate pre- or post column derivatisation. Gil-Av[85] and Linder[86] have been successful in resolving amino acids using this technique.

When enantiomers are separated on an achiral column using a C.M.P.A. the mechanics of separation are complex. Separation can result from a combination of differential stability of the diastereomeric complexes in the mobile phase, differential adsorbtion of the complexes themselves or adsorbtion of the C.M.P.A. onto the stationary phase so that the latter behaves as a C.S.P. The sense of stereoselectivity differs in each case and the various mechanisms may compete to degrees that vary with solute structure. Thus correlation of absolute configuration and elution order may become uncertain if extrapolation is carried too far from known examples.

The chromatographic techniques G.C. and H.P.L.C., particularly those involving chiral stationary phases, currently provide the most effective and accurate method of assay of enantiomeric excess.

1.4.1 Topism and N.M.R. Chemical Shift Non-equivalence[87,88]

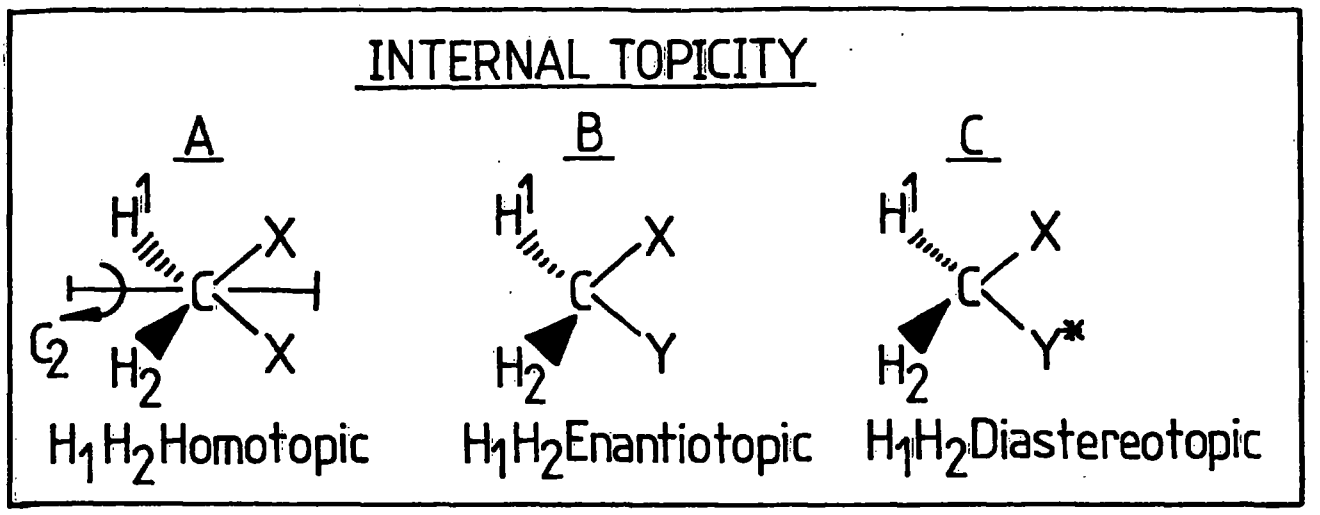
The concept of Stereotopicity introduced by Mislow and Raban[89] is extremely useful for predicting magnetic shielding anisochronicity in N.M.R. spectroscopy (i.e. chemical shift non-equivalence) on the basis of molecular symmetry. Nuclei are homotopic, or equivalent, when they are interchanged by rotation about a proper axis of rotation, C_n, otherwise they are heterotopic. Stereotopic nuclei are enantiotopic when they are interchanged by reflection symmetry (e.g. an improper axis of rotation, S_n), or they are diastereotopic when they are not permutable by any symmetry operation. Only diastereotopic or constitutionally heterotopic nuclei exhibit different physical and chemical properties, in an achiral medium.

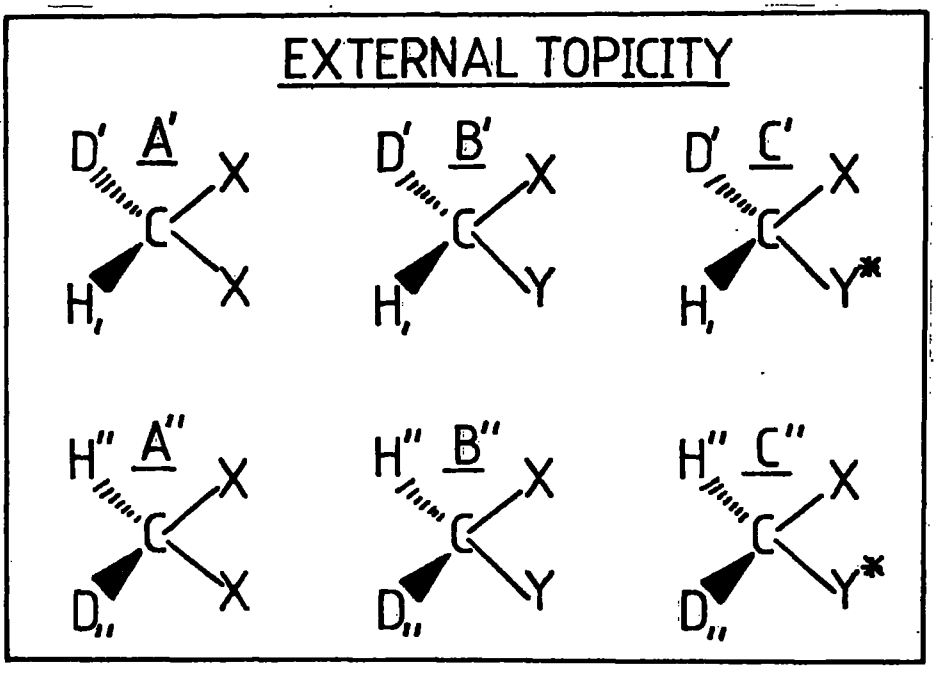


On the time scale of the N.M.R. experiment isochronicity (chemical shift equivalence) arises from symmetry equivalence of homotopic or enantiotopic nuclei whilst anisochronicity (chemical shift non-equivalence) arises from symmetry non-equivalence of diastereotopic nuclei.

Enantiotopic nuclei are rendered diastereotopic in a chiral, non-racemic environment. Thus in contrast to homotopic nuclei, isochronous enantiotopic nuclei can be transformed into anisochronous diastereotopic nuclei via desymmetrisation as a result of interaction with chiral environments (e.g. C.S.P.s or C.M.P.A.s, Chiral solvents or Chiral Shift Reagents).

In addition, it is important to distinguish between internal topicity, the symmetry comparison between nuclei in the same molecule (i.e. an intramolecular relationship), and external topicity, the symmetry comparison between nuclei in different molecules (i.e. an intermolecular relationship).





Stereotopic relationships may not only be classified by symmetry criteria but also be recognised by a simple substitution test.[89] This involves replacement, in turn, of each of the two groups in question by an achiral test group not already present in the molecule (e.g. ^{1}H replaced by ^{2}H). Inspection of the intermolecular relationship (i.e. external topicity) between the resulting structures reveals the stereotopic relationship of the homomorphous groups.

1. Replacement of H_1 and then H_2 by D in A gives A' and A'' which are identical. H_1 and H_2 are internally homotopic.
2. Replacement of H_1 and then H_2 by D in B gives B' and B'' which are enantiomers being related by reflection plane (the plane of the page). H_1 and H_2 are internally enantiotopic.

3. Replacement of H_1 and then H_2 by D in C gives C' and C'' which are diastereoisomers. H_1 and H_2 are internally diastereotopic.

Alternatively comparison of the homomorphous nuclei (i.e. either H or D) in the examples above shows:

1. A' and A'' are the same molecule.
   i.e. H' and H'' are externally homotopic
   and D' and D'' are externally homotopic.
2. B' and B'' are enantiomers, related by a reflection plane.
   i.e. H' and H'' are externally enantiotopic
   and D' and D'' are externally enantiotopic.
3. Introduction of the chiral group Y* of the same configuration destroys the symmetry plane so that nuclei, such as H' and H'' in the resulting diastereomers C' and C'' are externally diastereotopic.

Hanson proposed[90] the term "prochiral" to define molecules such as B "...in which a chiral assembly is obtained when a point ligand {H_1 or H_2} in a finite non-chiral assembly is replaced by a new point ligand {D}".

Only external stereotopic relationships are important in the prediction of chemical shift non-equivalence.[91] Externally enantiotopic nuclei are rendered externally diastereotopic (and hence distinguishable by N.M.R. spectroscopy) by Chiral Derivatising Agents, Chiral Solvating Agents or Chiral Shift Reagents. It is this property that permits the use of N.M.R. in detection of enantiomers and measurement of enantiomeric excess. Research carried out in this area, including that currently described, concentrates on the development of new or

improved chiral reagents designed to maximise chemical shift non-equivalence in as many classes of compounds as possible and thus afford a universal enantiomeric excess assay technique. Occurrence of internally diastereotopic nuclei in enantiomers can complicate the spectrum since in a chiral environment these become externally diastereotopic leading to a doubling of the resonance signals.

The degree of chemical shift non-equivalence for diastereotopic nuclei may not always be large enough to lead to observable signal splitting under certain conditions. In these cases a change of solvent, a lowering of temperature or an increase in spectrometer frequency may serve to remove accidental degeneracy.

Whilst enantiomeric nuclei are certainly isochronous in achiral media they may couple differently to an adjacent nucleus (i.e. they may be anisogamous).[92] It is worth remembering that the term "magnetic non-equivalence" encompasses both anisochrony and anisogamy and does not automatically imply chemical shift non-equivalence.[87]

1.4.2 Chiral Methyl Groups

Stereotopicity[91] is a specific example of two much more general concepts. Chirotopicity, which describes the topic environment of the substituent groups at the chiral centre. Stereogenicity, which incorporates not only enantiomers and diastereoisomers but also all molecules in which exchange of substituents generates structurally distinct species. These two ideas are best illustrated by a pair of examples. The halogen atoms in CHBrClF are chirotopic but non-stereogenic,

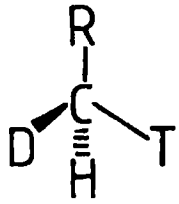
whilst the carbon atoms in the CHCl groups of 1,2-dichloroethene are stereogenic but achirotopic.

Perhaps the simplest chiral assembly consists of a stereogenic carbon atom with four different chirotopic but non-stereogenic substituents. Two distinct tetrahedral structures are possible which are non-superimposable mirror images of each other. These enantiomers may be assigned to have either the (R) or (S) configuration by application of the Cahn-Ingold-Prelog rules.[93]

A methyl group, CH_3R, which has three fold rotational symmetry, is a (pro)^2-stereogenic [pro-prochiral] centre, the three hydrogens are homotopic and are completely indistinguishable. If a methyl group was generated in an environment where free rotation was prevented then the methyl hydrogens would become chirotopic, but would remain non-stereogenic. The time constant for rotation of an unhindered methyl group, in ethane for example, is $10^{10}\,sec^{-1}$, thus a complete freezing-out of rotation is possible, in principle, although it is <u>extremely</u> unlikely to occur under conditions encountered during normal work.

Methyl groups provide useful probes in biochemical experiments, particularly in enzyme studies, and although they contain no elements of chirality, i.e. they are non-stereogenic, reactions involving methyl groups often proceed stereoselectivity. For example conversion of CH_3X to CH_3Y may occur with inversion or retention of configuration, protonation of a methylene group to give a methyl group may occur at only one face. The steric course of such reactions is <u>latent</u>, it cannot be inferred from a study of the products. However, if an

achiral CH_3 group is replaced by a chiral methyl group then the stereochemistry of transformations such as those above is evident from the configuration of the products. A chiral methyl group, is obtained by sequential isotope substitution of hydrogen by deuterium, (^2H), and tritium, (^3H), via stereospecific chemical or enzymic reaction.

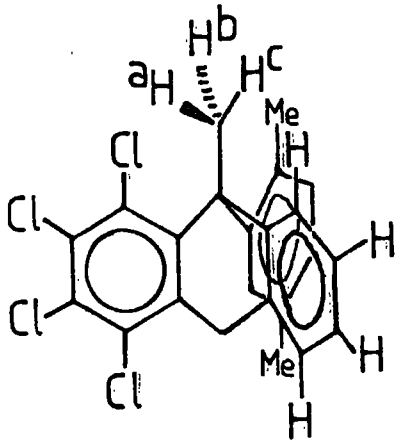


Physical separation of RCHDT enantiomers is virtually impossible, synthesis is relatively straight-forward, the conceptually difficult problem is the analysis of a chiral methyl group of unknown configuration.

The classical method of distinguishing enantiomers by their ability to rotate the plane of polarised light is not applicable since rotations are very small and only a small fraction of the molecules carry tritium. Floss[94] has cast doubt that any of the currently available spectroscopic techniques are, or will ever be, able to provide a practical method for determination of (R) or (S) configurations of chiral methyl groups. At present the practical solutions to this problem are all based on carrying out a reaction in which one of the hydrogens is replaced by a different group. Observation of the kinetic isotope effect for the replacement reaction together with careful study of the hydrogens remaining in the product allow the configuration of the original methyl group to be deduced. The approach is complicated by the fact that a

racemic methyl group will give <u>six</u> different structures when either ^{1}H, ^{2}H, or ^{3}H is replaced in the two enantiomers.

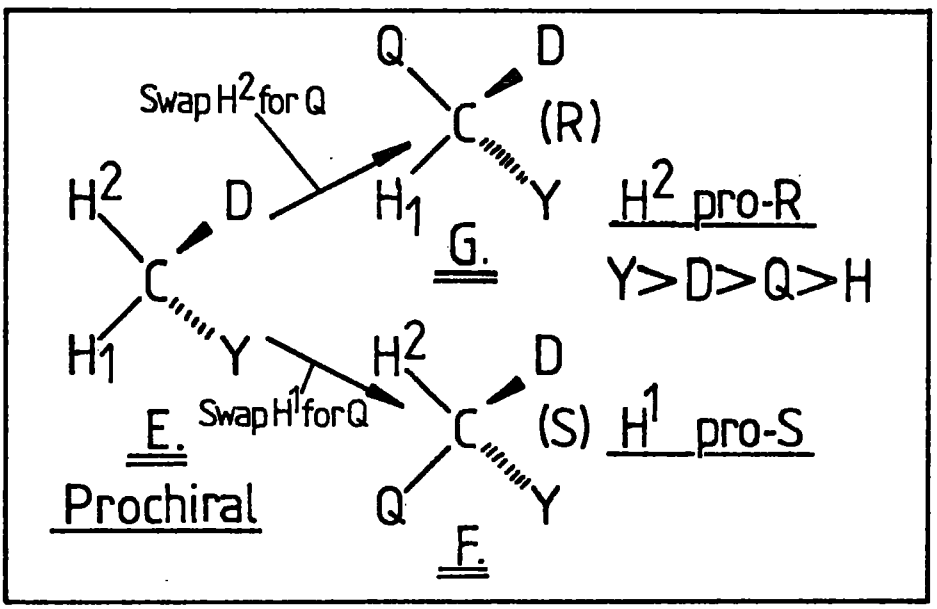
For ^{3}H N.M.R. to be effective in analysis of chiral methyl groups it is necessary for the group to preferentially populate one of the three possible rotamers. Ordinarily the differences in energies for the rotamers are minute - the atoms differ only in their number of neutrons. Hence the problem is to "design" a molecule in which energy differences between rotationally related conformations are accentuated. For example with 1,2,3,4-tetrachloro-5,8,9-trimethyltriptycene at -90°C three resonances are observed for the 9-methyl protons.[91]



1,2,3,4-tetrachloro-5,8,9-trimethyl triptycene

Tritium is usually generated by neutron bombardment of hydrogen in a nuclear reactor. It is a radioactive element, which causes handling problems. Consequently it is usual to carry out preliminary work without the tritium isotope and incorporate the labelled nucleus in the final stages of the study. A good model for a chiral methyl group is a deuterium

labelled methyl group, YCH_2D. If the Y group is achiral the two hydrogens are pro-stereogenic [pro-chiral].[90] If in E, (below), H_1 is replaced by Q and it is assumed that the priority sequence is Y>D>Q>H then the assembly obtained, F, has the (S) configuration and hence H_1 is known as the pro-S hydrogen. Alternatively if in E, H_2 is replaced by Q then the assembly obtained, G, has the (R) configuration and hence H_2 is known as the pro-R hydrogen. Further, if Y represents one configuration of a chiral substituent then H_1 and H_2 are diastereotopic and hence exhibit different N.M.R. chemical shifts.



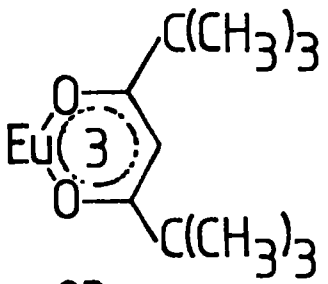
The observed chemical shift non-equivalence for diastereotopic methylene protons arises from two sources. First the intrinsic diastereotopicity, i.e. the inherent chemical shift difference between diastereotopic nuclei, and second the preferential population of certain low energy molecular conformations.[95] It

has been agreed that the first effect can usually be ignored in ^1H N.M.R. spectroscopy,[96] experimental results showing $\Delta\delta$ is a function of the separation of the chiral and pro-chiral centres, of the molecular rigidity and of temperature and solvent,[97,98] (i.e. factors which are directly related to molecular configurations), support this view. Hence the magnitude and sense of $\Delta\delta$ for diastereotopic methylene protons provides a useful probe for molecular configurations in molecules where chiral methyl group rotation is likely to be restricted.

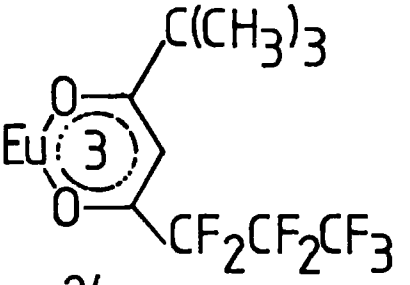
1.5 N.M.R. Determination of Enantiomeric Excess using Chiral Lanthanide Shift Reagents

Hinkley[99] demonstrated in 1969 that paramagnetic tris(β-diketonato) lanthanide(III) chelates are capable of inducing large shifts in the N.M.R. spectra of organic substrates in solution. The substantial shifts of resonance peaks, denoted $\Delta\delta$, observed were accompanied by only slight line broadening. The most popular achiral paramagnetic N.M.R. shift reagents are tris(2,2,6,6-tetramethylheptane-3,5-dionato)europium, Eu(thd)$_3$ ≡ tris(dipivoylmethanato)europium, Eu(dpm)$_3$,(23),[100] and tris(1,1,1,2,2,3,3,-heptafluoro-7,7,-dimethyl-4,6-octanedianato)europium, Eu(fod)$_3$, (24),[101] as well as the corresponding praseodymium and ytterbium tris chelates.
The induction of resonance shifts, $\Delta\delta$, depends on the establishment of a fast, reversible molecular association equilibrium between the Lanthanide Shift Reagent, which is able to expand its co-ordination number beyond six, and the organic donor substrate, which must contain nucleophilic donor

functionalities such as amino, hydroxy or carbonyl groups. The f-shell electrons of the rare earth metals are not available for covalent bonding, consequently induced shifts must result only from dipolar interactions through space, sometimes known as pseudo-contact interactions, rather than from direct contact interactions through bonds. The pseudo-contact shift decreases with the cube of the distance of the nucleus from the metal ion and also depends on the angle between the principal magnetic symmetry axis and the observed nucleus.



23 Eu(thd)$_3$

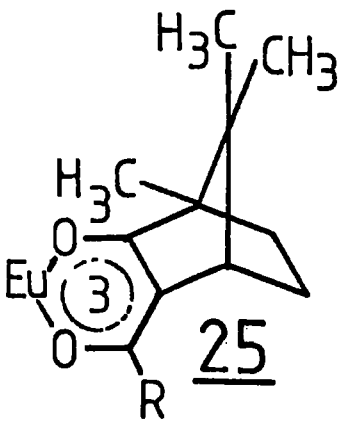


24 Eu(fod)$_3$

Achiral Lanthanide Shift Reagents are used primarily to simplify proton spectra by shifting peaks to less congested areas of the spectrum. Further, since the magnitude of $\Delta\delta$ depends directly on distance from the binding site in the organic substrate, L.S.R.s effectively differentiate between accidentally isochronous resonance signals and can yield information pertaining to molecular configuration and conformation in solution.

Following Hinckley's[99] report on the simplification of N.M.R. spectra by use of L.S.R.s, Whitesides and Lewis[46] observed a difference in the induced shifts $\Delta\Delta\delta_{S,R}$ in the proton spectrum of racemic α-phenylethylamine in the presence of the Chiral Lanthanide Shift Reagent, (C.L.S.R.), tris-(3-t-butyl-hydroxymethylene-(1R)-camphorato)europium(III), (25). The

induced high frequency shift for the methine proton is 17ppm. The chemical shift non-equivalence for (R) and (S) enantiomers is 0.05ppm. The corresponding praseodymium complex showed a low frequency shift of similar magnitude but with concomitant line broadening. C.L.S.R.s such as (25a) are rather poor acceptors, so that chemical shift non-equivalence is only observed with strong donors such as amines and amides. The perfluorocamphorato chelates of lanthanides such as Tris(3-trifluoro-methyl-hydroxymethylene-(1R)-camphorato)-europium(III), Eu(tfc)$_3$ [or Eu(facam)$_3$], (25b),[102] or tris(3-heptafluorobutyryl-(1R)-camphorato)europium(III), Eu(hfc)$_3$, (25c),[103] have been used extensively for differentiation of the enantiomers of chiral alcohols, aldehydes, ketones, esters, oxiranes, and sulphonamides.



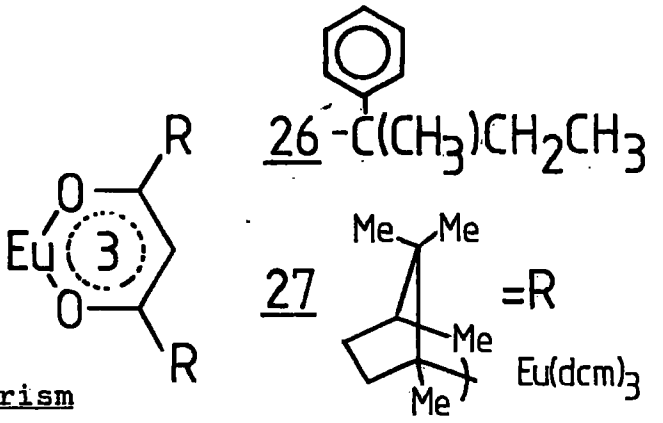
25

a R=C(CH$_3$)$_3$

b R=CF$_3$ Eu(tfc)$_3$

c R=CF$_2$CF$_2$CF$_3$ Eu(hfc)$_3$

Whitesides has prepared a number of C.L.S.R.s from terpene ketones other than camphor, such as menthone, pulegone, and carvone but none are superior to the original camphor based C.L.S.R. Acetylacetonate type ligands, in which the pendant methyl groups are replaced by chiral non-rigid groups give trichelate lanthanide complexes such as tris{(R,R)-3,7-diphenyl-4,6-nonanedianato}europium(III), (26), or tris{(R,R)-dicampholylmethanato}europium, Eu(dcm)$_3$, (27) which are particularly effective for the resolution of strong donor molecules.



1.5.1 C.L.S.R. Isomerism

Hexa-coordinate lanthanide complexes of symmetric diketones are chiral and exist in two enantiomeric forms. These Λ and Δ isomers interconvert rapidly on the N.M.R. time scale.[104] Thus with a chiral ketone ligand there are four rapidly interconverting diastereoisomers (cisΛ, cisΔ, transΛ and transΔ). Each cis isomer has four potential sites for donor/acceptor interactions whilst each trans isomer has two such sites. Fortunately a detailed knowledge of the chelate-donor structure in solution is not required to interpret the N.M.R. results obtained with these reagents. The true complexity of the system should not be forgotten, however, since it can manifest itself in unusual ways in the data obtained. For example Fraser[105] and Evans and deVillardi[106]

have observed that $\Delta\Delta\delta$ varies with some C.L.S.R./organic substrate mixtures for ten minutes after preparation due to equilibration between all the possible C.L.S.R./substrate complexes.

1.5.2 Resolution Mechanism and Assignment of Absolute Configuration

The chemical shift non-equivalence of enantiomers in the presence of a C.L.S.R. has been attributed to two mutually dependent contributions which are related to the stability and geometry of the diastereomeric complexes in solution.[46,104]

1. The equilibrium constants for association of the C.L.S.R. with each substrate enantiomer differ giving rise to different induced shifts. Resonance signals in the spectrum of the enantiomer which is more strongly bound would be shifted more than those in the spectrum of the weakly bound enantiomer. The sense of non-equivalence would be the same for all resonances.
2. Goldings work[45] with C.L.S.R. (25a) as a C.S.P. in G.C. shows that there is an intrinsic chemical shift difference between the two diastereomeric association complexes formed due to molecular geometry and the relative spatial displacement of nuclei in the complex. In this case the sense of non-equivalence would not necessarily be consistent for all resonances. Reversals should be expected, such as those observed by Capillon and Lacombe in a series of para-substituted benzhydrols.[107]

Most C.L.S.R.s function via a combination of these two effects and as a result, the sense of chemical shift non-equivalence is unpredictable. This limits the utility of the method for the

assignment of absolute configuration.

The use of C.L.S.R.s for the correlation of absolute configuration of compounds to a certain homologous series has been established by observation of mixtures of known enantiomer composition for α-amino acid esters,[108] certain 1-deuterated primary alcohols,[109] alkyl-aryl carbinols and secondary carbinols.[110] However, in view of the failure to assign absolute configuration in structurally related series of compounds, it is generally accepted that such assignments using C.L.S.R. data will be ambiguous. Most disturbing is the observation that the sense of $\Delta\Delta\delta$ may vary not only from one nucleus to another in the same spectrum but also as a function of the C.L.S.R./substrate concentration ratio.[111,112]

Although the chemical shift non-equivalence observed using a C.L.S.R. decreases with the decreasing reagent enantiomeric purity, the relative areas under peaks corresponding to diastereomeric complexes do not alter. i.e. since the C.L.S.R. approach is absolute, the measurement of enantiomeric excess by integration is not impaired by low C.L.S.R. enantiomeric excess.

1.5.3 Application of C.L.S.R.s

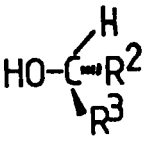
Although, in principle, any compound with functionalities capable of binding to a C.L.S.R. should lend itself to the determination of enantiomeric composition certain conditions must be met, for example the proximity of the chiral group to the functional group undergoing association. The most common nucleus studied is ^{1}H but ^{2}H, ^{13}C and ^{31}P are also suitable provided that instrumental conditions have been optimised to

provide fully relaxed spectra so that the integrals are representative of the enantiomeric composition. In cases where resonance peaks are overlaid or where it is necessary to establish the enantiomeric nature of the resolved peaks then the C.L.S.R. of opposite chirality can be employed. This causes peak reversal for enantiotopic nuclei due to formation of the complementary pair of diastereoisomers. Sullivan,[111] Schürig[88] and Fraser[105] have presented extensive reviews of the chiral organic substrates which have been successfully resolved using C.L.S.R.s. Substrates studied include primary, secondary and tertiary amines and alcohols, diols, ketones, aldehydes, esters, ethers, sulphoxides, amides, phosphine oxides and pheromones. Table 3 shows the results obtained for secondary alcohols in the presence of $Eu(hfc)_3$. Chiral Lanthanide Shift Reagents are usually employed in organic solvents, notably $CDCl_3$ or CCl_4, although europium(III)-(R)-propylenediamine-tetra-acetate ion has been used in aqueous solution to assay the enantiomeric purity of chiral hydroxy-, amino- and unsubstituted carboxylic acids.[113]

A limitation in the use of C.L.S.R.s is that the substrate must be at least a moderate donor in order to effect co-ordination with the Lanthanide ion. Consequently no induced shifts are obtained with saturated hydrocarbons and only very slight shifts with halogen compounds and π systems such as olefins or aromatics. Addition of silver heptafluorobutyrate to the mixture of an olefin and a C.L.S.R., however, does cause induced ^1H resonance shifts.[114] Wenzel and Sievers[115] have termed a related system, $Eu(fod)_3$ and Ag(fod) for inducing shifts in olefins and aromatics, a "binuclear L.S.R.".

Table 3

Proton Chemical Shift Non-equivalence Induced in Chiral Secondary Alcohols by Eu(hfc)$_3$



No	R_2	R_3	Magnitude[a] and Sense[b] of Chemical Shift Non-Equivln				C.L.S.R/ Alcohol
			R_2	R_3	CH		
1	CH_3	CH_2CH_3	0	0.06 Lf	0		0.53
2	CH_3	$CH(CH_3)_2$	0.07 Lf	0.01 Lf	0		0.56
3	CH_3	$C(CH_3)_3$	0.04 Lf	0.13 Lf	0.04	Lf	0.56
4	CH_3	$(CH_2)_5CH_3$	0.04 Lf		0		0.62
5	CH_3	CF_3	0.06 Lf		0.26	Hf	0.58
6	CH_3	C_6H_5	0.06 Lf	0	0.34	Hf	0.52
7	CH_2CH_3	C_6H_5		0	0.27	Hf	0.57
8	$CH_2CH_2CH_3$	C_6H_5	0.03 Lf	0	0.44	Hf	0.50
9	$CH(CH_3)_2$	C_6H_5	0.03 Lf	0.08 Lf	0.29	Hf	0.57
10	$C(CH_3)_3$	C_6H_5	0.14 Lf	0.22 Lf	0.09	Lf	0.52
11	$(CH_2)_3CH_3$	$C(CH_3)_3$		0.26 Lf	0.65	Lf	0.55
12	$C(CH_3)_3$	CF_3	0.09 Lf		0		0.59

a) In parts per million.

b) Sense of chemical shift non-equivalence is noted for the (R) enantiomer of the chiral alcohol.

Lf indicates chemically shifted to lower frequency relative to the corresponding group in the (S) enantiomer.

Hf indicates chemically shifted to higher frequency relative to the corresponding group in the (S) enantiomer.

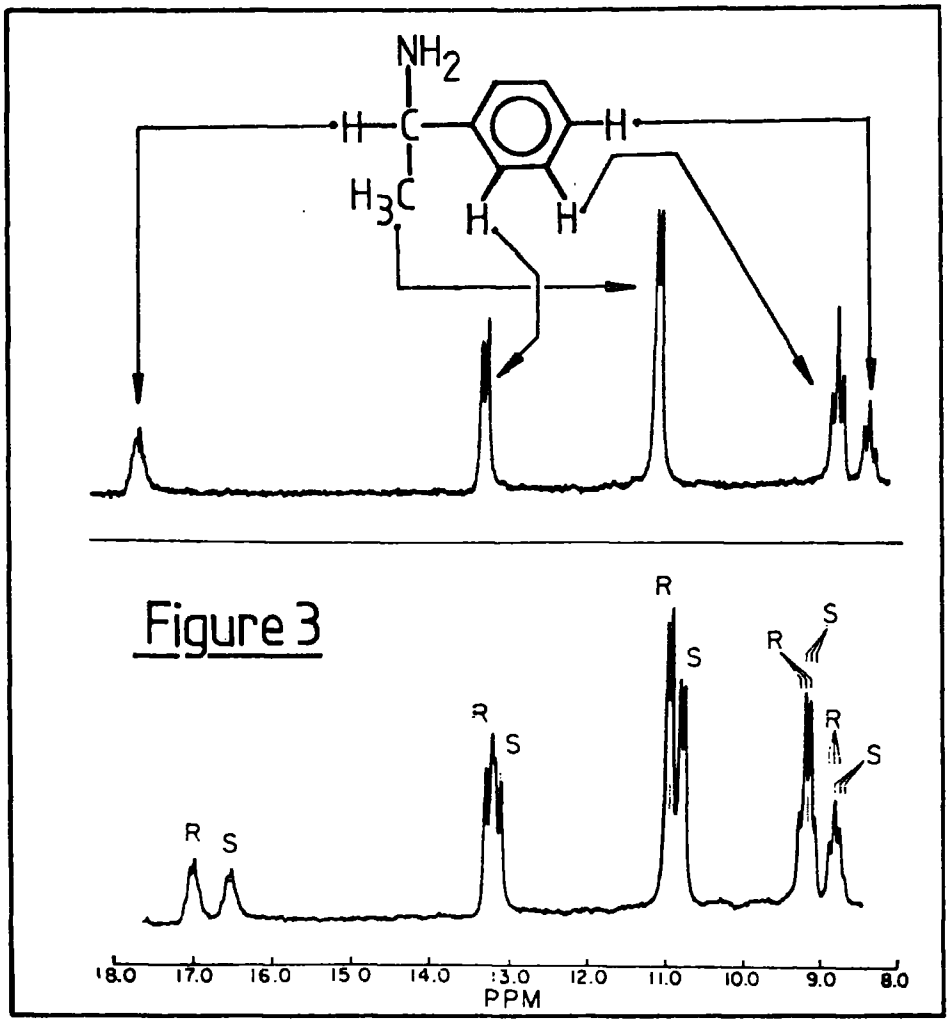


Figure 3

Spectra of solutions prepared from (S)-α-phenylethylamine (10μL) (upper), and a mixture of (R)- and (S)-phenylethylamine (7 and 5μL, respectively),in 0.3 ml of a carbon tetra-chloride solution of (25)≈0.15 M. The chemical shift scale applies only to the spectrum of the mixture; that of the pure (S) enantiomer was displaced slightly to higher frequency due to differences in concentrations of the samples.

Offermann and Mannschreck[116] have shown that $Eu(hfc)_3$, $Pr(hfc)_3$ and $Yb(hfc)_3$ each in conjunction with Ag(fod), gave good resolutions of selected chiral olefins and aromatics in both their ^1H and ^{13}C spectra.[117]

1.5.4 Accuracy of Enantiomeric Excess Determination using C.L.S.R.s

The accuracy of enantiomeric excess determination by C.L.S.R. depends on the accuracy of the integration of the resolved signals for non-equivalent nuclei. Highest accuracies are to be expected for well resolved peaks and simple spin systems. Reported enantiomeric purity determinations with C.L.S.R.s are in good agreement, (i.e. ±2% in 30%), with other methods.[103,112] A variation of ±5% was observed for e.e. determination of α-phenylethylamine using a C.L.S.R.[118] The best claimed deviation is ±2%[119] for e.e.≈40-60%, but Whitesides has shown that for values of e.e.>90% then the error is typically ±10%.[120] Obviously the N.M.R. C.L.S.R. approach can not compete with gas chromatography in determining precise enantiomeric ratios of e.e.>95%.

1.5.5 Temperature Effects on C.L.S.R.s

A detailed study of the influence of temperature on the magnitude of $\Delta\Delta\delta$ has shown that low temperature C.L.S.R. N.M.R. spectroscopy offers important advantages for the enantiomeric analysis of weakly co-ordinating substrates and of compounds which owe their chirality to only small differences in substituent groups e.g. CH_3 versus C_2H_5. Enantiomer shift differences were observed for 2-methyl-1-butanol, 2-nitro-butane, 2-butanol and 2-cyanobutane, but only at low temperature (-30°c). In the case of more strongly co-ordinating

substrates, low temperature measurement should be avoided since line broadening may become excessive below ambient temperature. [Achiral Lanthanide Shift Reagents have also been used to enhance the resolution of signals in systems where the enantiomers have been chemically converted to diastereoisomers or dissolved in chiral solvents. Pirkle and Sikkenga used $Eu(fod)_3$ to alter the magnitude and sense of non-equivalence for racemic sulphoxides in the presence of optically active perfluoroalkyl carbinols].

1.6 N.M.R. Determination of Enantiomeric Excess using Chiral Derivatising Agents

An enantiomeric mixture can be converted to a pair of diastereoisomers by chemical reaction with an appropriate Chiral Derivatising Agent, (C.D.A.). The externally enantiotopic groups in the original enantiomers are converted to externally diastereotopic groups which are anisochronous. Unlike a Chiral Solvating Agent, (C.S.A.), or Chiral Lanthanide Shift Reagent, (C.L.S.R.), which rely on exchange of substrate between the chiral reagent complex and the dissociated species, a C.D.A. forms a discrete species free from the effects of chemical exchange. As a result the magnitude of the chemical shift non-equivalence, $\Delta\delta$, is usually larger than that observed in the presence of a C.S.A.

There are a number of disadvantages in the use of a C.D.A.:

1. An additional chemical reaction is necessary before N.M.R. analysis of the sample can be performed.

2. Differential reaction rates of either (R) or (S) C.D.A. with (R) and (S) substrate enantiomers will lead to spurious enantiomeric composition values and, if the minor enantiomer reacts significantly faster than the major enantiomer, then assignment of absolute configuration could be made erroneously. Large excess of C.D.A. (which is wasteful of reagent) can be employed to ensure complete reaction.
3. The stereochemical integrity of the derivatisation and purification steps must be rigorously established, there must be no possibility of substrate racemisation accompanying derivatisation.
4. The C.D.A. must be enantiomerically pure, the presence of a small quantity of the opposite C.D.A. enantiomer will reduce the observed enantiomeric excess below the true value. As an example, if a mixture of an unknown contains 90% of the (R) enantiomer, (i.e. e.e. = 80%) and the (R)-C.D.A. is contaminated with 5% of the (S) enantiomer, the (S)-C.D.A. will react with the (R) substrate enantiomer to give a product which is enantiomeric with the derivative from the (R)-C.D.A. and the (S)-substrate. Since the chemical shift for (R)-C.D.A.-(R)-substrate and (S)-C.D.A.-(S)-substrate will be identical and likewise the chemical shifts for (R)-C.D.A.-(S)-substrate and (S)-C.D.A.-(R)-substrate, the observed enantiomeric ratio will be 86:14 (R):(S)-substrate (i.e. e.e.=72%) compared with the true value of 90:10.

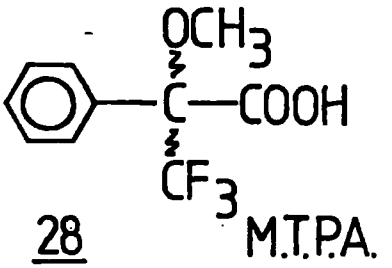
Despite these problems chiral derivatisation is the most widely used N.M.R. technique for enantiomer resolution. C.D.A.s tend to be simple molecules whose enantiomers are readily accessible via asymmetric synthesis. The derivatisation steps usually

involve simple reactions: selective reaction with enantiomers or racemisation of substrate during derivatisation have been avoided by careful C.D.A. design or shown to be non-existent in the case of most popular C.D.A.s. The method is reliable which is not always the case with C.S.A.s. The shift differences for diastereomeric groups are sufficiently large to permit integration affording enantiomeric excess measurements to within ±1%.[121]

1.6.1 Chiral Acids as C.D.A.s

Chiral acids react with chiral alcohol enantiomers to give diastereomeric esters or with amine enantiomers to give diastereomeric amides. Mislow and Raban[122] first described chemical shift non-equivalence for diastereomeric α-methyl-phenylacetic acid esters of 1-(2-fluorophenyl)-ethanol. Their diastereomeric mixture showed a 68:32 ratio for RR/SS to RS/SR despite the fact that racemic starting materials were used. It was concluded that partial racemisation had occurred during derivatisation. Mosher and coworkers[123] examined the application of a series of α-substituted phenylacetic acids as C.D.A.s for N.M.R. analysis of carbinols and also found that these reagents are prone to racemisation, especially on reaction with hindered carbinols. It was found that epimerisation was occurring α to the acid carbonyl group and hence the suggestion was made that acids without an α hydrogen should be resistant to racemisation. On the basis of their observation Mosher and Dale[124] developed the C.D.A. α-methoxy-

α-trifluoromethyl-phenylacetic acid, (M.T.P.A), (28), known as the Mosher reagent.



28 M.T.P.A.

This reagent has several advantages:

1. It is stable towards racemisation even under severe conditions of acidity, basicity and temperature because it does not have an α-hydrogen.
2. Derivatives of M.T.P.A. generally show substantial chemical shift differences in the signals of the diastereomeric groups.
3. The presence of the trifluoromethyl group permits the use of ^{19}F N.M.R. spectroscopy in addition to ^{1}H N.M.R. determination.
4. Derivatives of M.T.P.A. are reasonably volatile and can consequently be analysed by gas-liquid chromatography, (G.L.C.), and H.P.L.C. as well as by N.M.R. methods.

Derivatisation involves reaction of M.T.P.A.-chloride with the chiral alcohol or amine enantiomers, giving the corresponding diastereomeric esters or amides. In the case of hindered carbinols special conditions may be required to force the reaction to completion. Often, adding an excess of M.T.P.A. is sufficient to ensure quantitative reaction. 4-(Dimethylamino)-pyridine has been recommended as a suitable acylation

catalyst.[125] O-Methylmandelic acid, (29), has been used as a C.D.A. for secondary carbinols and primary carbinols that owe their chirality to deuterium substitution.[126] Mandelic acid, (30), and atrolactic acid, (31), have also been studied in this context. Dale and Mosher[127] in an authorititive paper compared all four acids. Resolution of methyl-tert-butyl- carbinyl esters with each acid C.D.A. is shown in (Figure 4).

Dale and Mosher proposed a simple model for correlating the sense of chemical shift non-equivalence with the absolute configuration of the alcohol (or amine) moiety of the diastereomers formed with acid C.D.A.s. With Mandelic acid, (30), and Atrolactic acid, (31), (Figure 5), the C-X, C=O and carbinyl C-H are coplanar, the conformation can be considered to be "locked" by the hydroxyl function hydrogen bonding to the carbonyl group. Inspection of the magnetic shielding environment of the alcohol/amine substituents R_2 and R_3 in the two diastereomers, I and II, shows that in I R_2 is close to the anisotropic phenyl ring whilst R_3 is remote; in II the situation is reversed. The alcohol functionality is replaced by an O-methyl group in M.T.P.A. and O-methyl mandelic acid. For M.T.P.A. a model similar to those proposed above, (Figure 6) correctly predicts the observed <u>reversal</u> of the sense of chemical shift non-equivalence for the substituents R_2 and R_3. In the case of O-methyl mandelic acid models based on those for "hydrogen bond locked" mandelic acid have been proposed by Dale and Mosher,[127] Yamaguchi[121] and Rinaldi[128] to predict sense of chemical shift non-equivalence, (Figure 7).

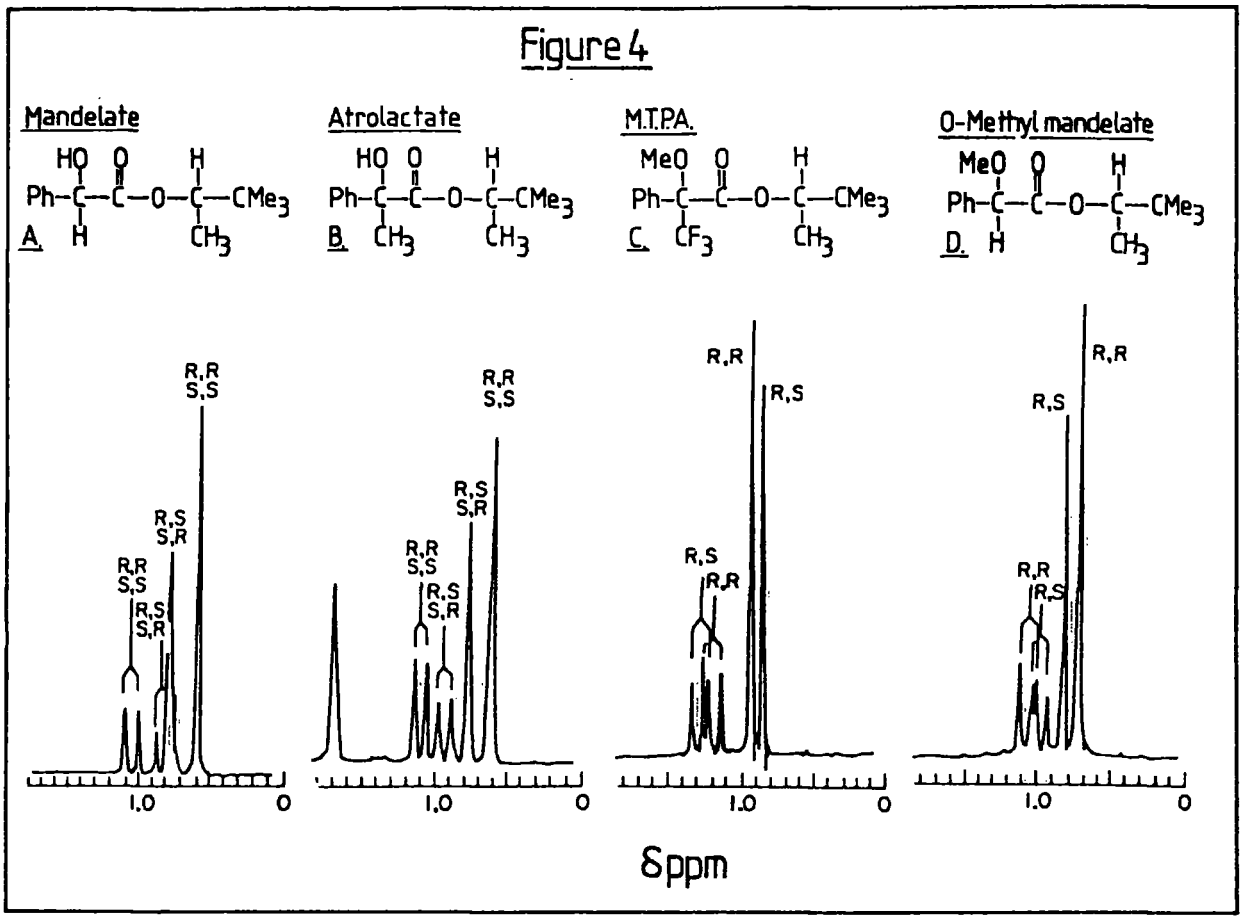


Figure 4. 60MHz Proton N.M.R. spectra of methyl-tert-butyl-carbinyl esters.

A). Mandelate, prepared by reduction of (R,S)-benzylformate ester with $LiAl(O\text{-}t\text{-}Bu)_3H$ at 3°C in THF to give a 22% excess of R,R-S,S diastereoisomer mixture over the R,S-S,R isomer mixture.

B). Atrolactate, prepared by reaction of (R,S)-benzoformate with methylmagnesium iodide in ether to give 18% excess of the R,R-S,S diastereoisomer over the R,S-S,R isomer mixture.

C). α-Methoxy-α-trifluoromethylphenylacetate (M.T.P.A. ester), prepared from (R)-(+)-M.T.P.A. and methyl-t-butyl-carbinol 7.8% enriched in the R-(-)-isomer.

D). O-Methyl-mandelate, prepared from S-(+)-O-methylmandelyl chloride and a sample of carbinol 11.7% enriched in the (R)-(-) isomer.

Figure 5

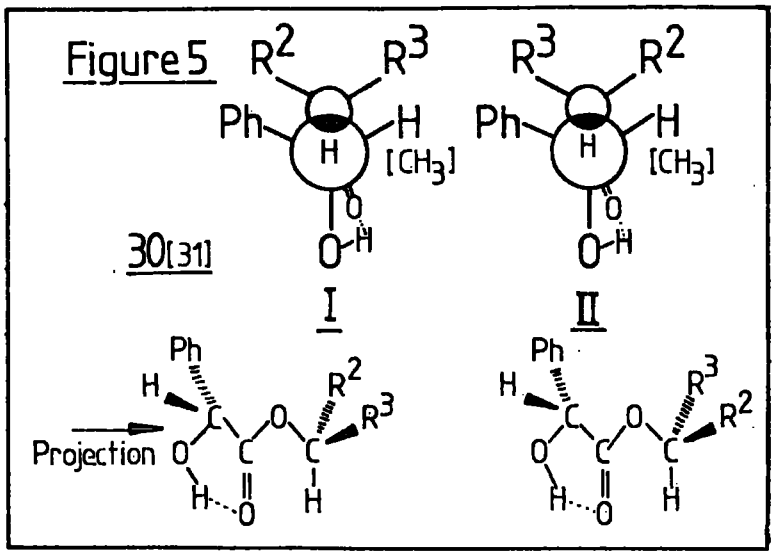


Figure 6

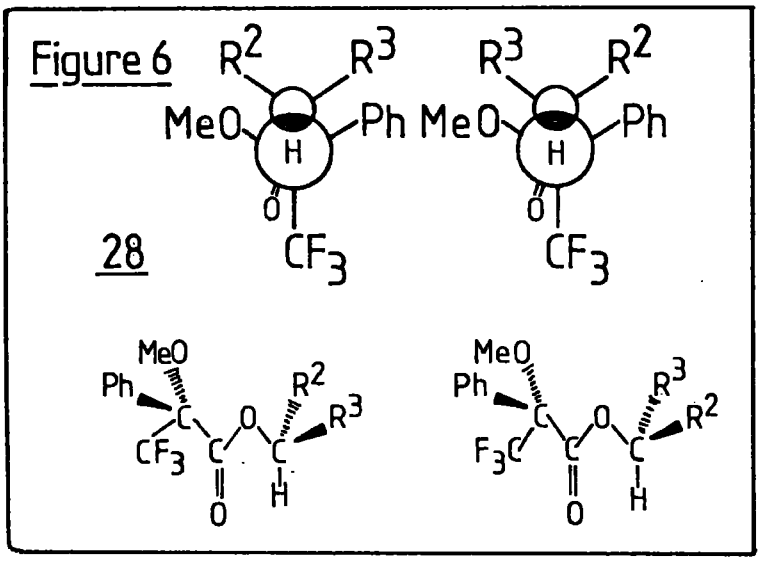
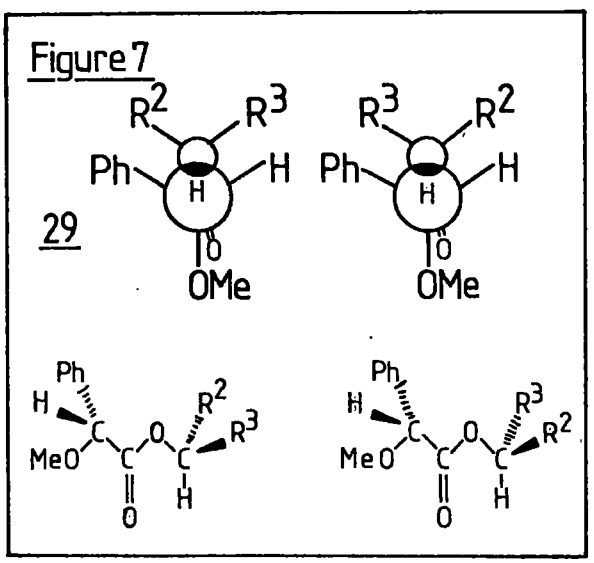


Figure 7



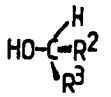
These models are equally successful in predicting chemical shift non-equivalence in esters or amides because both the O=C-O-C-H and O=C-NH-CH units, respectively, are coplanar. Several experimental facts justify this model. The carbinyl and α-protons exhibit little or no non-equivalence; non-equivalence is considerably reduced when the phenyl group is replaced by a cyclohexyl group; non-equivalence of the R_2 and R_3 substituents is always of opposite sense. In addition the observed shifts are much greater than those which usually accompany acylation to form acetate or phenylacetate esters.

Table 4 shows the results of derivatisation of a number of alcohols using M.T.P.A., O-methyl mandelic acid and mandelic acid in terms of the magnitude and sense of the observed chemical shift non-equivalence. Early work in correlating ^{19}F chemical shift non-equivalence with absolute configuration for the trifluoromethyl group in M.T.P.A. was discouraging because many diastereoisomers do not exhibit resolvable differences in their ^{19}F N.M.R. spectra. None of the models proposed to explain ^{1}H chemical shift non-equivalence is applicable, but a change in conformation involving rotation about the C-CO bond in the acid moiety gives two structures,[129] (Figure 8), which bring the CF_3 group into a different stereo-electronic arrangement with respect to the acid carbonyl group depending on the steric bulk of the substrate substituents.

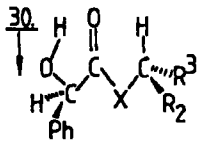
Pirkle and Simmons reported chemical shift non-equivalence for 2-butanol, 2-octanol and 6-hydroxy-2-methyl-2-heptene, when diastereomeric ester derivatives of α-(1-{9-anthryl}-2,2,2-trifluoroethoxy)acetic acid were prepared.[130]

Table 4

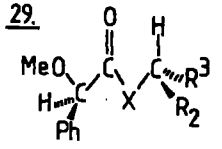
Proton Chemical Shift Non-equivalence for Ester Derivatives of Chiral Alcohols



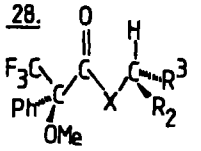
X=O



30.



29.

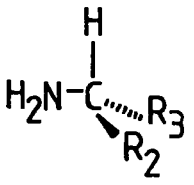


28.

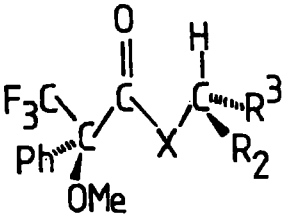
No	Alcohol Substituents		Mandelic Acid				O-Methylmandelic Acid				M.T.P.A			
			Magnitude of δ in ppm (Sense of non-equivalence)[a]											
	R2	R3	R2		R3		R2		R3		R2		R3		CF3[c]	
1	C_2H_5	CH_3	0.30	Lf	0.18	Hf	0.08	Lf	0.15	Hf	0.10	Hf	0.13	Lf	0.08	Hf
2	n-C_6H_{13}	CH_3	b		0.13	Hf	b		0.05	Hf	0.08	Hf	0.08	Lf	0.32	Hf
3	$CH(CH_3)_2$	CH_3	0.15	Lf	0.20	Hf	0.12	Lf	0.12	Hf	0.08	Hf	0.08	Lf	0.17	Hf
4	$(CH_2)_5CH_3$	CH_3					b		0.08	Hf						
5	$C(CH_3)_3$	CH_3	0.15	Lf	0.24	Hf	0.10	Lf	0.10	Hf	0.07	Hf	0.07	Lf	0.22	Hf
6	$C(CH_3)_3$	C_2H_5	0.22	Lf	0.34	Hf	0.13	Lf	0.10	Hf						
7	$C(CH_3)_3$	n-C_4H_9	0.32	Lf	b						0.06	Hf	b		0.25	Lf
8	CF_3	CH_3	0.17	Lf	0.21	Hf	b		0.12	Hf	0.12	Hf	0.41	Lf	0.28	Hf
9	Ph	CF_3	b		0.06	Hf					b		0.33	Lf	0.57	Hf
10	Ph	CH_3	b		0.15	Hf	b		0.08	Hf	b		0.06	Lf	0.51	Hf
11	Ph	C_2H_5	b		0.28	Hf	b		0.12	Hf	b		0.08	Lf		
12	Ph	$CH(CH_3)_2$	b		0.25	Hf	b		0.08	Hf					0.35	Hf
13	Ph	$C(CH_3)_3$	b		0.22	Hf	b		0.08	Hf	b		0.05	Lf	0.50	Hf

Table 5

Proton and Fluorine Chemical Shift Non-equivalence of Amide Derivatives of Chiral Amines



X=NH



No	Amine Substituents R2	R3	Magnitude of Δδ in ppm[a] R2	R3	CF3
1	CH_2CH_3	CH_3	0.07Hf	0.07Lf	0.04Hf
2	α-Naphthyl	CH_3	0.04Hf	0.11Lf	0.29Hf
3	Ph	CH_3		0.07Lf	0.25Hf
4	CH_2Ph	CH_3		0.08Lf	0.31Hf
5	$COOCH_3$	CH_3		0.08Lf	
6	n-C_6H_{13}	CH_3			0.01Hf
7	1-Menthyl	CH_3			0.10Hf

a) Hf = shifted to high frequency relative to same substituent in other diastereoisomer.

Lf = shifted to low frequency relevant to same substituent in other diastereoisomer.

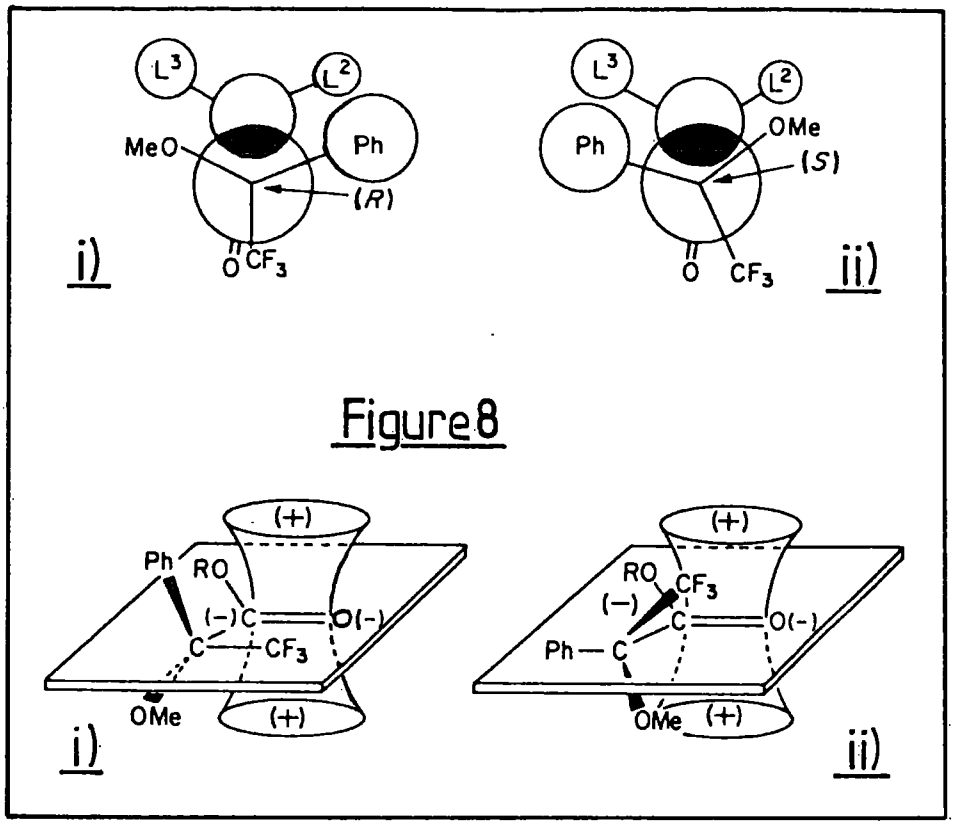


Figure 8

Configurational correlation models for ^{19}F N.M.R. shifts of diastereomeric M.T.P.A. derivatives. The projections show the orientations of L_2 (small) and L_3 (large) substituents relative to the large (Ph) and small (OMe) substituents of the M.T.P.A. moiety. In (ii) interactions between L_3 and Ph cause the CF_3 group to lie away from the deshielding region of the carbonyl group relative to (i) as seen in the lower diagrams.

Jacobus and coworkers first reported[126] chemical shift non-equivalence for a number of mandelamides derived from chiral amines. Since then, M.T.P.A. and α-(1-{9-anthryl}-2,2,2-trifluoroethoxy) acetic acid have been used extensively to study the enantiomeric purity of amines by conversion to diastereomeric amides. Table 5 lists the magnitude and sense of chemical shift non-equivalence for a series of amines. Helmchen verified that esters and amides derived from 1-phenyl-propionic acid showed chemical shift non-equivalence consistent with the Dale and Mosher model.[131] Subsequently Valente and coworkers have studied a number of amides derived from α-methyl-α-methoxy-pentafluorophenyl acetic acid, (M.M.P.A.).[132]

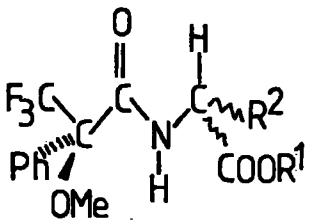
1.6.2 Chiral Acid C.D.A.s and Lanthanide Shift Reagents (L.S.R.s)

Extension of the work with M.T.P.A. from amines to amino acids and hydroxy acids requires the combination of two techniques. The preparation of diastereotopic derivatives followed by N.M.R. study in the presence of a Chiral Lanthanide Shift Reagent, (C.L.S.R.). For example Yasuhara[133] studied $Eu(fod)_3$ induced shifts of amide derivatives of M.T.P.A. and amino esters observing large chemical shifts rationalised in terms of strong binding of the shift reagent to the more polar amide rather than the ester carbonyl group. Yamaguchi has extended the approach to secondary carbinols.[134] Tables 6 and 7 summarise the results obtained with some amino esters and hydroxy esters.

Camphanic acid is a valuable C.D.A. for use in L.S.R. ^1H N.M.R. studies of α-deuterated primary carbinols.[135] In the diastereomeric esters formed the signal due to the pro-S carbinyl hydrogen resonates to higher frequency than the pro-R carbinyl hydrogen.

Table 6

Lanthanide Induced Proton Chemical Shift for (R)-(+)-M.T.P.A. Amide Derivatives of Amino Acid Esters in the presence of $Eu(fod)_3$



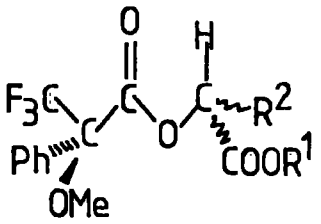
No	R_1	R_2	$\Delta\delta$ (OCH_3) ppm[a] R,R	R,S	$\Delta\Delta\delta$ ppm[b]
1	CH_3	CH_3	9.7	8.5	+1.2
2	CH_2CH_3	CH_3	8.0	7.1	+0.9
3	$C(CH_3)_3$	CH_3	8.0	7.3	+0.7
4	CH_3	$CH(CH_3)_2$	10.0	7.4	+2.6
5	1-Menthyl	$CH(CH_3)_2$	12.1	9.0	+3.1
6	CH_3	$CH_2CH(CH_3)_2$	12.4	9.1	+3.3
7	CH_3	$CH_2CH_2SCH_3$	10.1	9.8	+0.3
8	CH_3	CH_2Ph	7.1	8.8	-1.7
9	CH_2Ph	CH_2Ph	6.9	8.4	-1.5
10	$C(CH_3)_3$	CH_2Ph	7.9	10.2	-2.3
11	1-Menthyl	CH_2Ph	9.3	10.3	-1.0
12	CH_3	CH_2-p-CH_3OPh	7.5	9.8	-2.3

a) Lanthanide induced shifts for M.T.P.A. OCH_3 function.

b) Difference in induced shifts i.e. induced chemical shift non-equivalence.

Table 7

Lanthanide Induced Proton Chemical Shifts of(R)-(+)-M.T.P.A. Esters of Hydroxyesters in the presence of Eu(fod)3



No	R_1	R_2	CO_2CH_3 $\Delta\delta$ppm R,R[a]	R,S[a]	$\Delta\Delta\delta$ppm b	α-CH $\Delta\delta$ppm R,R[a]	R,S[a]	$\Delta\Delta\delta$ppm b
1	CH_3	CH_3	3.0	4.4	1.4	6.4	7.6	1.2
2	CH_2CH_3	CH_3				7.5	8.7	1.2
3	CH_3	$CH(CH_3)_2$	1.6	2.5	0.9	4.4	5.4	1.0
4	CH_3	$(CH_2)_3CH_3$	1.4	2.3	0.9	4.2	5.3	1.1
5	CH_3	$CH(CH_3)CH_2CH_3$	1.2	2.1	0.9	4.3	5.0	0.7
6	CH_3	$CH_2CH(CH_3)_2$	1.1	1.9	0.8			
7	CH_3	$C(CH_3)_3$	1.0	1.7	0.7	4.1	5.0	0.9
8	CH_3	Ph	0.8	1.3	0.5	2.7	3.1	0.4
9	1-menthyl	Ph				3.4	4.6	1.2
10	CH_3	CH_2Ph	2.0	3.1	1.1	5.4	6.6	1.2
11	CH_3	CH_2CH_2Ph	1.2	2.0	0.8	4.3	5.3	1.0
12	CH_3	$(CH_2)_6CH_3$	1.5	2.5	1.0	4.6	5.4	0.8

a) Lanthanide induced shifts.
b) Difference in induced shifts i.e. induced chemical non-equivalence.

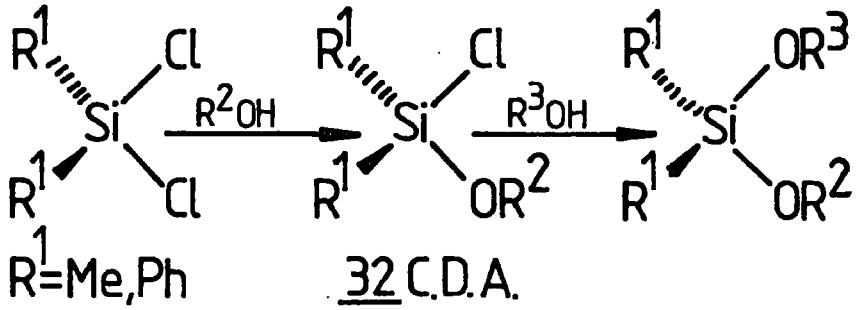
1.6.3 Derivatisations using other C.D.A.s

Brown and Parker[136] have assayed the enantiomeric purity of α-deuterated carboxylic acids by preparing esters with enantiomerically pure (S)-methylmandelate [(S)-2-hydroxy-2-phenylethanoate] and used deuterium (^2H), N.M.R. to study the resulting diastereomers. Chemical shift non-equivalence for α-protons was large (≥ 0.1ppm). Less than 0.05% racemisation occured during derivatisation.[137] In the complementary experiment Parker[137] has used (S)-O-acetylmandelic acid as a C.D.A. to determine the enantiomeric purity of a series of alcohols. In addition Parker has demonstrated that camphanic acid is an effective C.D.A. for chiral amines.[137]

Derivatisation involves their conversion to amides. Floss and coworkers[138] have used both ^1H and ^2H N.M.R. to study the (S)-O-acetylmandelate[137] mono-esters of the 1,3-propane-diols obtained from enantiomerically enriched, deuterium labelled, malonate prepared via asymmetric synthesis. Helmchen has prepared amides from enantiomerically pure amines and racemic acids, however, chemical shift non-equivalence is generally small (i.e. <0.05 ppm).[131,139,52]

The use of silyl acetals, (32), as C.D.A.s for determination of enantiomeric purity of alcohols was recently reported.[140] A dichlorosilane is reacted first with an alcohol of 100% enantiomeric purity such as methylmandelate, quinine or menthol to give the C.D.A. which is then derivatised with the alcohol of unknown e.e. to give a pair of ^1H, ^{13}C or ^{29}Si N.M.R. chemical shift anisochronous diastereomers. In general

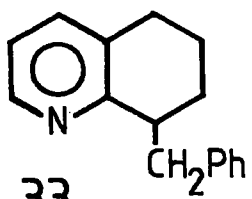
agreement between integrated e.e. determinations and optical purity is within ±3%.



Carbon-13, N.M.R. has been reported to be a useful technique for determination of enantiomeric composition for cyclic and acyclic ketones.[141] However, in ^{13}C (pulse) N.M.R. spectroscopy signal intensities are not always proportional to the number of nuclei in a certain environment, (i.e. integrals are unreliable), because of differences in relaxation times and Nuclear Overhauser Effects. It has been argued that, in cases where compounds have similar structures, (e.g. diastereo-isomers), differences in these factors are negligible implying that integrals can give reliable quantitative information. Substantial ^{13}C chemical shift non-equivalence is observed for cyclic ketals and thioketals derived from the corresponding enriched ketones using enantiomerically pure 1,2-butanediol or 1,2-butanedithiol as C.D.A.s.

The absolute configuration of carbinols has been assigned using ^{13}C N.M.R. spectroscopy and a glycosidation shift rule.[142] The N.M.R. spectra for alcoholic glycopyranosides are compared with those for the parent alcohol and methyl glycoside. Glycosidation shifts for the glycoside and aglycone moiety are obtained, which can be correlated with the absolute configuration of the original carbinol. This method can be used to determine absolute stereochemistry for secondary carbinols in five membered rings, medium sized flexible rings and macro-rings.

The interaction of salts from racemic 8-benzyl-5,6,7,8-tetrahydroquinoline, (33), and optically active acids with the chiral complexing agent β-cyclodextrin results in substantial diastereotopic splitting in the ^{15}N N.M.R. spectrum.[143]

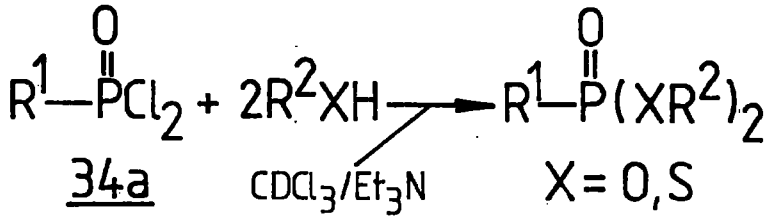


33

Phosphorus-31 N.M.R. provides a useful alternative for determination of enantiomeric excess in cases where the ^{1}H and ^{13}C spectra are complex. Feringa and coworkers have demonstrated[144] that phosphorus trichloride can be used as a reagent for chiral self recognition.[145] Two molecules of an enantiomerically enriched alcohol react with each PCl_3 molecule to form phosphonates. Four stereochemically distinct species are possible: R,R/S,S, (a {±} pair), R,S and S,R which are meso compounds. The first pair are enantiomeric and hence have

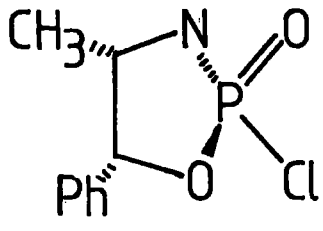
isochronous chemical shifts, however the {±} pair and the two meso compounds are diastereomeric and hence have anisochronous chemical shifts, (i.e. there are three resonance signals in the ^{31}P spectrum). ^{31}P N.M.R. chemical shift non-equivalence is typically 0.25-0.62ppm, integration of split signals gives enantiomeric excess within ±2% of those obtained by G.C. This indicates that there is no stereoselection during derivatisation with PCl_3.

Subsequent work has shown that methyl phosphorus (V) dichloride, (34), offers improved performance as a C.D.A.[146] (i.e. increased $\Delta\delta \approx 1$ppm) for both alcohols and thiols. Again three diastereomeric signals are observed, one for each meso compound and one for the {±} pair, the integrals for the first two peaks must be combined before comparison with that for the latter when determining e.e. Johnson and coworkers[147] have used the chiral coupling reagent (34b) to measure the enantiomeric composition of chiral alcohols.

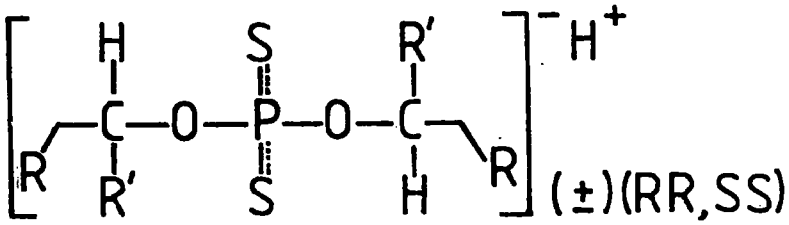


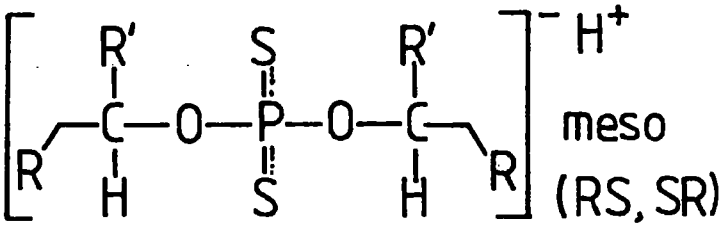
34a

34b



Most recently the method has been extended to provide "in situ" derivatisation for chiral alcohols,[148] an approach which combines the ease of a C.S.A. with the δ magnitude advantage of a C.D.A. The racemic alcohol is reacted with a phosphorothioic acid at 20°C in $CDCl_3$ to give O,O-dialkyl phosphorodithionate esters, (35).





35

As salts all four species contain planes of symmetry i.e. the {±} pair are enantiomers as before; but, in this case, the two meso compounds are also enantiomers. Hence there are only two resonances in the ^{31}P N.M.R. spectrum.[149]

Chiral tertiary amines have been used to discriminate between the meso and {±} pairs for phosphothioic acid. However the diastereomeric salts formed belong to the dynamic diastereomeric systems[150] akin to C.S.A.s covered in the next section.

1.7 N.M.R. Determination of Enantiomeric Excess using Chiral Solvating Agents

1.7.1 General Comments

Since Mislow and Raban proposed[89] and Pirkle[151] demonstrated experimentally that chiral solute enantiomers exhibit different N.M.R. chemical shifts in a non-racemic chiral solvent, approximately forty chiral substances have been reported to be effective Chiral Solvating Agents, (C.S.A.s).[152] In nearly every case the C.S.A. contains a group of high diamagnetic anisotropy close to its asymmetric centre. In contrast to Chiral Derivatising Agents, which form diastereoisomers via chemical reaction with the racemic substrate, C.S.A.s form diastereomeric solvation complexes via rapid reversible equilibria. The mode of operation of a C.S.A. is most easily understood in terms of the binary solvation complexes formed between R and S enantiomers of the chiral solute and the enantiomerically pure C.S.A.

$$R(\text{solute}) + R(\text{C.S.A.}) \underset{K_R}{\rightleftharpoons} R(\text{solute}).R(\text{C.S.A.})$$

$$S(\text{solute}) + R(\text{C.S.A.}) \underset{K_S}{\rightleftharpoons} S(\text{solute}).R(\text{C.S.A.})$$

Chemical shift non-equivalence of enantiomers in the presence of a C.S.A. arises as a result of several mechanisms. The most easily recognised is the intrinsic anisochrony due to the stereochemically dependent disposition of groups with large magnetic anisotropy relative to other substituents in the two diastereomeric solvation complexes.

Since exchange between solvated and unsolvated solute is rapid on an N.M.R. time scale, the magnitude of the chemical shift

non-equivalence, $\Delta\delta$, is influenced by the position of the above equilibria. The observed resonance signals correspond to weighted averages of solvated and unsolvated solute chemical shifts. Thus if the chemical shift for unsolvated solute enantiomers is $\delta(\pm)$, the fractional populations for R and S solutes are ϕ_R and ϕ_S respectively and the chemical shifts for the solvation complexes are δ_R and δ_S then the <u>observed</u> chemical shifts for each C.S.A.-solute system, δ_{obs} and δ'_{obs}, in ppm, are given by:

$$\delta_{obs} = \phi_R\,\delta(\pm) + (1-\phi_R)\,\delta_R$$

$$\delta'_{obs} = \phi_S\,\delta(\pm) + (1-\phi_S)\,\delta_S$$

Hence

$$\Delta\delta = \delta_{obs} - \delta'_{obs}$$

$$= \delta(\pm)(\phi_R-\phi_S) + (\delta_R-\delta_S) - (\phi_R\,\delta_R-\phi_S\,\delta_S)$$

Alternatively in terms of the equilibrium constants K_R and K_S:

$$K_R = (1-\phi_R)/\phi_R \quad , \quad K_S = (1-\phi_S)/\phi_S$$

$$\delta_{obs} = \phi_R(\delta(\pm) + K_R\,\delta_R)$$

$$\delta'_{obs} = \phi_S(\delta(\pm) + K_S\,\delta_S).$$

Thus $\Delta\delta$ is directly dependent on the equilibrium constant for solvation. In addition, the chemical shift non-equivalence can be affected by the relative amounts of solute and C.S.A.

The advantages of the C.S.A. approach are:

1. The method is quick and simple being applicable "in situ", (i.e. in the N.M.R. tube), requiring no separate derivatising reaction.
2. There is no chance of accidental enrichment or racemisation of sample due to differential reaction rates or chemical manipulations, (provided that the sample remains in solution).

3. Enantiomeric excess measurements are <u>not</u> affected by incomplete C.S.A. enantiomeric purity. A reduction in observed chemical shift non-equivalence will result if a C.S.A. of less than 100% e.e. is employed but the relative signal intensities are not affected. This is a direct consequence of the time averaged view of the rapid exchange processes involved.
4. Extensive studies concerning the nature of the diastereomeric solvates and the mechanism of shift non-equivalence induction permit assignments of absolute configuration to be made with confidence and defines design constraints for new C.S.A.s.

There are also a number of disadvantages:

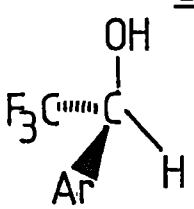
1. The magnitude of the observed chemical shift non-equivalence is generally less than that found with C.D.A.s.
2. Non-polar aprotic solvents such as d_6-benzene, d-chloroform or carbon tetrachloride must be used to maximise $\Delta\delta$. Potential chiral solutes soluble only polar solvents such as d_6-D.M.S.O. cannot be studied since competitive solvation between the C.S.A. and the achiral solvent will reduce $\Delta\delta$ to zero.
3. Two or three equivalents of C.S.A. are sometimes needed to "push" the solvation equilibria in favour of the solvation complexes.
4. Non-equivalence arises from a complicated combination of effects which can be difficult to interpret. For example in the case of diastereomeric salts, these salts may dissociate from a "close ion-pair" to a "solvent separated

ion-pair", the chemical shifts of each type of ion-pair will be different and their contributions to the observed shift will be weighted by the different equilibrium constants for dissociation.[153]

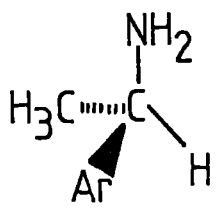
5. In order to establish that resolution is sufficient for non-equivalence to be observed both enantiomers of the solvate must be available.

1.7.2 Perfluoroalkyl-arylcarbinols and Alkyl-arylamines as C.S.A.s

The most commonly used C.S.A.s are a series of perfluoroalkyl-arylcarbinols, (36), and alkyl-arylamines, (37). It is generally accepted that for effective chemical shift non-equivalence induction, the C.S.A.- solute complex must feature a minimum of three interactions. Two interactions are necessary to form a rigid "chelate-like" structure; the third interaction must be stereochemically dependent and is responsible for causing non-equivalence in the chemical shifts of solvate substituents. Therefore, a prerequisite for C.S.A. applicability is that the C.S.A. and solute have complementary functionality. Thus if the solute is a hydrogen bond acceptor, such as a tertiary amine, the C.S.A. choice is an efficient hydrogen bond donor, for example (36); whilst if the solute is a hydrogen bond donor, such as an alcohol, the C.S.A. choice is a hydrogen bond acceptor, for example (37).



36 a) Ar = 9-Anthryl
b) Ar = 9-(10-methylanthryl
c) Ar = 1-Naphthyl
d) Ar = Phenyl
e) Ar = Cyclohexyl

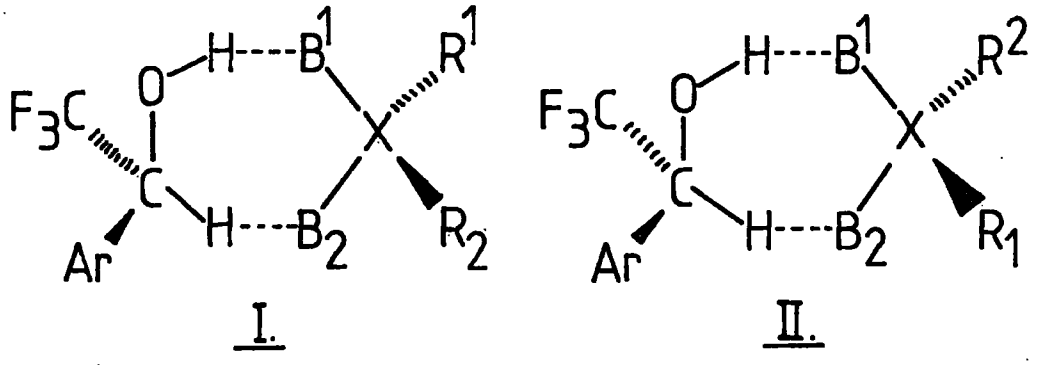


37 a) Ar = Phenyl
b) Ar = 1-Naphthyl

Several types of interaction other than hydrogen bonding may contribute primarily (i.e. provide the first interaction) or secondarily (i.e. provide the second interaction) to C.S.A. -solute association. Anisochrony has been induced through formation of diastereomeric charge transfer complexes (π acid - π base),[154,155] through dipole-dipole interactions[156] and via formation of diastereomeric salts involving complete proton transfer resulting in ion-pairing.[157,149]

The alcohols (36) behave in a general manner and serve to illustrate the mechanism of chemical shift non-equivalence induction. In (Figure 9), the two relatively acidic hydroxyl and methine protons are involved in hydrogen bonding with the primary and secondary basic sites of the solvate, B_1 and B_2, to give the complexes (I) and (II).

Figure9

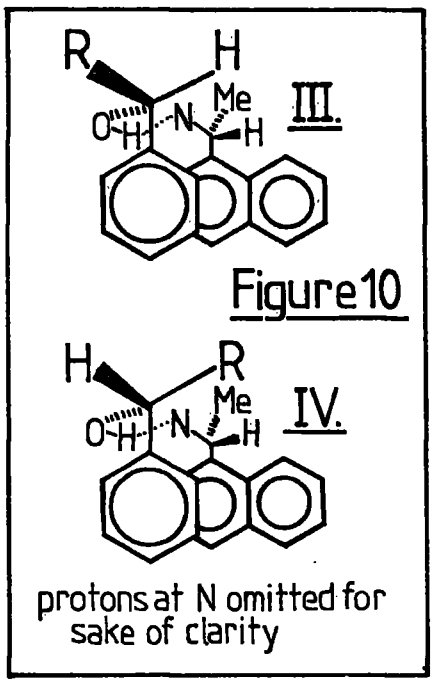


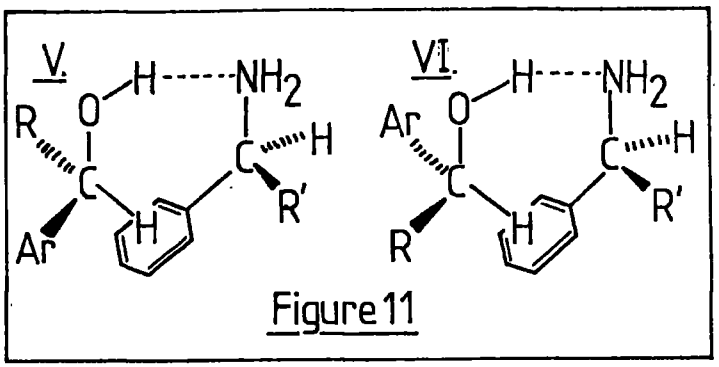
These solvation complexes are proposed[152] as the major contributors to induced chemical shift non-equivalence. The primary basic site, B_1, can be substituents such as hydroxyl, amine carbonyl, sulphonyl or phosphonyl groups; secondary sites, B_2, can be substituents such as ether, thioether or phenyl groups.

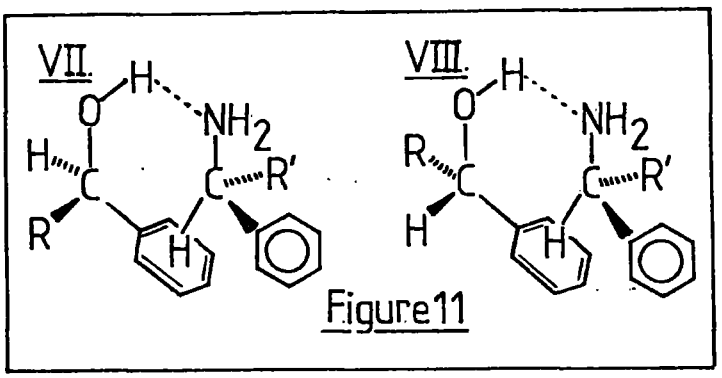
Once chelate formation has occurred the solvate enantiomer substituents, R, experience different shieldings due to the aryl rings in structures (I) and (II); in (I) R_1 is close to the anisotropic aryl ring of the C.S.A. whilst R_2 is remote, in (II) the situation is reversed. The resulting opposite senses of non-equivalence for substituents on opposite sides of the chelate plane is the hallmark of the C.S.A. technique.[127] Obviously two basic sites must be present in the solvate molecule, if there are more than two then complications arise from site interchange.

Burlingame and Pirkle[158] first observed distinct ^{19}F N.M.R. resonances for enantiomers of 2,2,2-trifluoro-1-phenyl ethanol, (T.P.E.), in the presence of (-)-phenylethylamine and reasoned that the amine phenyl ring was responsible for chemical shift non-equivalence. Replacement of phenyl by 1-naphthyl gave increased $\Delta\delta$ in the ^{19}F N.M.R. spectrum for the T.P.E. and also caused the diastereomeric carbinyl protons in 2-methyl-1-phenyl-propanol to be split. A systematic study of a series of alkyl-arylcarbinols in the presence of (-)-phenyl-ethylamine shows a consistent correlation between sense of non-equivalence and absolute configuration. Pirkle originally proposed the model shown in (Figure 10) to explain these observations, involving charge transfer between the two aryl rings and hydrogen bonding between the hydroxyl proton and the amine nitrogen. Alcohol substituents, R, are then shielded by the aryl rings in a stereochemical manner, (III and IV). The observed enhancement of $\Delta\delta$ for nitrocarbinols, due to increased charge transfer between the aryl rings, and the total loss of non-equivalence with 1-cyclohexylethylamine in place of

phenylethylamine has been given as evidence supporting this model.







Later, having studied a large number of other chiral solutes, Pirkle proposed[152] alternative models for alcohol-amine systems illustrated in (Figure 11). The same primary interaction is involved (i.e. hydrogen bonding between the hydroxyl proton and the amine nitrogen), but the secondary interaction involves the weakly acidic carbinyl proton of the alcohol (in V and VI) or the amine (in VII and VIII) and the electron rich aryl ring of the amine or alcohol respectively. These models are self-complementary and fit well with the "reciprocity" of the C.S.A. technique; i.e. racemic alcohols can be assayed by enriched amines and racemic amines by enriched alcohols. Thus (V) and (VI) predict non-equivalence for amine substituents whilst (VII) and (VIII) predict non-equivalence for the alcohol substituents.

Following Pirkle's observation[158] for amine C.S.A.s that $\Delta\delta$ increases with aryl substituent size 1-(9-anthryl)-2,2,2-trifluoro ethanol, (36a), was synthesised and has proved to be an effective C.S.A. for chiral amines. Results are summarised in Table 8. The observed sense of non-equivalence agrees with that predicted using models (V) and (VI) in (Figure 11). Entries 12 and 13 illustrate that $\Delta\delta$ tends to zero if either of the two aryl rings are not present; i.e. these C.S.A.s apply only to arylamines.

Chemical shift non-equivalence has also been observed for a limited number of chiral alcohols in the presence of alkyl arylcarbinols. Sense of non-equivalence can be correctly predicted with models (V) and (VI) if R=CF_3 and the NH_2 group is replaced by an OH function. Double and triple bonds (i.e. species with π electron density) appear to be interchangeable with phenyl rings at interaction sites.

Pirkle and Beare[159] have studied a series of O-methylated-α-amino acids using 2,2,2-trifluoro-1-phenyl ethanol, (36d). For the sixteen esters examined, of which a representative sample is shown in Table 9, the carbomethoxy and α-proton resonances always occur to lower frequency and the α-substituent resonances always occur to higher frequency in the (S) enantiomer than the corresponding resonances in the (R) enantiomer. (Figure 12)[159] illustrates the proposed models for correlation of chemical shift non-equivalence and absolute configuration. Primary interaction involves hydroxyl proton hydrogen bond formation with the amine nitrogen, secondary interaction occurs between the positively charged end of the carbonyl group and the aryl ring.

Table 8

Proton Chemical Shift Non-equivalence of Chiral Amines Induced by the presence of Alkyl-arylcarbinol C.S.A.s (36)

No	Ar	R	e.e.[a]	C.S.A.	Non-equivalence, Δδ (sense)[b] CH		R		$[\alpha]_D$	c
1	2-Naphthyl	CH_3	36	(+)-(36d)	0.03	Hf			-7.56	S
2	1-Naphthyl	CH_2CH_3	15	(+)-(36d)	0.05	Lf			+4.57	R
3	1-Naphthyl	CH_3	16	(+)-(36d)	0.045	Lf	0.02	Hf		R
4	Phenyl	CF_3	33	(+)-(36d)	0.027	Hf			-8.01	R
5	Phenyl	CH_3	16	(+)-(36d)	0.17	Hf			-6.26	S
6	p-$CH_3OC_6H_4$	CH_3	60	(+)-(36d)	0.03	Lf			+21.62	R
7	2-Thienyl	CH_3	24	(+)-(36d)	0.015	Lf	0.014	Hf	+1.38	R
8	2-Thienyl	CH_3	24	(-)-(36c)	0.025	Hf	0.034	Lf	+1.38	R
9	1-Naphthyl	CH_3	16	(-)-(36c)	0.062	Hf	0.015	Lf	+	R
10	Phenyl	CF_3	33	(-)-(36c)	0.014	Lf			-8.01	R
11	p-$NO_2C_6H_4$	CH_3	17	(-)-(36c)	0.058	Hf			+3.43	R
12	C_6H_{11}	CH_3	0	(-)-(36c)	0		0		0	
13	1-Naphthyl	CH_3	25	(R)-(36e)	0		0		+	

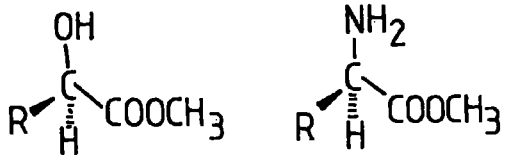
a) Determined from optical rotations.

b) Lf = Low frequency sense of non-equivalence.
Hf = High frequency sense of non-equivalence.

c) Absolute configuration.

Table 9

Proton Chemical Shift Non-equivalence of α-Aminoesters (entries 1-7) and α-Hydroxy Esters (entries 8-11) in the presence of C.S.A.s



No	R	A[b]	Non-equivalence, Δδ (sense)[a]						C.S.A.
			$COOCH_3$		H_α		R		
1	Ph	R	0.04	Hf					(-)(36d)
2	CH_3	S	0.01	Lf	0.02	Lf	0.03	Hf	(-)(36d)
3	$CH^\beta(CH_3)_2$	S	0.04	Hf	0.04	Hf	H^β 0.01 H 0.01	Lf Lf	(-)(36d)
4	$CH^\beta CH^{\beta'}CH(CH_3)_2$	S	0.024	Lf	0.03	Lf	H^β 0.024 $H^{\beta'}$ 0.036 H 0.02	Hf Hf Hf	(-)(36d)
5	$CH^\beta H^{\beta'}$ Ph	S	0.02	Lf	0.02	Lf	H^β 0.025 $H^{\beta'}$ 0.020	Hf Hf	(-)(36d)
6	CH_2OH	S	0.004	Lf	0		0		(-)(36d)
7	$CHOHCH_3$	S	0.010	Lf	0.03	Lf	0		(-)(36d)
8	CF_3	S	0.010	Hf					(+)(37b)
9	H	R	0.030	Lf					(+)(37b)
10	CH_3	R	0.030	Lf					(+)(37b)
11	CCl_3	S	0.010	Hf					(+)(37b)

a) Hf implies that high frequency non-equivalence is observed for the listed configuration.

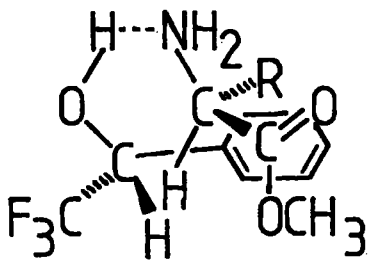
Lf implies that low frequency non-equivalence is observed for the listed configuration.

b) A = Absolute configuration.

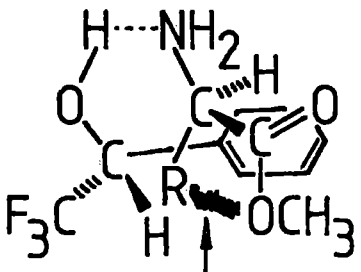
The steric hindrance of the R substituent results in a larger than predicted perturbation of the carbomethoxy resonance for the (S) enantiomer complexed in (X), compared with the less hindered (R) enantiomer complexed in (IX).

Figure12

IX.



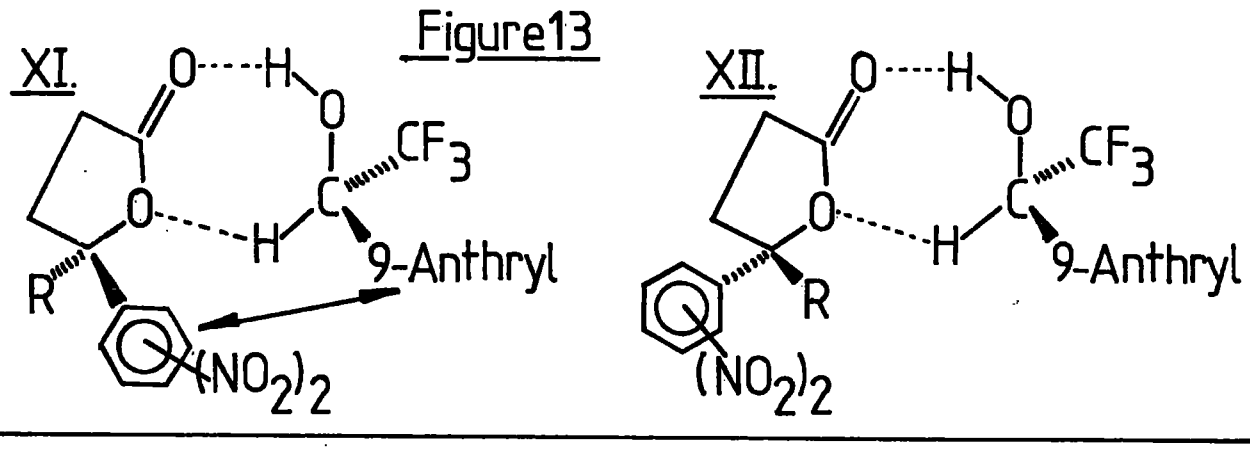
X.



α-Naphthylethylamine has been used to render the carbomethoxy resonances of α-substituted α-methyl-α-hydroxyphenyl-lactate enantiomers non-equivalent.[160] A number of γ and δ lactone enantiomers have been studied using (36a) as a C.S.A. Interaction models (I) and (II), (Figure 9), have been used to explain the sense of non-equivalence where B_1 and B_2 (the primary and secondary basic sites) are the carbonyl and alkoxy oxygens respectively. Since five membered lactone rings are almost planar, substituents on opposite sides of the ring exhibit opposite senses of non-equivalence.[161]

The C.S.A. method can only provide reliable assignments of absolute configuration within a series of compounds if the fractions of the enantiomers complexed to the C.S.A.s are consistent within that series. In the case of lactones bearing a nitrophenyl ring, then an extra stabilising π-π charge transfer may cause one enantiomer to be bonded much more strongly than the other in the solvation complexes, giving rise to anomalous chemical shifts and the possibility of unique reversal of non-equivalence sense. (Figure 13) shows a situation in which π-π charge transfer can occur in (XI) but not in (XII). Differential solvate stabilities thus predicted have been verified by the differing H.P.L.C. retention times for nitrophenyl lactones.

Figure13



When the possibility of forming diastereomeric solvates with significantly different stabilities exists the hallmark of the C.S.A. technique (i.e. opposite senses of non-equivalence for substituents on opposite sides of the C.S.A. chelate plane) is lost.[127]

Sulphoxides have been studied extensively by the C.S.A.

technique.[162-166] Pirkle first reported observations of chemical shift non-equivalence using (36d); in the solvation models (I) and (II), (Figure 9), the sulphonyl oxygen and the sulphur lone pair of electrons behave as B_1 and B_2. Table 10 shows typical results with aryl-alkylcarbinol C.S.A.s.

Table 10

Proton Chemical Shift Non-equivalence Induced in Chiral Sulphoxides by Alkyl-Arylcarbinols (36)

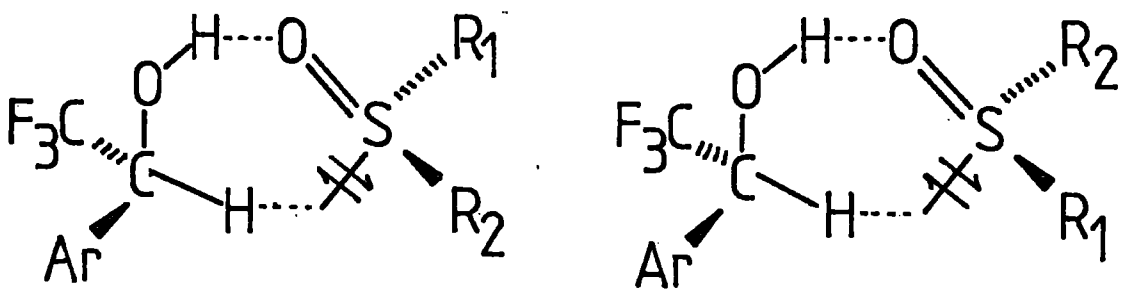
No	R_1	R_2	C.S.A.	$\Delta\delta^a$ R_1	$\Delta\delta^a$ R_2
1	CH_3	CD_3	R-(36d)	0.017	
2	CH_3	$CH_2{}^{\alpha}CH_3{}^{\beta}$	R-(36d)	0.025	-0.024 (α) -0.025 (β)
3	CH_3	$CH_2CH^{\alpha}=CH^{\beta}H^{\gamma}$	R-(36d)	0.019	-0.008 (α) -0.013 (β) -0.018 (γ)
4	CH_3	$CH(CH_3{}^{\beta})(CH_3{}^{\beta'})$	R-(36d)	0.031	-0.026 (α) -0.011 (β) -0.030 (β')
5	CH_3	CH_2Ph	R-(36d)	0.025	
6	CH_3	$C(CH_3)_3$	R-(36d)	0.026	-0.012
7	CH_3	Ph	R-(36d)	0.012	
8	CH_3	p-$CH_3C_6H_4$	R-(36d)	0.014	
9	CH_3	p-$CH_3{}^{\alpha}OC_6H_4{}^{\beta}$	R-(36d)	0.018	-0.008 (α) -0.025 (β)[b]
10	CH_3	1-Naphthyl	R-(36d)	0.013	
11	CH_2-SO-$CHCH_3$		R-(36d)	0.003 0.008	0.010 -0.015
12	CH_2-SO-$CHC(CH_3)_3$		R-(36d)	-0.002 0.001	-0.001 -0.003

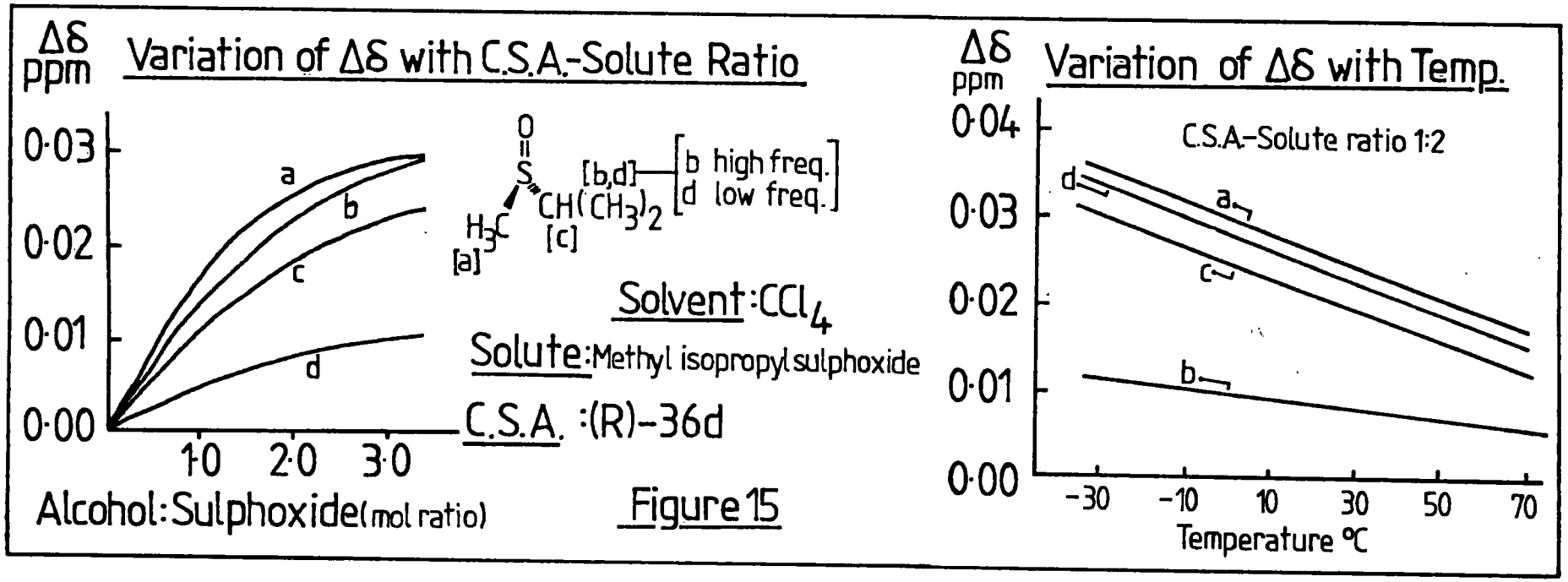
a) $\Delta\delta = \delta_R - \delta_S$

b) Observed for the low frequency portion of the aromatic AA'BB' pattern.

$\Delta\delta$ rises to a maximum after three equivalents of the C.S.A. alcohol have been added and is invariant thereafter if further C.S.A. is added. Non-equivalence is independent of bulk concentration and increases in linear proportion for all substituent groups in the same solute molecule with decreasing temperature. This implies that non-equivalence stems from only one conformation of the diastereomeric solvates, that shown in (Figure 14), which is preferentially populated at lower temperatures. If a variety of conformations made weighted contributions to the observed shift then the temperature dependence of $\Delta\delta$ for different substituents in the same molecule would not be expected to be the same.

Figure 14

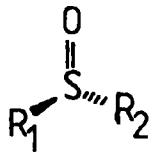


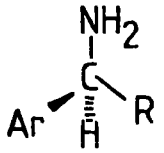

Δδ ppm
Variation of Δδ with C.S.A.-Solute Ratio
0·03
0·02
0·01
0·00
1·0
2·0
3·0
a
b
c
d
Alcohol:Sulphoxide(mol ratio)
[b,d]
b high freq.
d low freq.
[a]
[c]
Solvent: CCl_4
Solute: Methyl isopropyl sulphoxide
C.S.A. : (R)-36d
Figure 15
Δδ ppm
Variation of Δδ with Temp.
C.S.A.-Solute ratio 1:2
0·04
0·03
0·02
0·01
0·00
-30
-10
10
30
50
70
Temperature °C

Kagan has reported[167] the use of N-3,5,-dinitrobenzoyl-phenylethylamine as an effective C.S.A. for sulphoxides, Table 11 presents the results for a number of sulphoxides.

Table 11

Proton Chemical Shift Non-equivalence Induced in Chiral Sulphoxides in the Presence of N-3,5-Dinitrobenzoyl-phenylethylamine





No	R_1	R_2	$\Delta\delta$ for R_2[b]
1	p-$CH_3C_6H_4$	CH_3	0.016
2	p-$NO_2C_6H_4$	CH_3	0.011
3	p-$HOCH_2C_6H_4$	CH_3	0.014
4	p-HOC_6H_4	CH_3	0.020
5	2-Pyridyl	CH_3	0.024
6	n-C_8H_{17}	CH_3	0.011
7	t-Butyl	CH_3	0.013
8	c-C_6H_{12}	CH_3	0.013
9	$Ph(CH_2)_3$	CH_3	0.011
10	2-$C_{10}H_7$	CH_3	0.012[c]
11	2-$C_{10}H_7$	CH_3	0.025
12	2-$C_{10}H_7$	n-Pr	0.014
13	p-$CH_3C_6H_4$	CH_3	0.020[d]
14	p-$CH_3C_6H_4$	CH_3	0.028[e]

a) One molar equivalent unless stated otherwise.

b) At 400MHz in $CDCl_3$

c) 0.5 Molar equivalent.

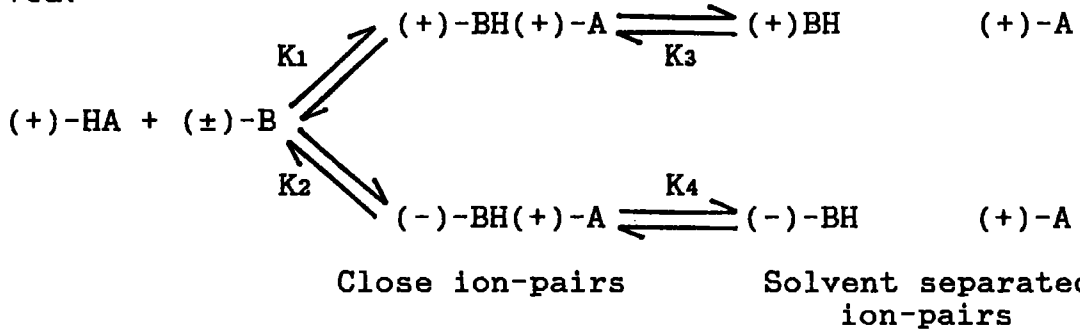
d) 1.6 Molar equivalents.

e) In CCl_4.

Episulphides,[164] epoxides,[168] N,N-dialkylamine oxides,[169] oxiridines,[170] sulphinate esters and thio ester derivatives of chiral thiols[171] are all amenable to C.S.A. analysis of enantiomeric excess.

1.7.3 Diastereomeric Salt Formation

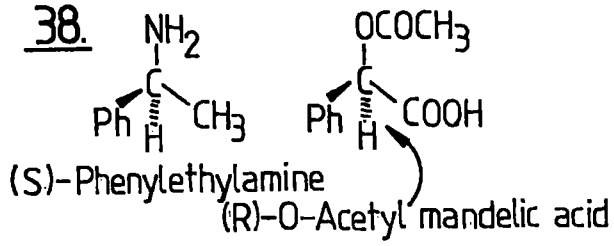
Diastereomeric salts formed in solution between optically active aromatic acids and amines, each employed as chiral resolving agents in there own right, frequently exhibit large chemical shift non-equivalence. Salt formation can be considered as a special type of C.S.A. - solute interaction because there is rapid exchange between the free acid and base and those constituting a close ion-pair. The solvation is complicated by the possibility of dissociation of the close ion-pair to give a solvent separated ion-pair in which the stereochemically dependent interaction responsible for rendering substituent groups chemical shift non-equivalent is lost. Polar solvents tend to promote dissociation of the close ion-pair and hence reduce $\Delta\delta$ to zero. Non-polar solvents such as d_6-benzene and d-chloroform maximise the non-equivalence observed.



No models have been proposed to account for salt non-equivalence although the consistent correlation between sense of non-equivalence and absolute configuration observed appears to indicate that such a model would be applicable to these systems. In non-polar solvents, salts may exist as aggregates of close ion-pairs. Since the composition and size of the aggregate, both of which may vary between salts of different

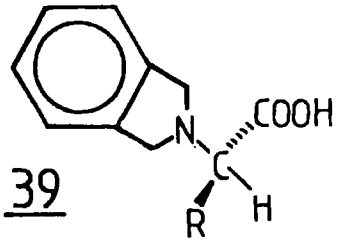
compounds in the same series, affect the chemical shift of salts,[172] it might be assumed that sense of non-equivalence is also dependent on these two factors. Mikolajczyk and coworkers[153] have studied the phenylethylamine/O-acetyl mandelic acid salt system, (38), in $CDCl_3$, in detail and have observed that $\Delta\delta$ varies linearly with enantiomeric composition and depends on the concentration of solution, but that the sense of non-equivalence is invariant. The temperature dependence of $\Delta\delta$ for (S)-(-)-phenylethylamine and racemic O-acetyl mandelic acid in hexachlorobutadiene solvent is such that $\Delta\delta$ tends asymptotically to zero as temperature increases. This is explained in terms of salt dissociation at higher temperatures. Subsequently N-phthaloyl-α-aminoacid derivatives, (39), have been studied using phenylethylamine as a C.S.A.: $\Delta\delta$ is typically 0.06ppm and the (S) configuration acid derivative always corresponds to the lower frequency alkyl substituent resonance.

38.



(S)-Phenylethylamine (R)-O-Acetyl mandelic acid

39



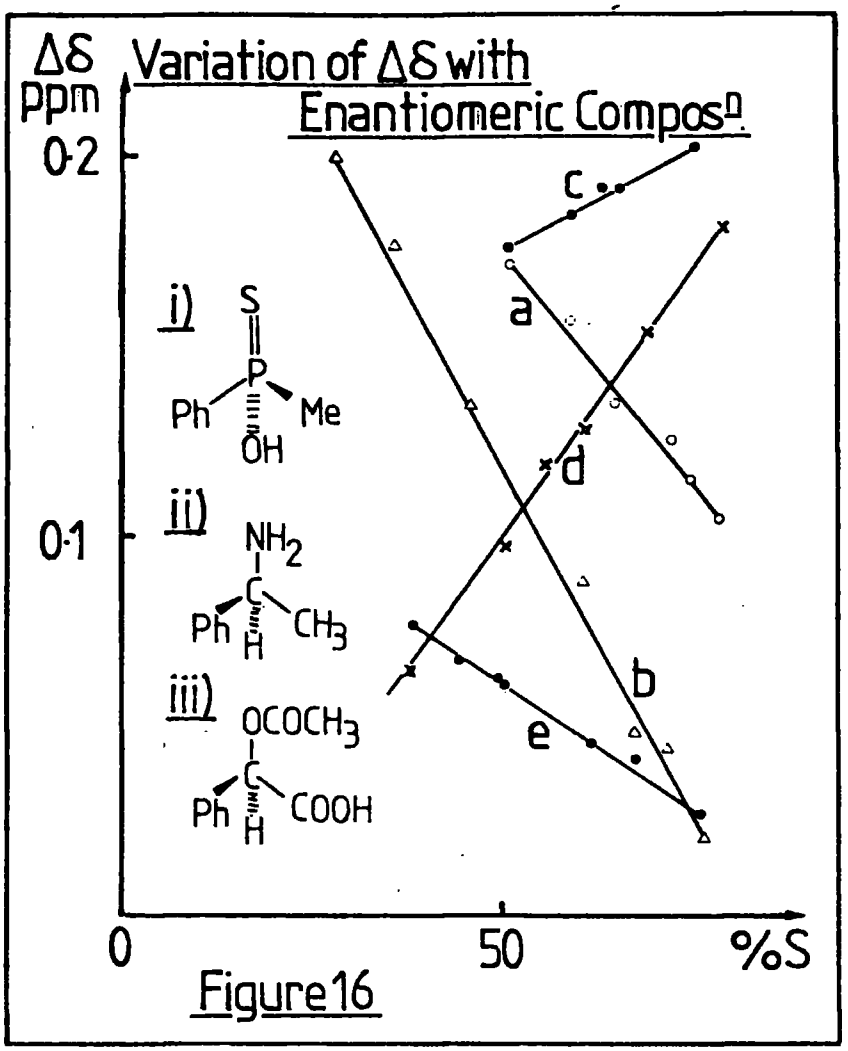


Figure 16

a) (S)-(-)-Amine (ii)/Acid (iii) [(S)-(-)-Enantiomer 50%-78%]

b) (S)-(-)-Amine (ii)/Acid (i) [(S)-(-)-Enantiomer 27%-76%]

c) (R)-(+)-Amine (ii)/Acid (iii) [(S)-(-)-Enantiomer 50%-74%]

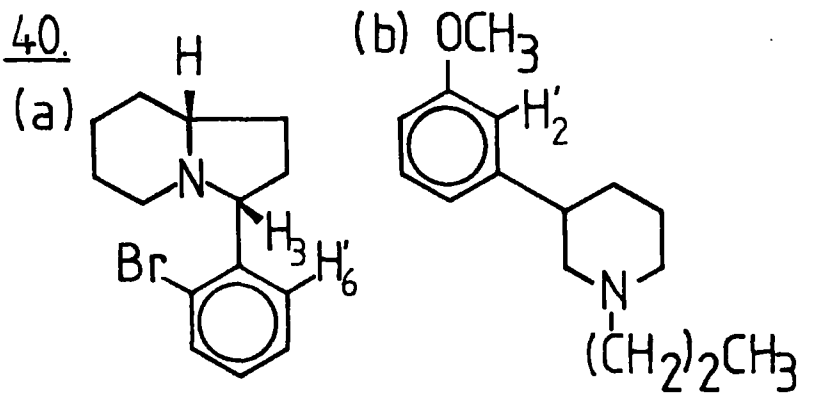
d) (R)-(+)-Amine (ii)/Acid (i) [(S)-(-)-Enantiomer 34%-78%]

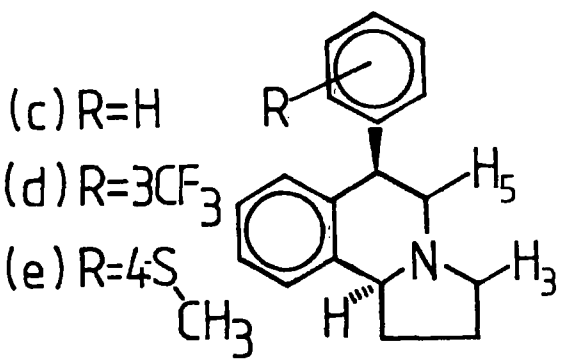
e) (S)-(-)-Acid (iii)/Amine (ii) [(S)-(-)-Enantiomer 38%-76%]

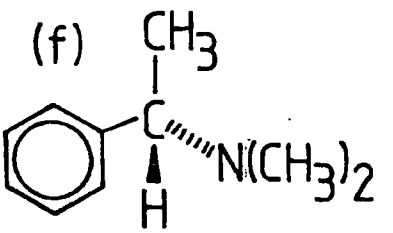
Chiral crown ethers have been reported to differentially bind and as a consequence, differentially perturb proton and carbon chemical shifts, for enantiomeric amine salts.[173-175] Cram and coworkers have performed similar experiments with chiral binaphthyl analogues of crown ethers.[176]

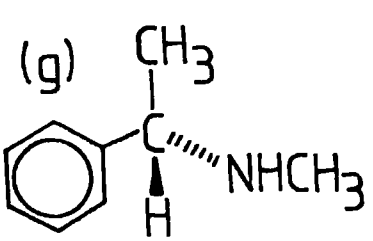
Mosher's M.T.P.A. has also been used as a C.S.A. for α-amino acid esters[157] and more recently for primary, secondary and tertiary amines,[177] (40), Table 12.

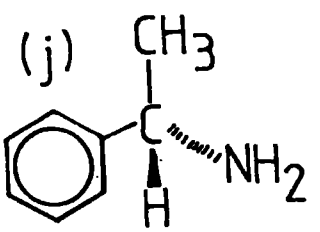
40.











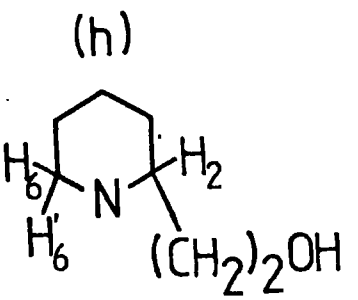


Table 12

Proton Chemical Shift Non-equivalence Induced in Chiral Amines in the Presence of M.T.P.A.

No	Compound	Affected Proton	$\Delta\delta^k$	Absolute Configuration[l]
1	(40a)	H'6	0.067	3R, 8aR
		H3	0.016	not assigned
2	(40b)	CH_3	0.013	R
		H'2	0.052	R
3	(40c)	H3	0.160	6R, 10bS
		H5	0.120	6R, 10bR
4	(40d)	H5	0.130	6S, 10bR
5	(40e)	H3	0.156	6R, 10bS
		H5	0.110	6S, 10bR
6	(40f)	CH_3	0.019	S
		H	0.017	R
7	(40g)	H	0.233	R
		CH_3	0.070	R
		NCH_3	0.020	R
8	(40h)	H2	0.089	S
		H6	0.034	S
		H'6	0.095	R
9	(40j)	H	0.035[m]	R
		H	0.061[n]	R
		CH_3	0.007[n]	R

k) Spectra obtained in d_6-benzene unless otherwise noted.

l) Configuration giving high frequency sense of non-equivalence.

m) In d-chloroform.

n) In d_5-pyridine.

The magnitude of chemical shift non-equivalence is markedly insensitive to dilution varying only slightly over the typical N.M.R. concentration (range 0.1-0.005M). In highly concentrated solutions $\Delta\delta$ decreases due to aggregation of ion-pairs. This result is in agreement with Mikolajczyk's observation that aggregation decreases $\Delta\delta$ but does not affect the sense of non-equivalence. The chemical shift non-equivalence increases up to a limiting value for an M.T.P.A./amine ratio of 1:1, an increase to 2:1 caused no significant increase in $\Delta\delta$. This was taken as evidence for a strong 1:1 diastereomeric salt system with rapid exchange of M.T.P.A. anion. No variation of $\Delta\delta$ with enantiomeric purity was observed implying that the dissociation constants, K_3 and K_4, (and also the association constants K_1 and K_2), must be nearly equal. Within a certain related series of amines it was found that non-equivalence correlates well with absolute configuration. The reciprocal experiment, i.e. the use of chiral amines as C.S.A.s for assay of chiral acids is mentioned only once[153] and has yet to be fully explored.

Chiral solvating agents are the most elegant solution to the problem of assay of e.e. by N.M.R. The full potential of the technique has yet to be realised, the main drawback being that, as with other resolving agents, there is no "universal reagent" applicable to all systems. The best that can be achieved at present is to make an informed choice of C.S.A. according to the specific problem to hand based on the knowledge of C.S.A. functionality and performance in analogous

situations. The main advantage of C.S.A.s over C.D.A.s is their ease of use, which allows the researcher to quickly identify the appropriate C.S.A. for the problem. Although $\Delta\delta$ is smaller when using C.S.A.s than when using C.D.A.s the advent of very high field N.M.R. spectrometers (600MHz) has gone some way to assuage this difficulty.

RESULTS AND DISCUSSION

CHAPTER TWO

N.M.R. Assay of Enantiomeric Excess using Chiral Derivatising Agents-I

2.1 (S)-Methylmandelate as a C.D.A. for Chiral Acids

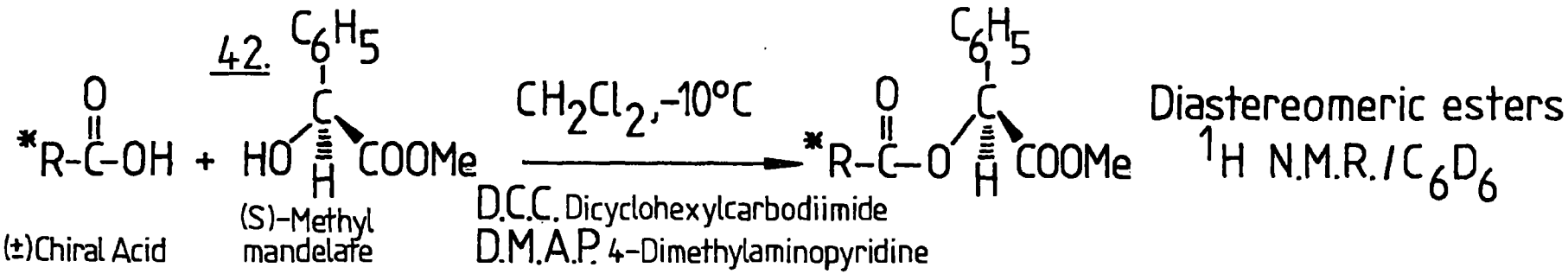
The use of enantiomerically pure acids as Chiral Derivatising Agents for racemic alcohols and amines is well established, (section 1.6). The reciprocal experiment, i.e. the use of enantiomerically pure chiral alcohols or amines as C.D.A.s for the assay of e.e. for racemic acids has received little attention. A suitable reagent requires at least one magnetically anisotropic group and must be readily available as a single enantiomer. Parker[137] has studied α-deuterated carboxylic acids using (S)-methylmandelate, (42), in which both the phenyl and carbomethoxy groups are potential magnetic non-equivalence inductors; in addition the methine proton is not spin coupled and hence is an excellent "probe" nucleus for the system.

(S)-Methyl mandelate is now shown to be an efficient C.D.A. for a range of primary, secondary, and tertiary chiral acids, (43). The derivatising reaction involves esterification under non-racemising conditions, (Scheme 1), i.e. at -10°C in dichloromethane using dicyclohexylcarbodiimide, (D.C.C.), and 4-dimethylamino-pyridine, (D.M.A.P.).[178,179] A 10% excess of (S)-methyl mandelate was used and the reaction was left to go to completion. The product esters were purified by preparative thin layer chromatography. In order to establish that no accidental enrichment or racemisation of the acid accompanies derivatisation, compounds of known enantiomeric excess were

Derivatisation of Chiral Primary, Secondary and Tertiary Acids

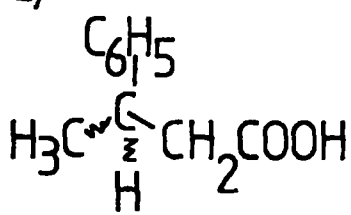
Scheme 1.

Esterification under non-racemising conditions



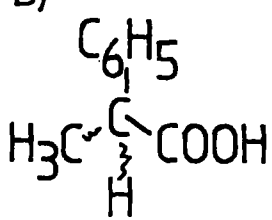
SUBSTRATES 43.

a)



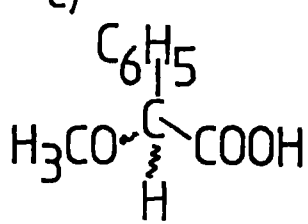
3-Phenylbutyric acid

b)



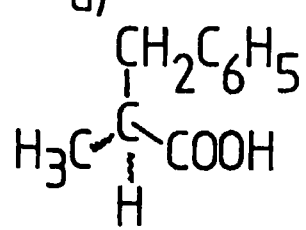
2-Phenylpropionic acid

c)



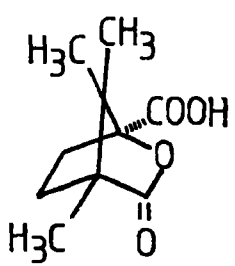
α-Methoxyphenylethanoic acid

d)



2-Methyl-3-phenylpropionic acid

e)



Camphanic acid

derivatised. Comparison was then made between the actual e.e. and the enantiomeric purity values obtained by integration of diastereomeric signals. The proton N.M.R. spectra 1-5 illustrate the results obtained for the tertiary acid (±)-3-oxo-4,7,7-trimethyl-2-oxa-bicyclo-[2.2.1]-heptane-1-carboxylic acid, (camphanic acid). Spectrum 6 collects these into one "stacked" plot. The proton N.M.R. spectra 7-11 illustrate the results obtained with the secondary acid (±)-2-phenylpropionic acid. Spectrum 12 collects these spectra into one "stacked" plot. Table 13 summarises the observed chemical shift non-equivalence for the diastereomeric substituent groups in derivatised substrates (43) and presents a comparison of actual and measured enantiomeric compositions.

1. Integrated enantiomeric purity values are within ±3% of the actual enantiomeric purity. This confirms that the derivatisation step does not cause racemisation or enrichment of the acid substrate. This result also implies that the method is accurate to ±3% except in the case of M.T.P.A. where derivatisation appears to be diastereoselective.[122] This could result from incomplete derivatisation of M.T.P.A. enantiomers reacting at different rates with the C.D.A.
2. The method is sufficiently sensitive to detect and permit measurement of the residual enantiomeric impurity in commercial samples of chiral acids supplied as single enantiomers (see Table 13 note a).
3. The sense of non-equivalence for the mandelate methine proton is constant for all the esters studied, but that for the mandelate $COOCH_3$ protons is reversed when the acid methoxy substituent is exchanged for a methyl group.

Spectrum 1

SUBSTRATE:

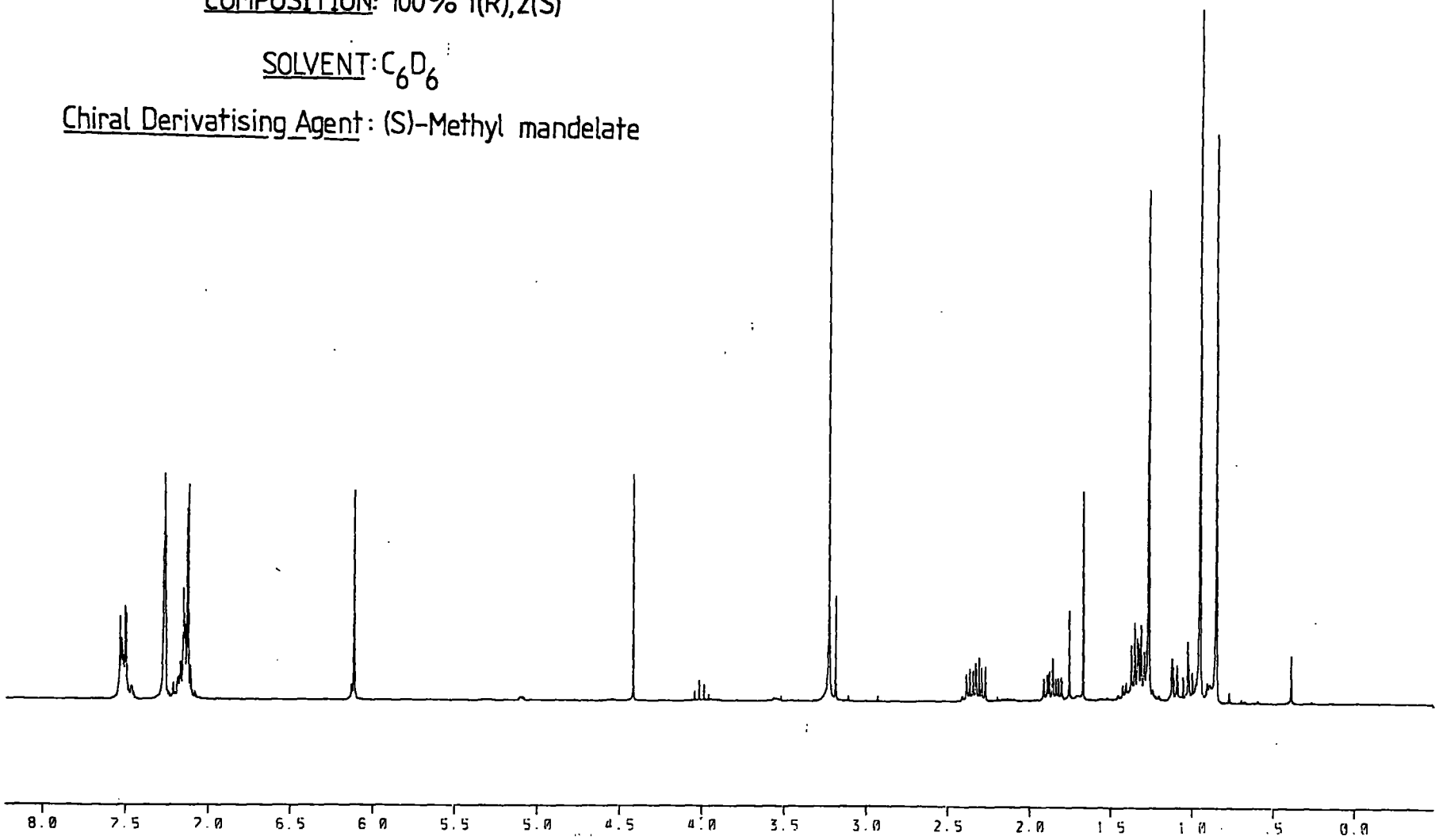
3-Oxo-4,7,7-trimethyl-2-oxabicyclo[2.2.1.]heptane-1-carboxylic acid

(Camphanic acid)

COMPOSITION: 100% 1(R),2(S)

SOLVENT: C_6D_6

Chiral Derivatising Agent: (S)-Methyl mandelate



Spectrum 2

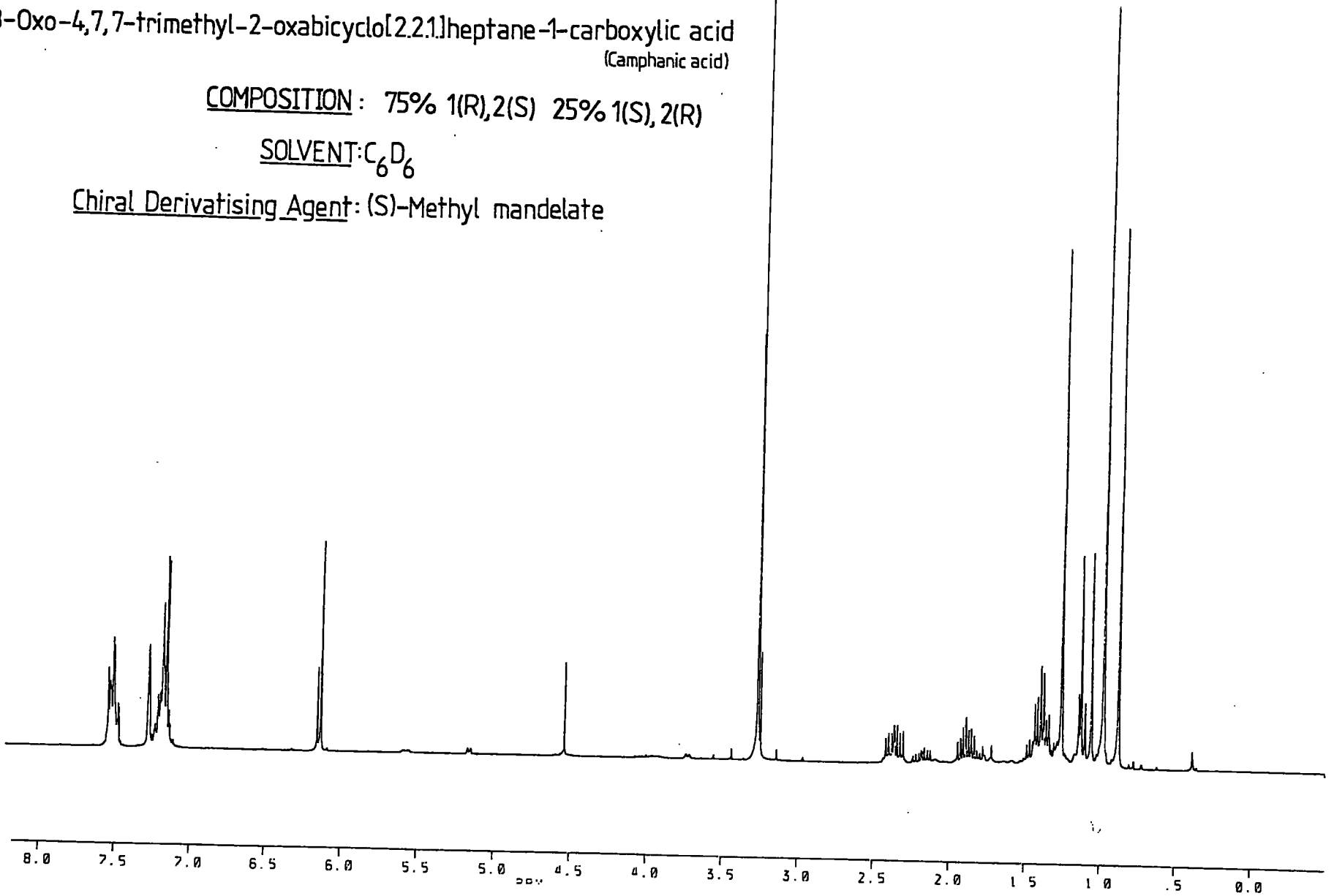
SUBSTRATE:

3-Oxo-4,7,7-trimethyl-2-oxabicyclo[2.2.1.]heptane-1-carboxylic acid
(Camphanic acid)

COMPOSITION : 75% 1(R),2(S) 25% 1(S), 2(R)

SOLVENT: C_6D_6

Chiral Derivatising Agent: (S)-Methyl mandelate



Spectrum 3

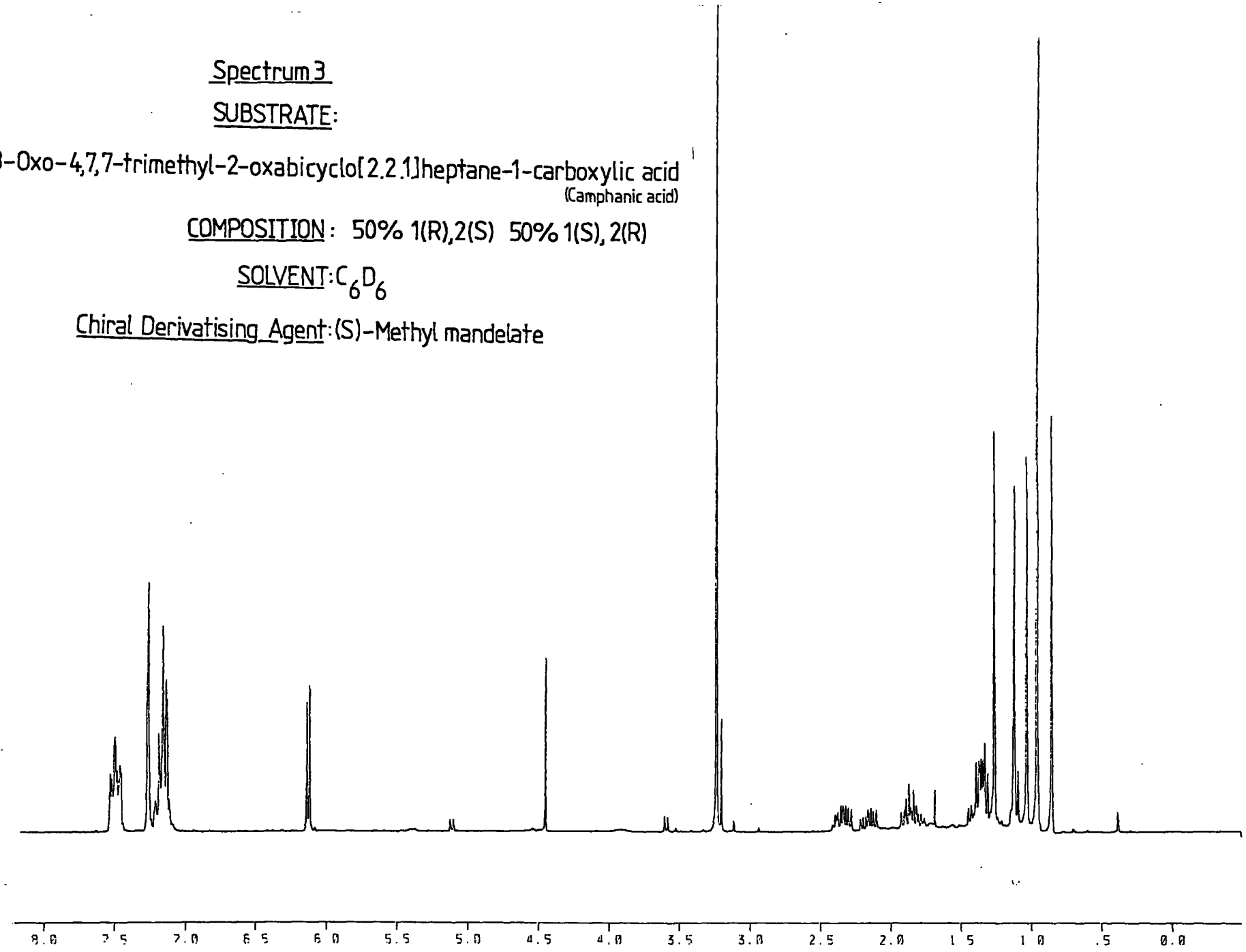
SUBSTRATE:

3-Oxo-4,7,7-trimethyl-2-oxabicyclo[2.2.1]heptane-1-carboxylic acid
(Camphanic acid)

COMPOSITION: 50% 1(R),2(S) 50% 1(S), 2(R)

SOLVENT: C_6D_6

Chiral Derivatising Agent: (S)-Methyl mandelate



Spectrum 4

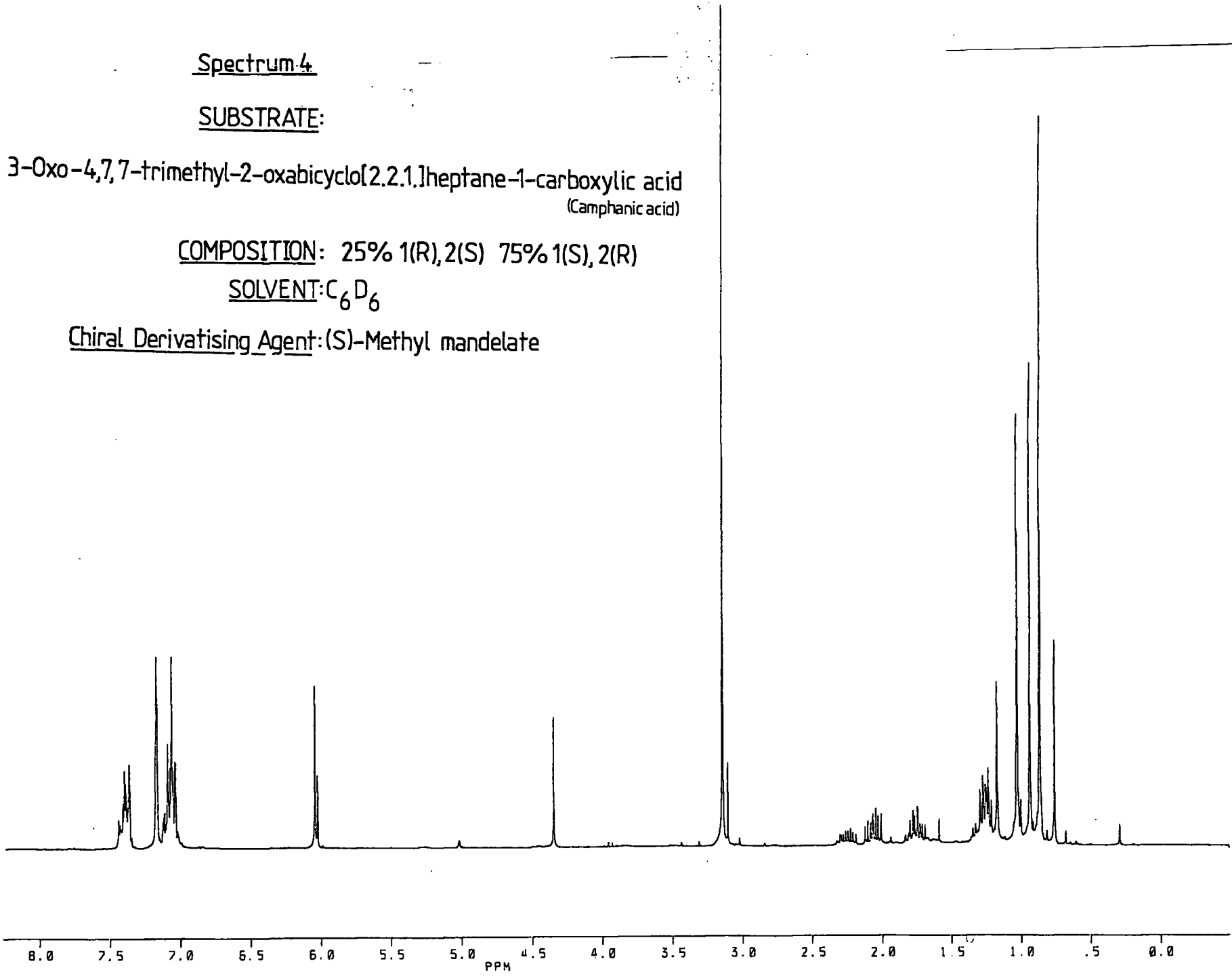
SUBSTRATE:

3-Oxo-4,7,7-trimethyl-2-oxabicyclo[2.2.1.]heptane-1-carboxylic acid
(Camphanic acid)

COMPOSITION: 25% 1(R),2(S) 75% 1(S),2(R)

SOLVENT: C_6D_6

Chiral Derivatising Agent: (S)-Methyl mandelate



Spectrum 5

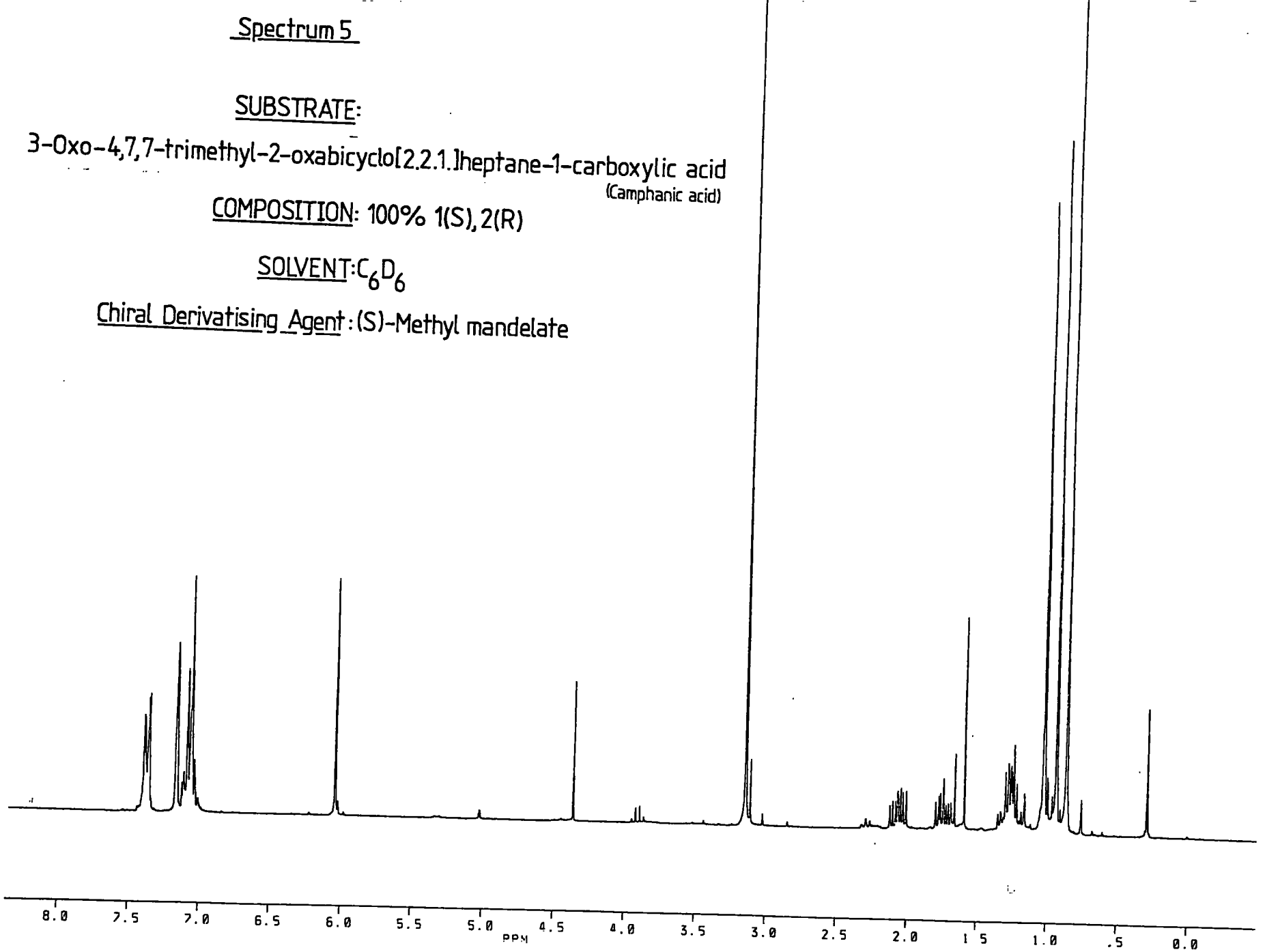
SUBSTRATE:

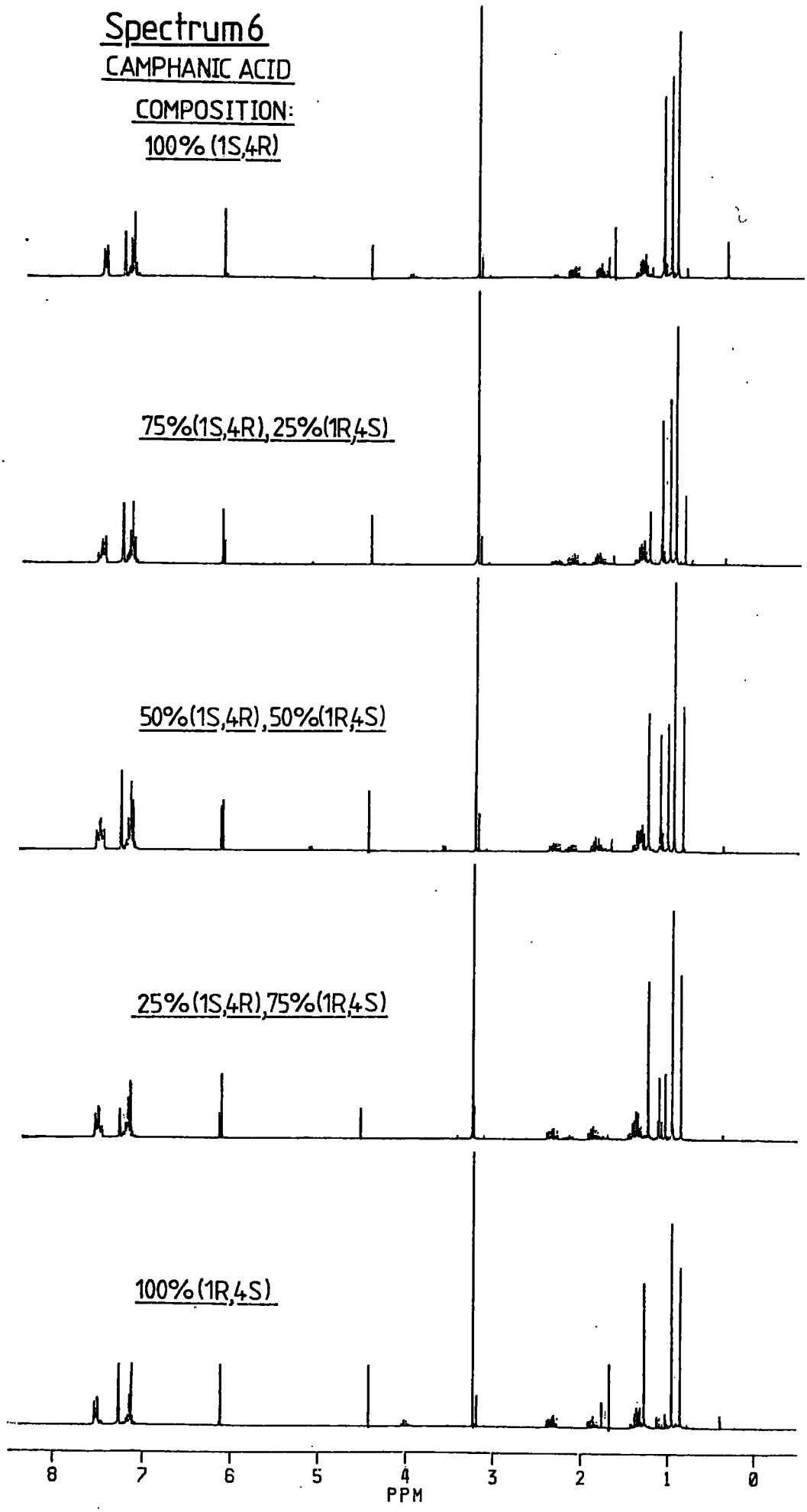
3-Oxo-4,7,7-trimethyl-2-oxabicyclo[2.2.1.]heptane-1-carboxylic acid
(Camphanic acid)

COMPOSITION: 100% 1(S), 2(R)

SOLVENT: C_6D_6

Chiral Derivatising Agent: (S)-Methyl mandelate




Spectrum 6
CAMPHANIC ACID
COMPOSITION:
100% (1S,4R)
75%(1S,4R), 25%(1R,4S)
50%(1S,4R), 50%(1R,4S)
25%(1S,4R), 75%(1R,4S)
100%(1R,4S)
8
7
6
5
4
3
2
1
0
PPM

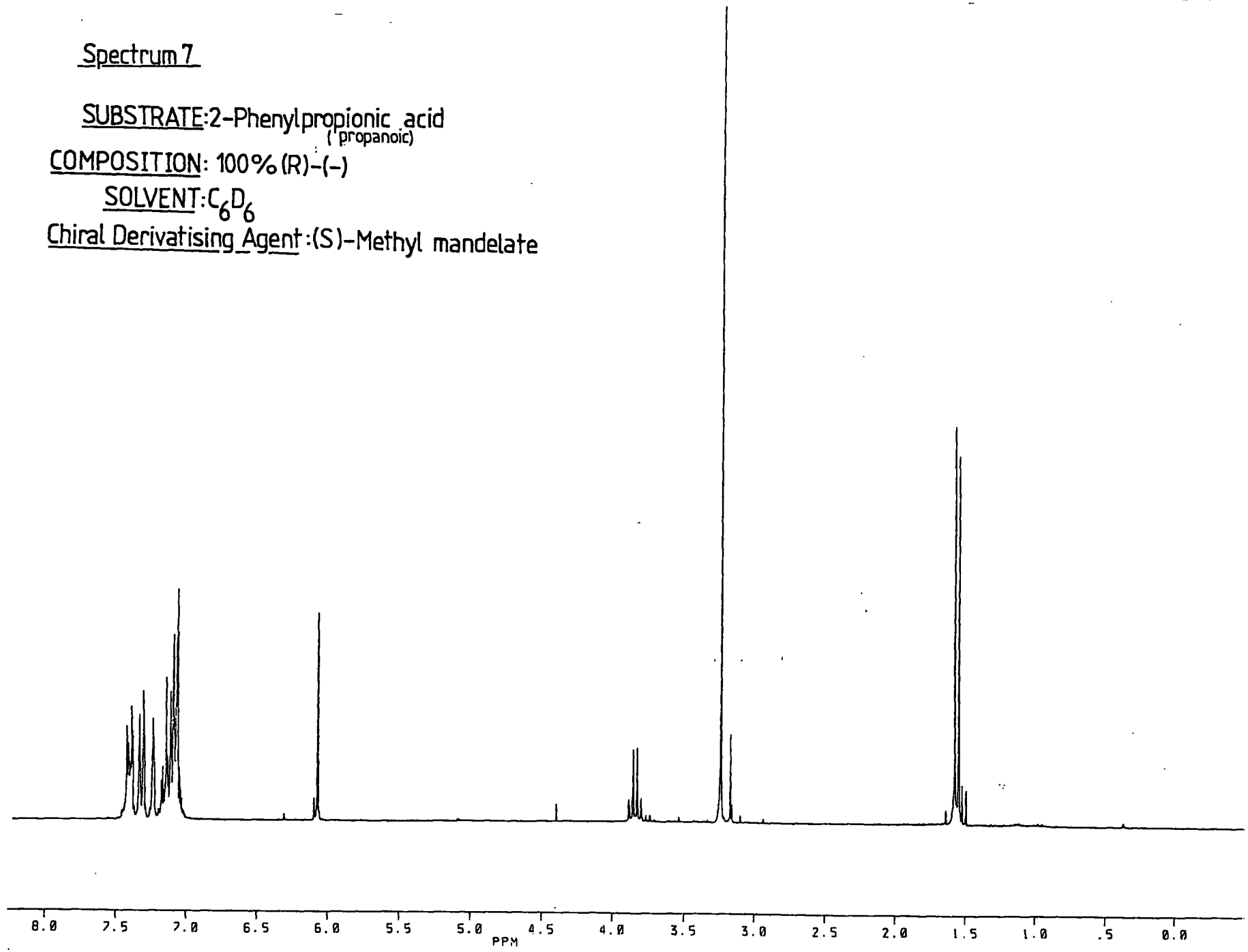
Spectrum 7

SUBSTRATE: 2-Phenylpropionic acid ('propanoic)

COMPOSITION: 100% (R)-(-)

SOLVENT: C_6D_6

Chiral Derivatising Agent: (S)-Methyl mandelate



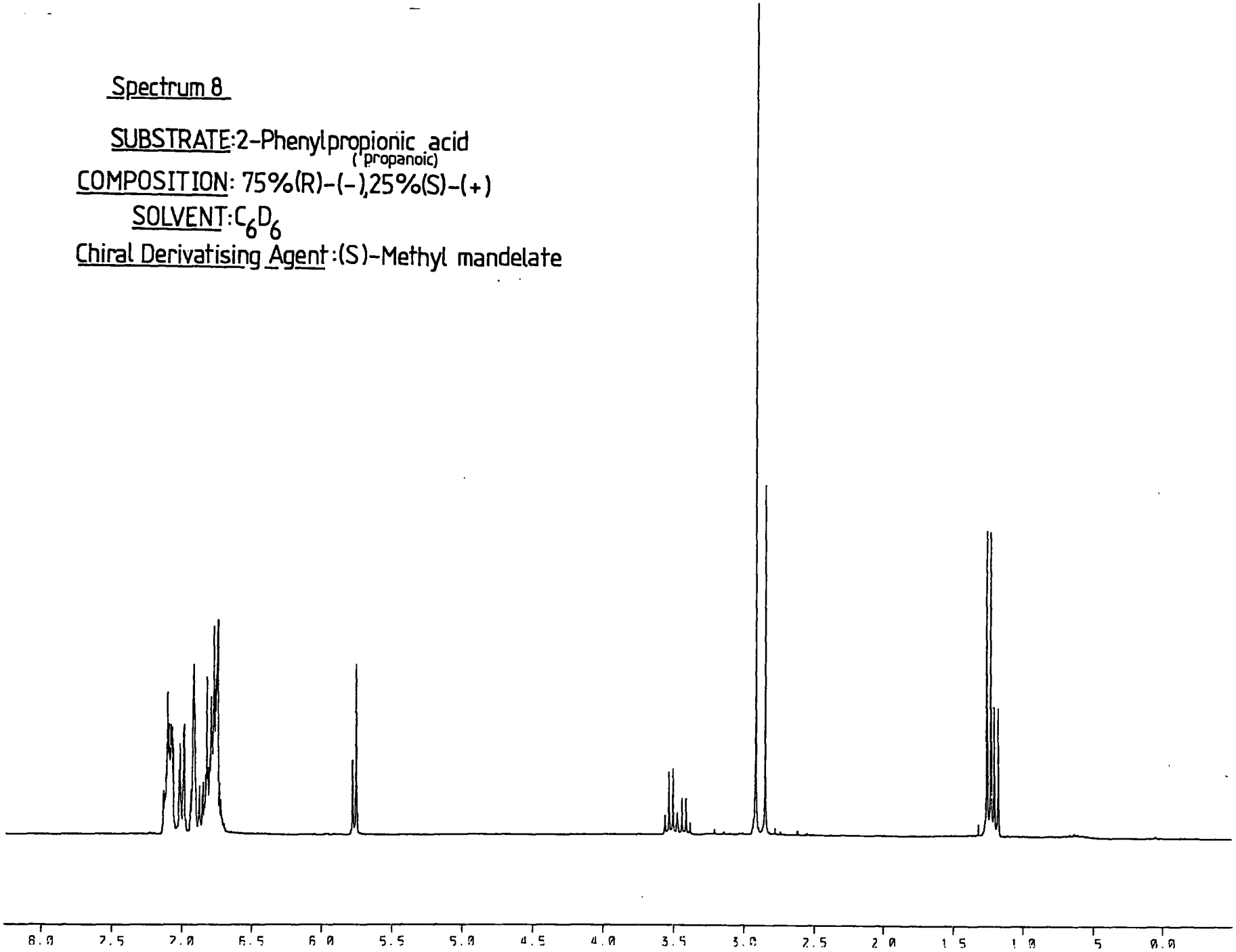
Spectrum 8

SUBSTRATE: 2-Phenylpropionic acid (*propanoic)

COMPOSITION: 75%(R)-(-),25%(S)-(+)

SOLVENT: C_6D_6

Chiral Derivatising Agent: (S)-Methyl mandelate



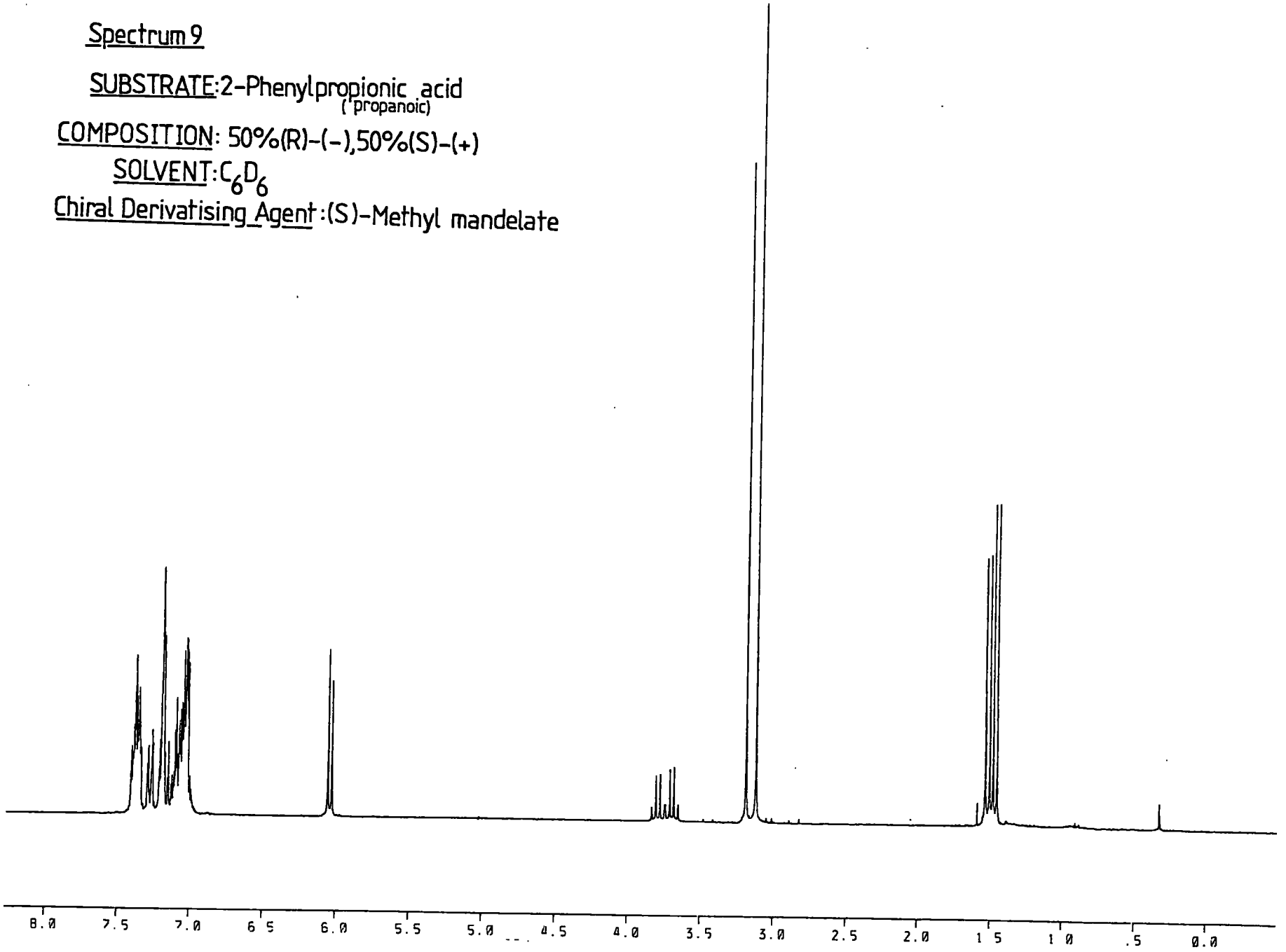
Spectrum 9

SUBSTRATE:2-Phenylpropionic acid ('propanoic)

COMPOSITION: 50%(R)-(-),50%(S)-(+)

SOLVENT:C_6D_6

Chiral Derivatising Agent:(S)-Methyl mandelate



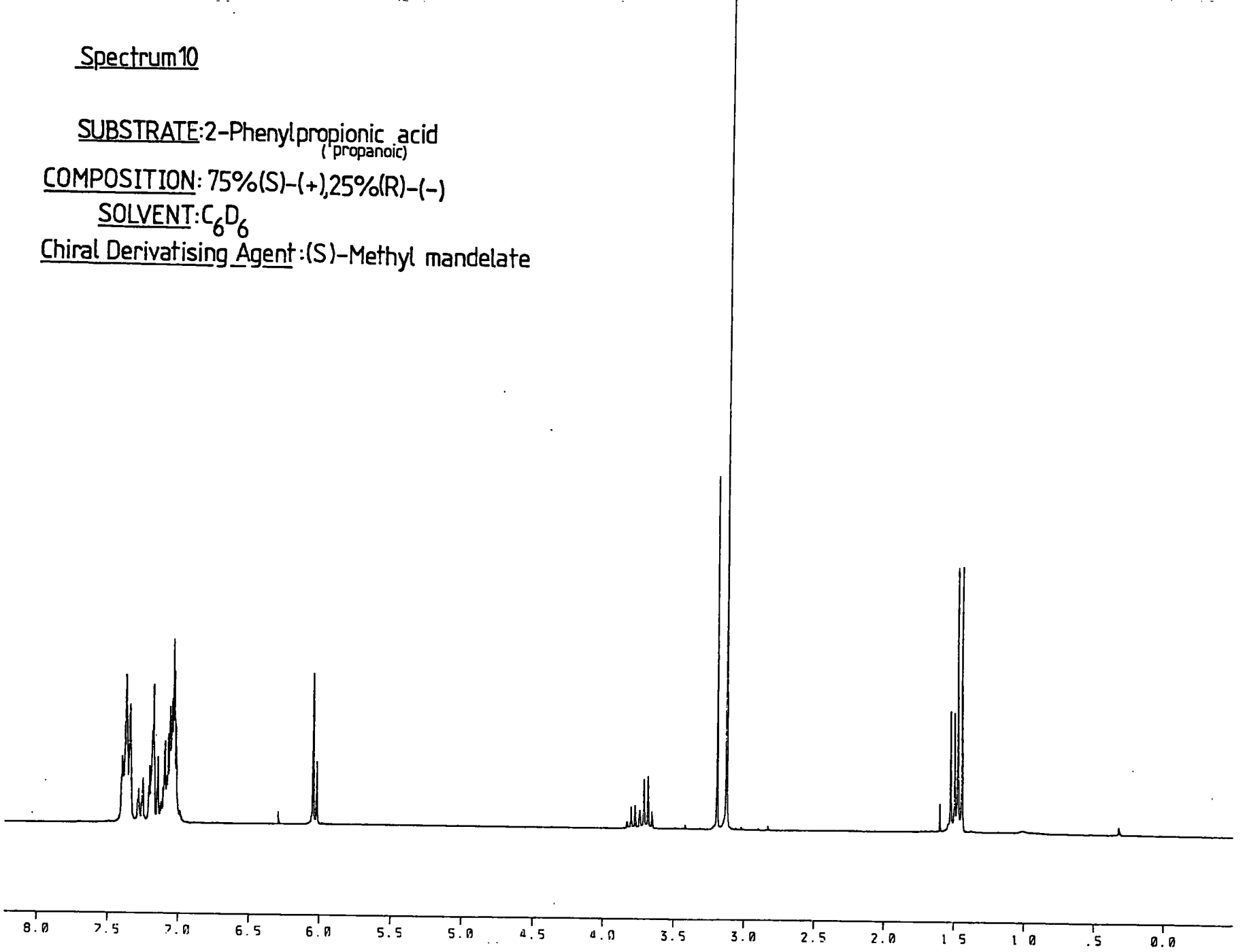
Spectrum 10

SUBSTRATE: 2-Phenylpropionic acid ('propanoic)

COMPOSITION: 75%(S)-(+), 25%(R)-(-)

SOLVENT: C_6D_6

Chiral Derivatising Agent: (S)-Methyl mandelate



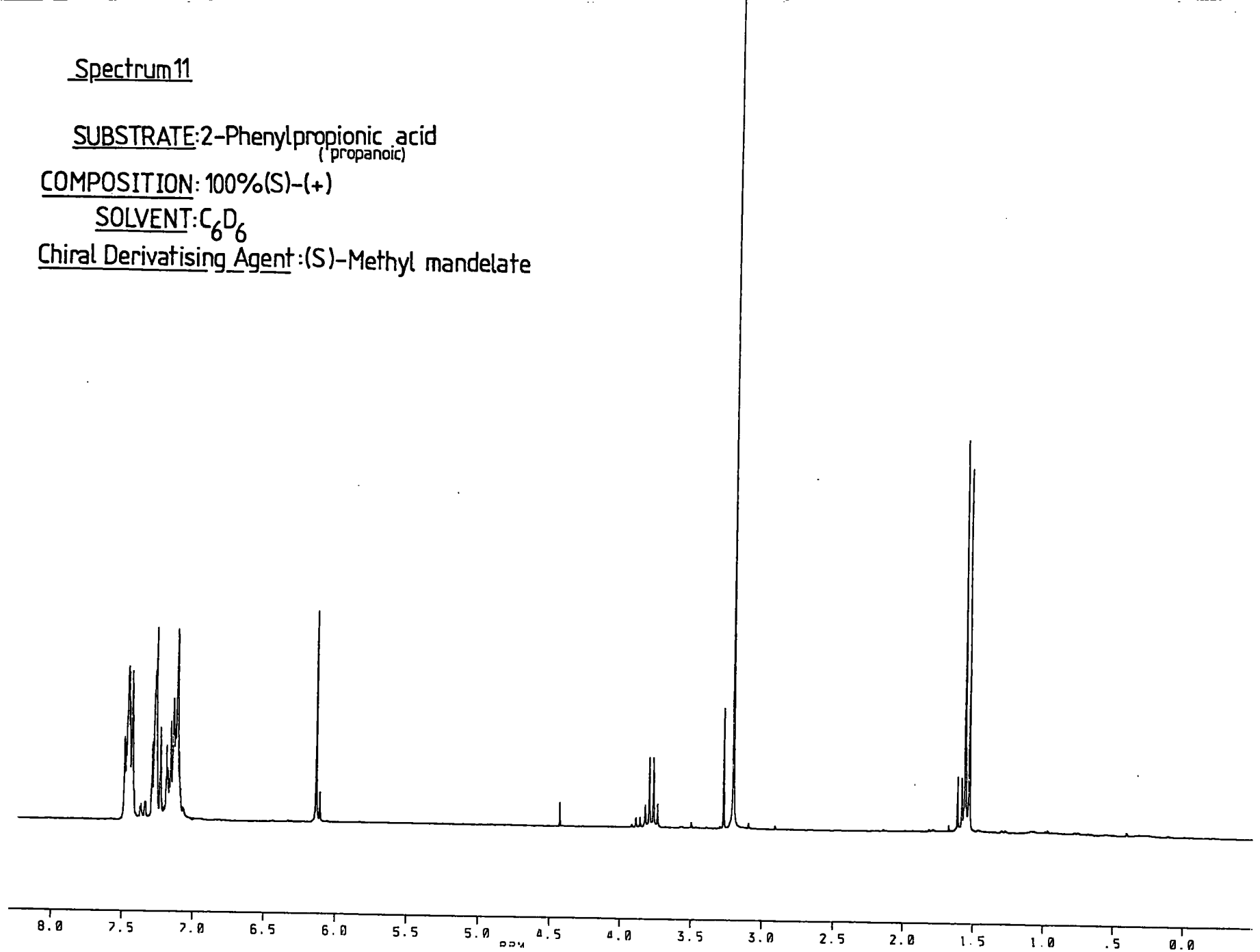
Spectrum 11

SUBSTRATE: 2-Phenylpropionic acid
(2-propanoic)

COMPOSITION: 100%(S)-(+)

SOLVENT: C_6D_6

Chiral Derivatising Agent: (S)-Methyl mandelate



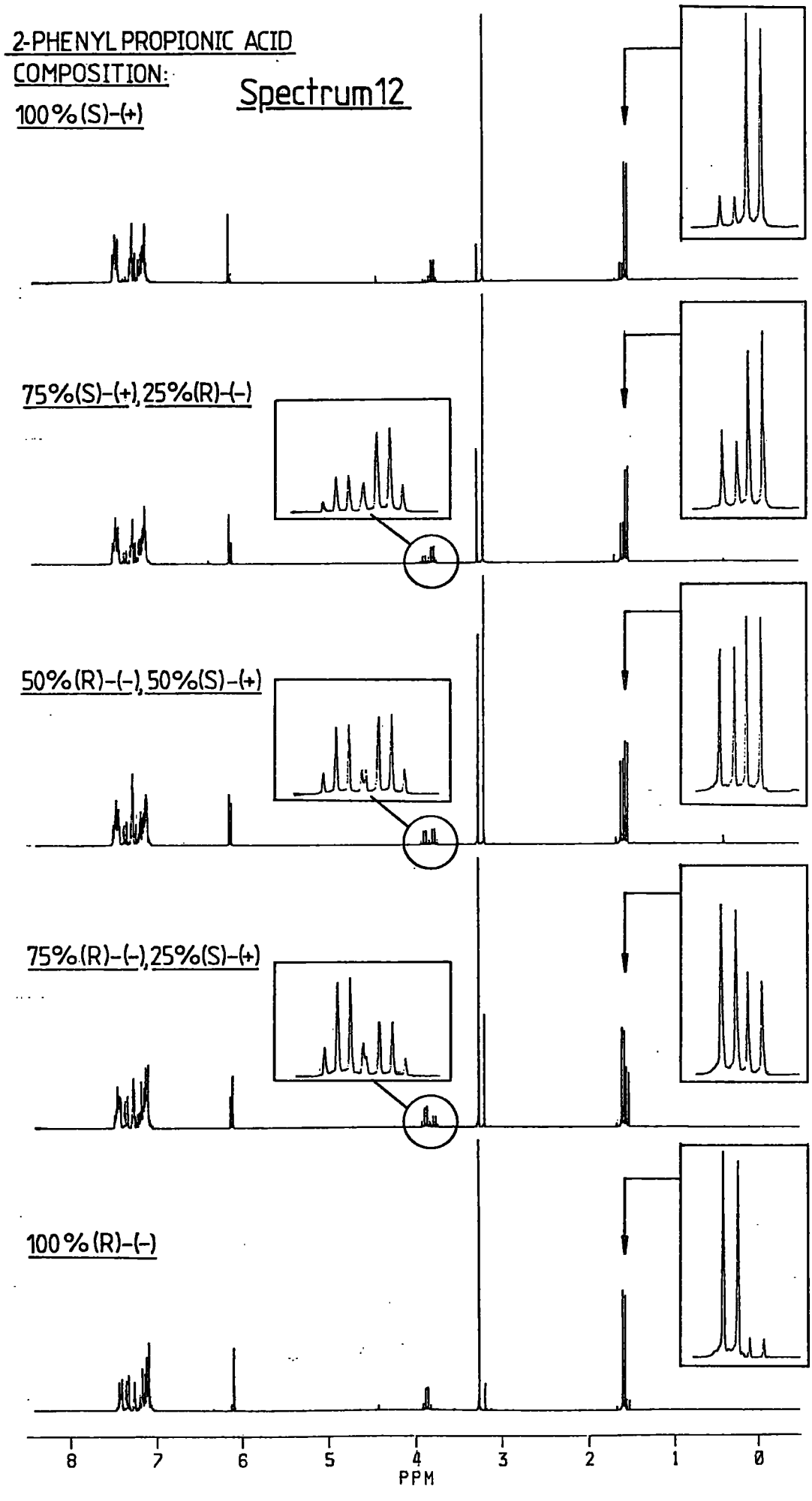

2-PHENYL PROPIONIC ACID
COMPOSITION:
100% (S)-(+)
Spectrum 12
75% (S)-(+), 25% (R)-(-)
50% (R)-(-), 50% (S)-(+)
75% (R)-(-), 25% (S)-(+)
100% (R)-(-)
8
7
6
5
4
3
2
1
0
PPM

Table 13

Proton Chemical Shift Non-equivalence for Diastereomeric Esters Derived from Chiral Acids of Known Composition and (S)-Methyl mandelate*

No	Composition[a]	Magnitude[b] and Sense[c] of Chem.Shift Non-equivaln						Integrated[d] Composition	
Compound: α-Methoxy-phenylacetic acid, (43c).[f]		Mand.CH		Acid CH		COOMe	OMe		
1	99%RS 1%SS	0.03	Lf	e		e	0.07 Hf	97%RS	3%SS
2	74%RS 26%SS	0.03	Lf	0.09	Hf	0.04 Lf	0.08 Hf	76%RS	24%SS
3	51%RS 49%SS	0.04		0.09		0.04	0.08	50%RS	50%SS
4	27%RS 73%SS	0.03	Hf	0.10	Lf	0.05 Hf	0.08 Lf	25%RS	75%SS
5	1%RS 99%SS	e		e		e	0.07 Lf	4%RS	96%SS
Compound: 2-phenylpropanoic acid, (43b).		Mand.CH		Acid CH		COOMe	Acid Me		
6	97%RS 3%SS	0.03	Lf	e		0.06 Hf	0.06 Hf	88%RS	12%SS
7	71%RS 29%SS	0.03	Lf	0.09	Hf	0.06 Hf	0.06 Hf	70%RS	30%SS
8	52%RS 48%SS	0.03		0.08		0.07	0.05	54%RS	46%SS
9	32%RS 68%SS	0.03	Hf	0.08	Lf	0.07 Lf	0.05 Lf	31%RS	69%SS
10	3%RS 97%SS	0.03	Hf	e		0.06 Lf	0.05 Lf	7%RS	93%SS
Compound: Camphanic acid, (43e).		Mand.CH		CH_3		CH_3	COOMe		
11	>99% 1R,4S	e		0.15	Lf	0.17 Hf	e	97%	1R,4S
12	74% 1R,4S	0.02	Lf	0.14	Lf	0.18 Hf	e	73%	1R,4S
13	51% 1R,4S	0.02		0.14		0.18	e	50%	1R,4S
14	73% 1S,4R	0.02	Hf	0.16	Hf	0.19 Lf	e	73%	1S,4R
15	>98% 1S,4R	e		0.14	Hf	0.19 Lf	e	96%	1S,4R
Compound: 3-Phenylbutanoic acid, (43a).		Mand.CH				COOMe			
16	50%RS 50%SS	0.06				0.02		50%RS	50%SS
Compound: 2-Methyl-3-phenylpropanoic acid, (43d).[g]		Mand.CH		Acid CH_3		Acid CH	Acid CH'		
17	50%RS 50%SS	0.04	Lf	0.12	Hf	0.02 Lf	0.02 Lf	49%RS	51%SS
Compound: M.T.P.A.,(28).		Mand.CH		COOMe		^{19}F CF_3			
							^{1}H	64%RS	36%SS
18	50%RS 50%SS	0.02		0.23		0.61	^{19}F	62%RS	38%SS

Notes for Table 13

(*) Methyl mandelate (S)-(+)-, 99% Gold Label, Aldrich
(R)-(-)-, 99% Gold Label, Aldrich

If it is assumed that the 1% impurity is enantiomeric and not chemical in nature, then this will cause an inherent error of ±2% in all measurements of enantiomeric excess whenever methyl mandelate is used as a C.D.A.

(a) In spectra 1-6 and 7-12 the enantiomeric compositions quoted are the ideal values.

Compositions as specified by commercial suppliers are listed.

43a) 3-Phenylbutanoic acid Aldrich Chemical Company

43b) 2-Phenylpropanoic acid (S)-(+)-, 97%, Aldrich Chem. Co.
(R)-(-)-, 97%, Aldrich Chem. Co.

43c) α-Methoxyphenylacetic acid
(S)-(+)-, 99%, Aldrich Chem. Co.
(R)-(-)-, 99%, Aldrich Chem. Co.

43d) 2-Methyl-3-phenylpropanoic acid

43e) Camphanic acid (1R,4S)-(+)-, >99%, Merck-Schuchart
(1S,4R)-(-)-, >98%, Merck-Schuchart

The "Composition" column entries 1 and 5; 6 and 10; 11 and 15 in Table 13 are those specified by the manufacturers as above. The corresponding "Integrated Composition" column shows clearly that, in all cases, the enantiomeric purity is less than that specified.

As a consequence mixtures prepared from these compounds will not agree with the ideal values {i.e.75%,25% 50%,50% and 25%,75%}. The compositions calculated for 3:1, 1:1 and 1:3 mixtures are shown in the appropriate "composition" column. The integrated compositions are within ±3% of these actual values.

(b) Chemical Shift Non-equivalence in ppm, d_6-benzene solvent at 298K, 250MHz ^1H Spectra except f at 200MHz.

(c) Sense of chemical shift non-equivalence noted for the more abundant enantiomer:

Hf Shifted to higher frequency than the corresponding signal for the minor enantiomer.
Lf Shifted to lower frequency than the corresponding signal for the minor enantiomer.

(d) Integration was performed on all resolved peaks in the spectrum, an average value is presented:

For example with 2-phenylpropanoic acid[h] (43b)

Ideal Composition	Calculated Composition	Integrated Composition Mand.CH	COOMe	Acid Me
100%(S)		88%(S)	88%(S)	89%(S)
0%(R)		12%(R)	12%(R)	11%(R)
75%(S)	68%(S)	71%(S)	71%(S)	69%(S)
25%(R)	32%(R)	29%(R)	29%(R)	31%(R)
50%(S)	48%(S)	46%(S)	45%(S)	46%(S)
50%(R)	52%(R)	54%(R)	55%(R)	54%(R)
25%(S)	29%(S)	30%(S)	29%(S)	30%(S)
75%(R)	71%(R)	70%(R)	71%(R)	70%(R)
0%(S)		10%(S)	9%(S)	9%(S)
100%(R)		90%(R)	91%(R)	91%(R)

(e) Not resolved.

(g) Assignments made by comparison with enantiomerically enriched acid.

(h) 2-Phenylpropanoic acid is supplied as a liquid, consequently errors in its handling are likely to be greater than those encountered with the remaining acids all of which are solids.

2.1.1 Assignment of Absolute Configuration

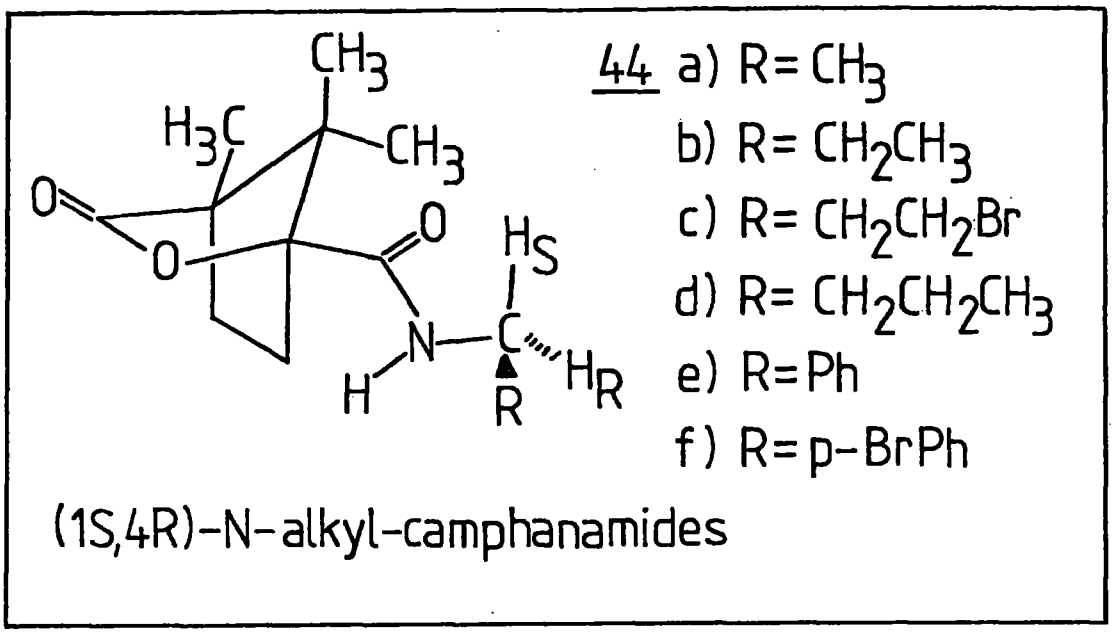
Trost[180,181] has used Mosher's[127] models for M.T.P.A. and Mandelic acid, (Figure 5), to correlate absolute configuration and sense of chemical shift non-equivalence for a limited number of mandelate esters. The sense of non-equivalence of the alcohol moiety substituents R_2 and R_3 is explained in terms of the differential shielding effect of the acid phenyl ring in (I) and (II). Thus in this, the reciprocal case, the anisochronicity of the acid substituents should be comprehensible in terms of the deshielding effects of the (S)-methylmandelate phenyl ring. The flaw in this argument is that the acid substituents are predicted to have opposite senses of non-equivalence. Table 13 shows that with substrates (43b) and (43c), both the acid substituents have the same sense of non-equivalence. This observation calls into question the applicability of the models in these specific situations. There is, however, one important factor that has been overlooked in previous models and attempted explanations of non-equivalence in esters and amides. The substituents disposed around the "racemic" {acid} terminal group in such molecules are very much closer to the magnetically anisotropic carbonyl of the link unit, (either ester or amide C=O), than they are to the remote substituents at the opposite "chiral" {mandelate} end of the molecule to which recourse is usually made for induction of anisochronicity. Hence it might be envisaged that, in the case of esters derived from (S)-methyl-mandelate, the alcohol moiety is only important in influencing the molecular conformations and that the group responsible for

induction of chemical shift non-equivalence in those conformations is the carbonyl group of the ester link.

This model, which is proposed to explain anisochronicity in acid substituents when using (S)-methylmandelate as a C.D.A., is based on the one which best explains the non-equivalence of diastereotopic methylene groups in mandelates and camphanamides. This approach uses the internally diastereotopic proton non-equivalence as a probe for molecular conformation. The next section is central to the understanding of non-equivalence resulting from molecular conformations and thus has implications in the assignment of absolute configuration for externally diastereotopic esters and amides as well as for the origins of internal diastereotopicity. It also relates directly to chiral methyl groups, (which can be "modelled" by the CH_2D function, section 1.4.2).

2.2 Origins of Chemical Shift Non-equivalence in the Diastereotopic Methylene Protons of Camphanamides

In the proton N.M.R. spectra of a series of N-alkyl-(1S,4R)-3-oxo-4,7,7-trimethyl-2-oxa-bicyclo-[2.2.1]-heptane-1-carboxamides, (camphanamides) (44), the pro-S hydrogen, H_S, consistently resonates to high frequency of the pro-R hydrogen, H_R. The chemical shift non-equivalence for the diastereotopic methylene protons, in a series of camphanamides (44a-f), is recorded in Table 14. Spectra 13a and 14a illustrate the 360MHz ^1H N.M.R. spectra for (44c) [N-(3-bromopropyl)-camphanamide] and (44f) [N-(p-bromobenzyl)-camphanamide] in d_6 benzene; the diastereotopic methylene groups are shown expanded in spectra 13b and 14b. In both cases the upper spectrum was recorded



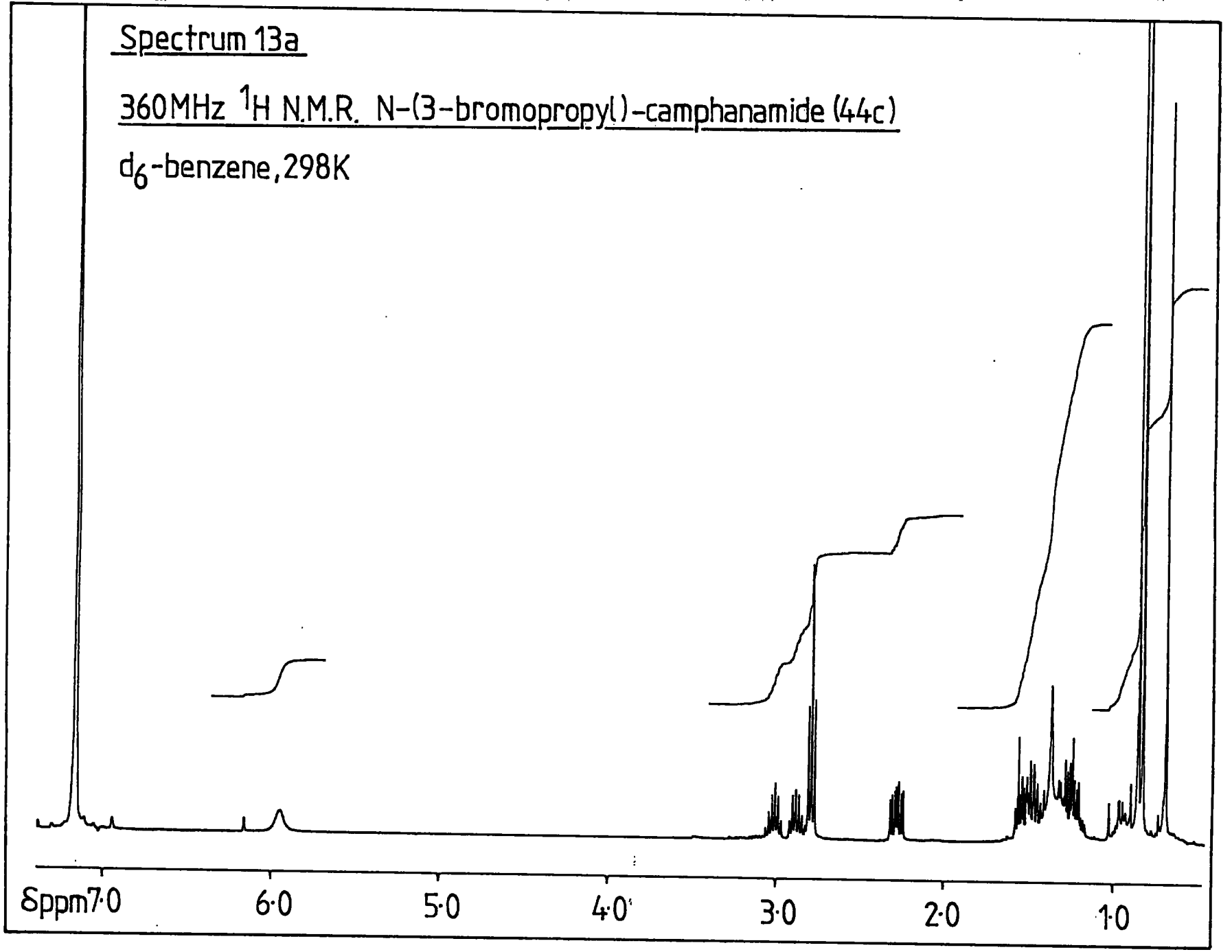
whilst decoupling the NH proton; Hs and HR couple with each other and, in the case of (44c), they also couple anisogamously with the adjacent protons. To probe the origins of the anisochronism of the geminal methylene protons in (44a-f) the p-bromobenzyl, derivative (44f), has been studied in detail. Examination of molecular models suggests that the observed chemical shift non-equivalence for the diastereotopic methylene protons is due to the neighbouring amide carbonyl anisotropy.

Table 14

Chemical Shift Non-equivalence for Diastereotopic Methylene Protons in Camphanamides (44a-f)*

No	Compound	R	δHs ppm	δHR ppm	ΔδHs HR ppm	JHs HR Hz
1	44a	Me	3.03	2.89	0.14	13.5
2	44b	Et	3.12	2.91	0.21	14.3
3	44c	CH_2CH_2Br	3.00	2.88	0.12	13.7
4	44d	n-Pr	3.11	2.95	0.16	13.6
5	44e	Ph	4.25	4.12	0.13	14.8
6	44f	p-BrC_6H_4	4.12	3.96	0.16	14.7

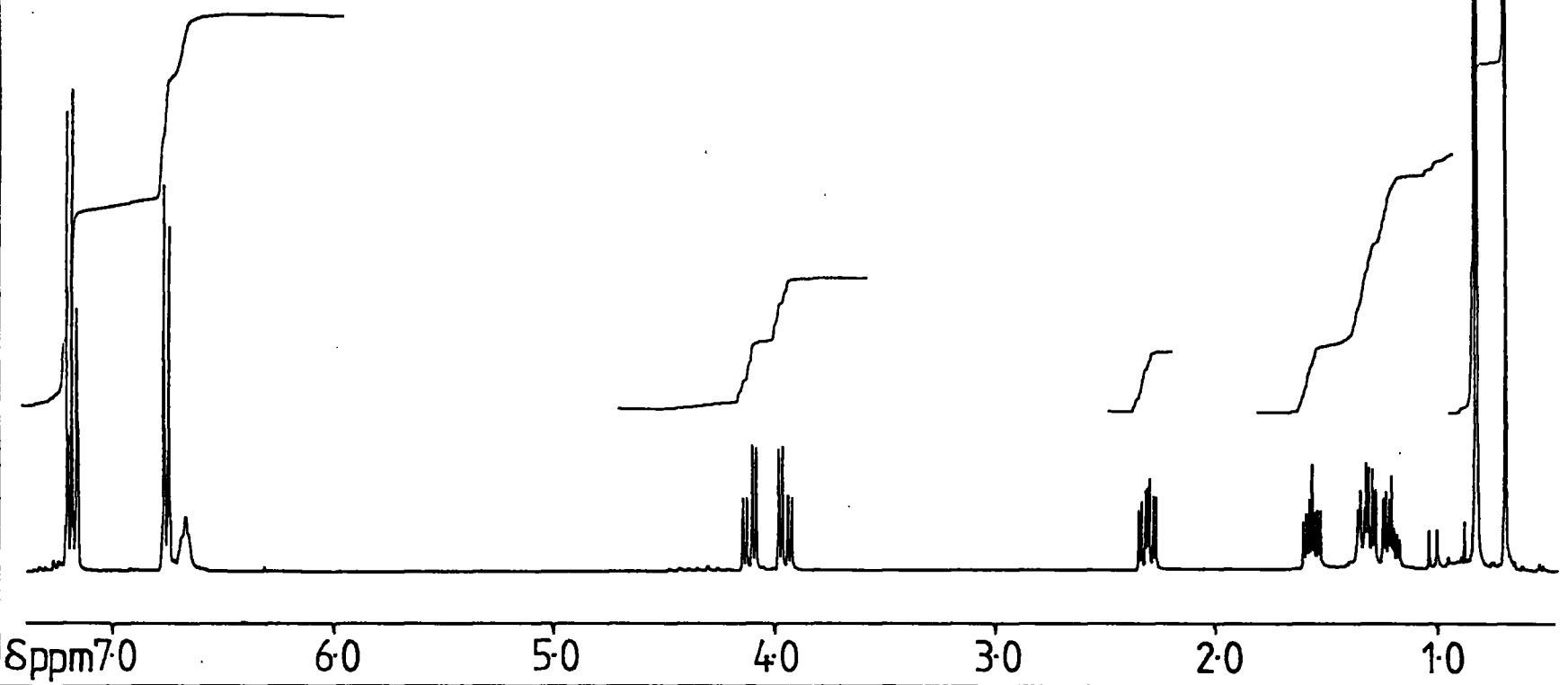
* Recorded in d_6-benzene at 298K


Spectrum 13a
360MHz ^{1}H N.M.R. N-(3-bromopropyl)-camphanamide (44c)
d_6-benzene, 298K
δppm 7·0
6·0
5·0
4·0
3·0
2·0
1·0

Spectrum 14a

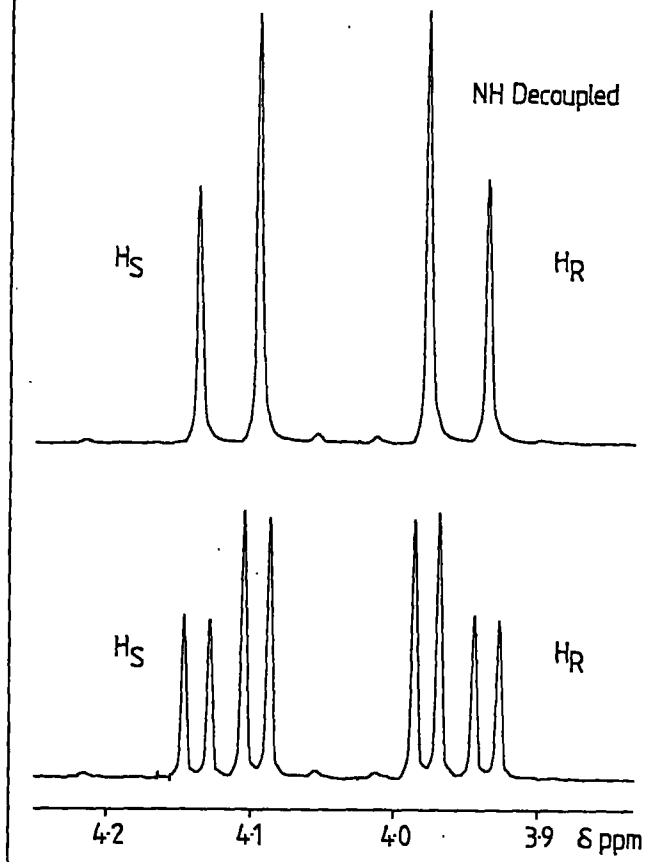
360 MHz ^{1}H·N.M.R. N-(p-bromobenzyl)-camphanamide(44f)

d_6 benzene, 298K



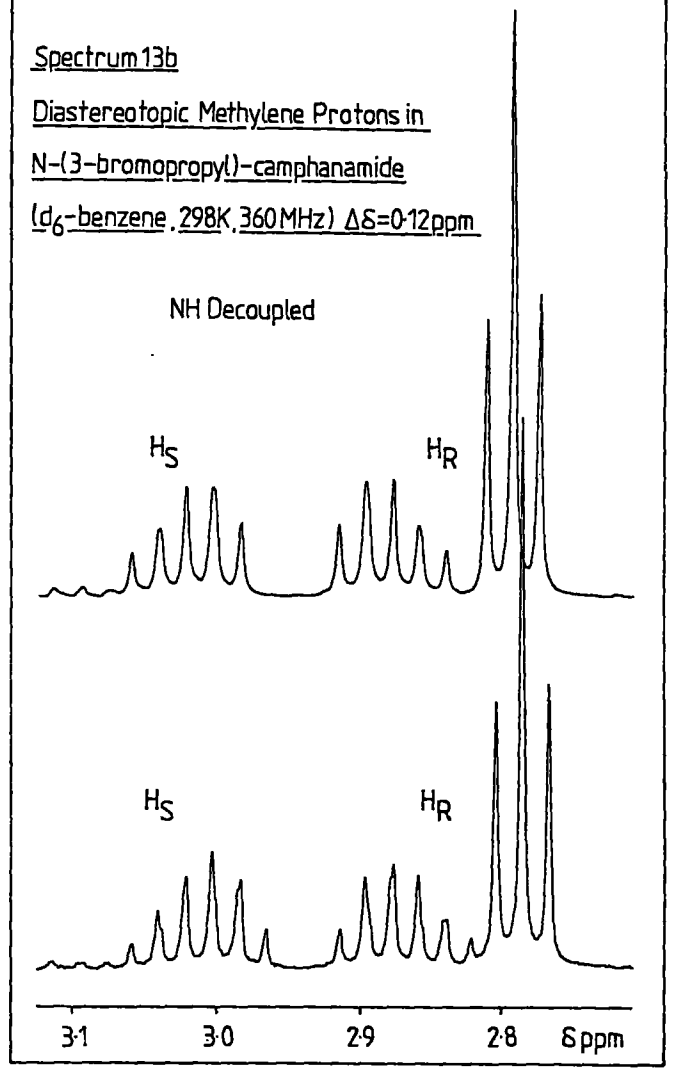
Spectrum 14b

Diastereotopic Methylene Protons in N-(p-Bromobenzyl)-camphanamide (d_6-benzene, 298K, 360MHz) $\Delta\delta$=0·16ppm



Spectrum 13b

Diastereotopic Methylene Protons in N-(3-bromopropyl)-camphanamide (d_6-benzene, 298K, 360MHz) $\Delta\delta$=0·12ppm

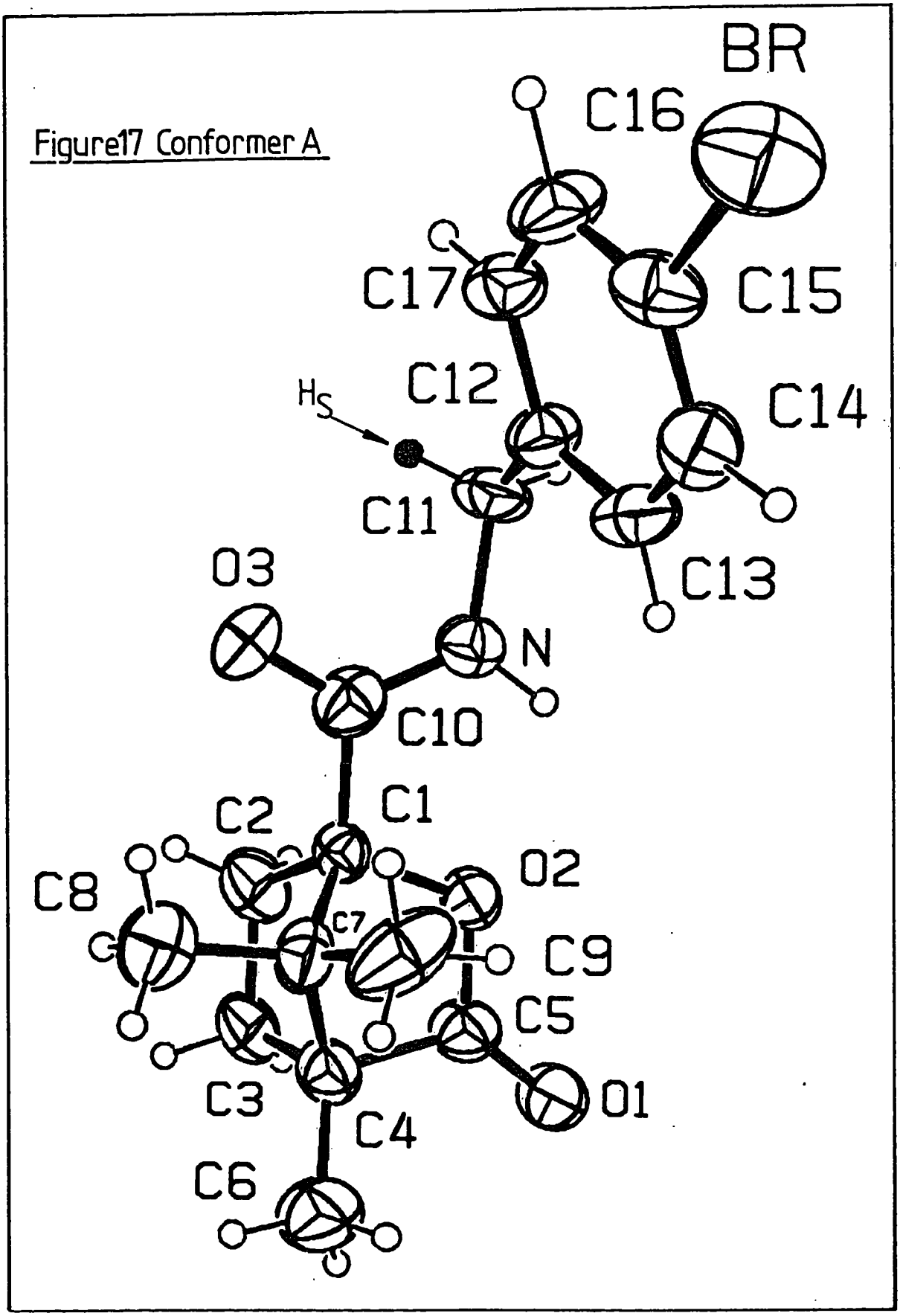


2.2.1 X-ray Structural Studies

The structure of (44f) has been determined by single crystal X-ray diffraction. There are two independent molecules A and B in the asymmetric unit. These molecules are linked into A-B pairs by NH---O hydrogen bonds between the NH group of one molecule and the lactone carbonyl of another. A view of the two molecules is shown in (Figure 17) together with the crystallographic numbering scheme. Molecules A and B are conformers related by rotation about the N-C(11) bond with simultaneous re-orientation of the phenyl ring. The values of the C(10)-N-C(11)-C(12) torsion angles are 96.6° and 286.4° for the A and B molecules respectively. The bromophenyl rings are orientated about the C(11)-C(12) bond such that the N-C(11)-C(12)-C(13) torsion angles are 31.1° and 325.7° for A and B respectively.

In molecule A the pro-S hydrogen, H_S, is closer to the magnetically anisotopic carbonyl group than the pro-R hydrogen, H_R; in molecule B the situation is reversed. Furthermore H_S is closer to the amide carbonyl in A than H_R is in B. In the solid state M.A.R. ^{13}C N.M.R. spectrum, (spectrum 15), of (44f) the lactone carbonyl signal appears as two peaks at 180.4 and 178.7 ppm which is consistent with the existence of two different molecular conformations as found in the crystal structure determination. The amide carbonyl resonance occurs at 167.0 ppm. The corresponding resonances in the solution spectra occur at 177.4 and 167.1 ppm respectively.

Figure17 Conformer A



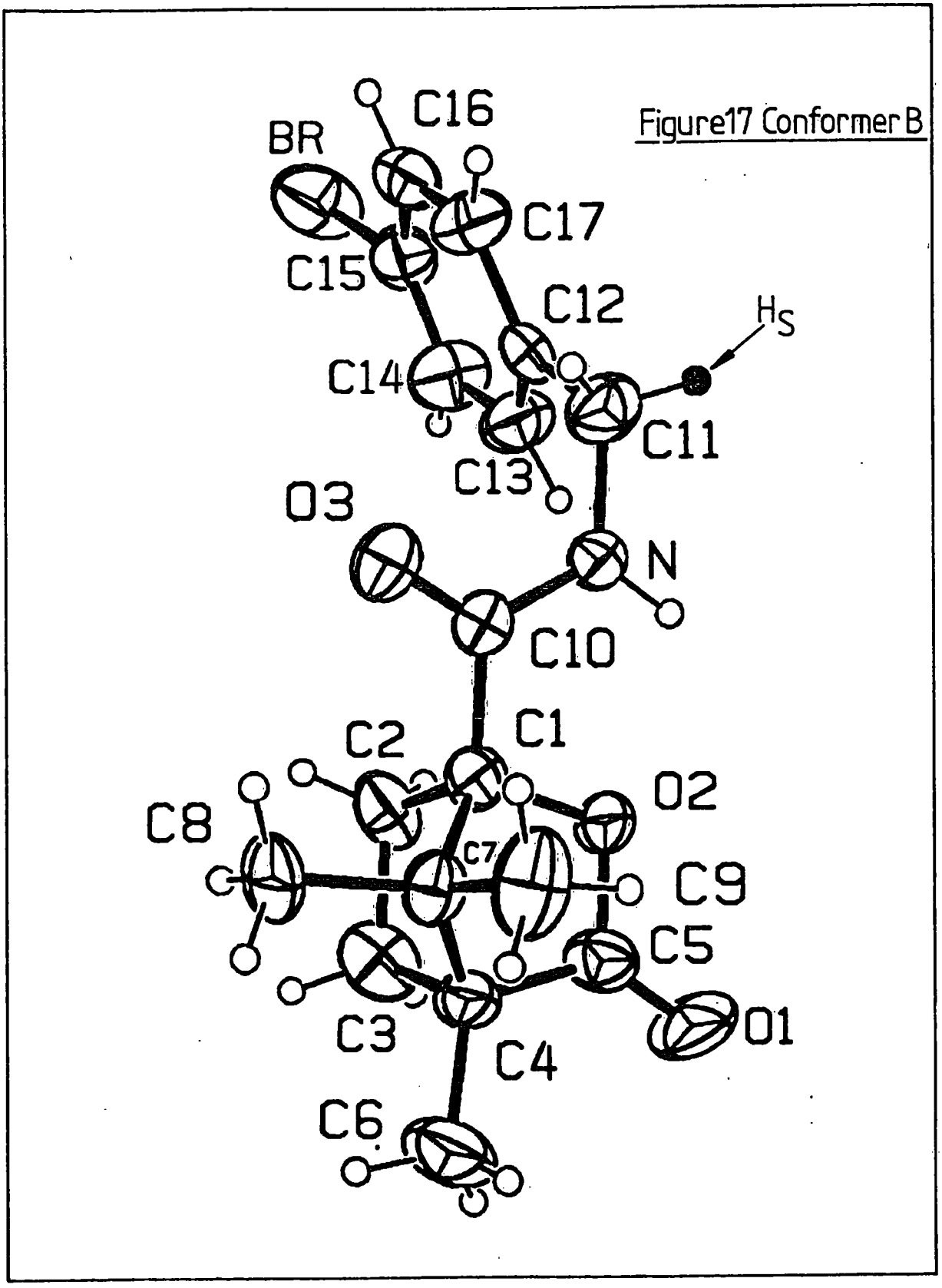
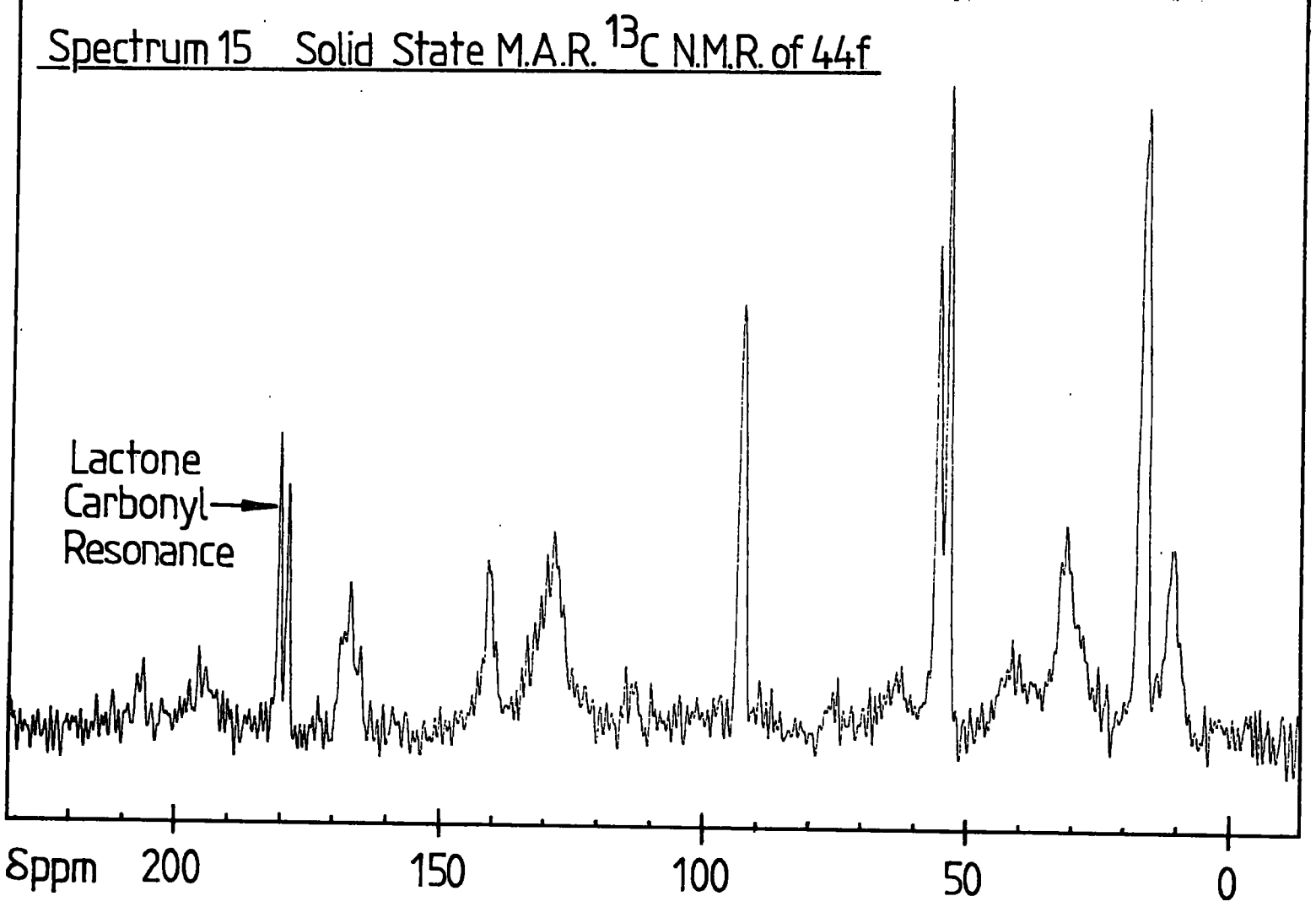


Figure17 Conformer B


Spectrum 15 Solid State M.A.R. ^{13}C N.M.R. of 44f
Lactone
Carbonyl
Resonance
δppm 200
150
100
50
0

2.2.2 Solution N.M.R. Studies

In the proton N.M.R. spectrum of (44f), [in d_6-benzene at 298K], spectra 14a and 14b, two doublet of doublets may be observed at δ 4.11 and 3.95ppm corresponding to H_S and H_R respectively. The chemical shift non-equivalence can be considered as a time averaged view of the chemical shifts, δ_i, for the protons H_R and H_S in the various possible molecular conformations, A or B. In solution each is weighted by a fractional population term ϕ_i (section 1.4.3).

Thus, $\delta(R) = \phi_A\delta(R)_A + \phi_B\delta(R)_B$

$\delta(S) = \phi_A\delta(S)_A + \phi_B\delta(S)_B$

Hence, $\Delta\delta(RS) = \phi_A(\delta(R)_A - \delta(S)_A) + \phi_B(\delta(R)_B - \delta(S)_B)$ {1}

The chemical shift non-equivalence between H_S and H_R increases linearly with decreasing temperature for both (44a) and (44f), Table 15, (Figure 18).

Table 15

Temperature and Solvent Dependence of Chemical Shift Non-equivalence in Camphanamides[a]

	Compound: 44a		Compound: 44f			
No	Temp. K	$\Delta\delta H_S H_R$[b] ppm	Temp. K	$\Delta\delta H_S H_R$[b] ppm	Solvent	$\Delta\delta H_S H_R$[c] ppm
1	323	0.120	320	0.137	C_6D_6	0.15
2	313	0.127(5)	310	0.148	$C_6D_5CD_3$	0.14
3	303	0.135	300	0.162	C_5D_5N	0.09
4	293	0.142(5)	295	0.171	$CDCl_3$	0.08
5	283	0.150	290	0.177	CCl_4	0.07
6			285	0.185	$(CD_3)_2CO$	0.07
7					CD_3OD	0.06

a) Recorded at 200 MHz.

b) In d_6-benzene

c) At 308K.

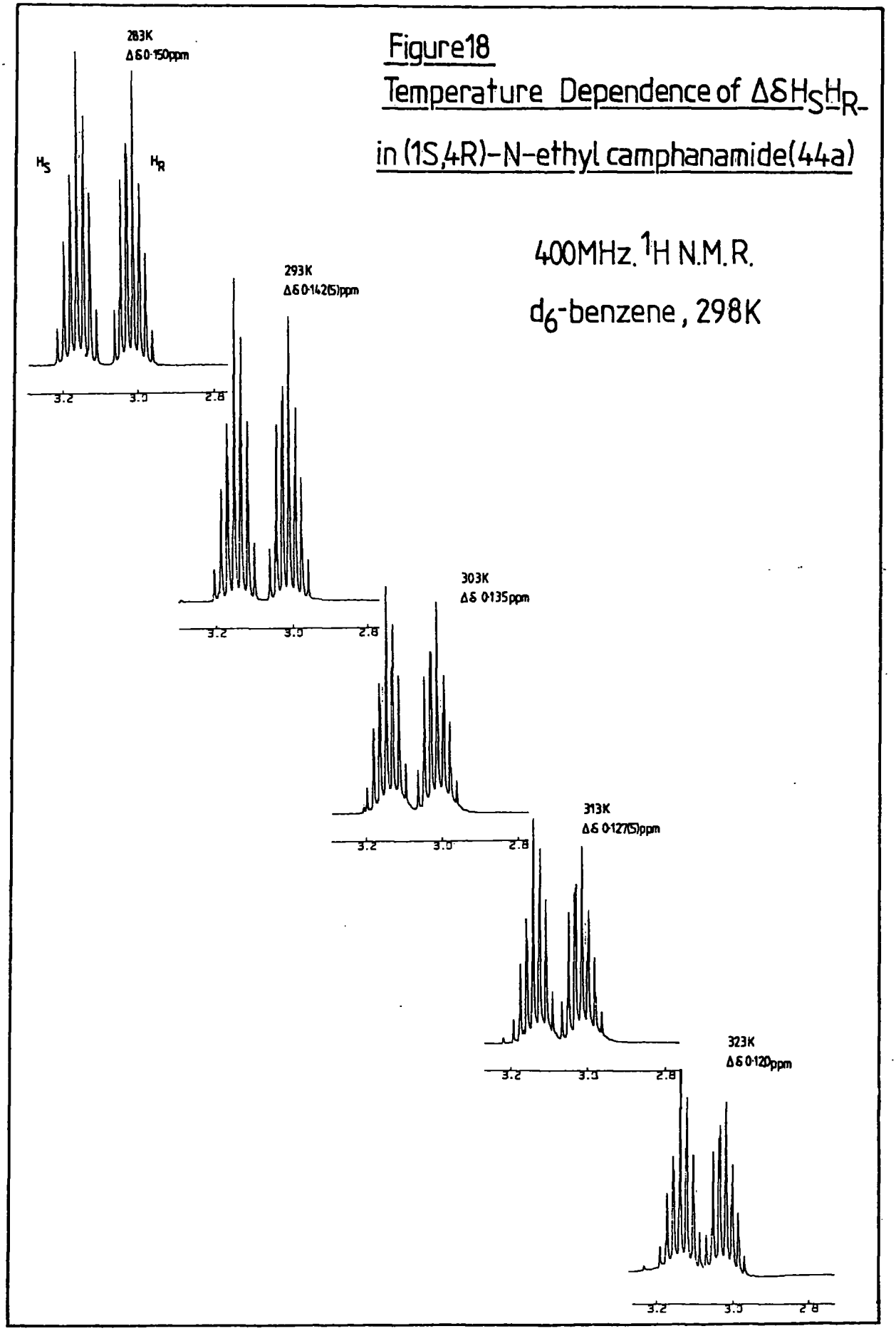


Figure18
Temperature Dependence of ΔδHSHR-
in (1S,4R)-N-ethyl camphanamide(44a)
400MHz. 1H N.M.R.
d6-benzene, 298K
283K
Δδ 0·150ppm
HS
HR
293K
Δδ 0·142(5)ppm
303K
Δδ 0·135ppm
313K
Δδ 0·127(5)ppm
323K
Δδ 0·120ppm
3.2
3.0
2.8

There are three possible sources of this effect:[87]

1. A temperature variation in the individual chemical shift terms for the diastereotopic protons, (the δ_i terms in equation 1), likely to be small in non-polar solvents.
2. Intermolecular association as temperature decreases.
3. Variation in the relative populations of molecular conformations in solution, (the ϕ_i terms in equation 1).

[Ln($\Delta\delta$) is linearly dependent on 1/T implying that there is a simple Boltzmann distribution between molecular conformations.]

(Figure 19) shows that the chemical shift non-equivalence is independent of amide concentration ruling out increased aggregation at lower temperature as a contributor to the $\Delta\delta$ temperature dependence. Careful examination of the temperature dependence of $\Delta\delta H_S H_R$ shows that as temperature decreases it is the H_S resonance which shifts to higher frequency relative to H_R and other resonances in the molecule. This observation is consistent with H_S spending more time, on average, in a magnetically deshielding environment, i.e. proximate to the carbonyl group.

The observed anisochronism is sensitive to N.M.R. solvent, (Figure 20), Table 15, $\Delta\delta H_S H_R$ is maximised for (44f) in non-polar aromatic solvents and is reduced in polar aliphatic solvents. The observation that non-equivalence is at a maximum in aromatic solvents suggests that one of the aromatic solvent molecules may lie close to the amide group. A weak π-π^* interaction between the carbonyl double bond and the aromatic π cloud may then occur enhancing the anisotopic environment experienced by H_S and H_R.

Effect of Varying Concentration on $\Delta\delta H_S H_R$ for 44f

Figure19

360MHz.

d_6-benzene

298K

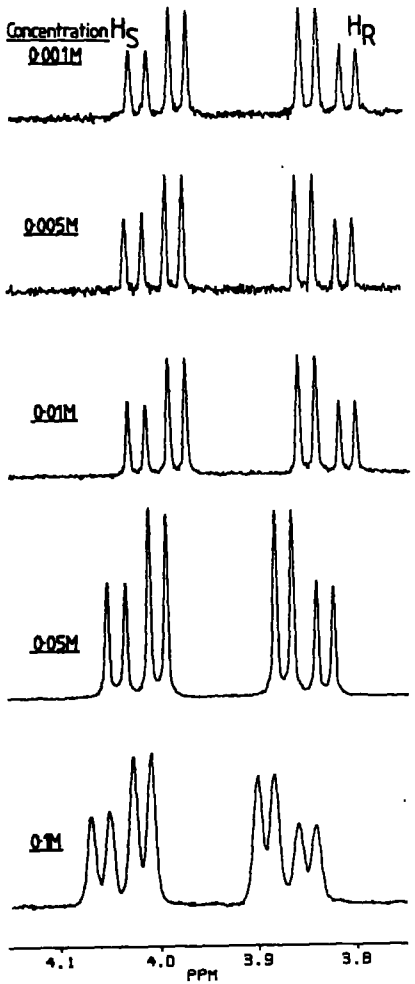
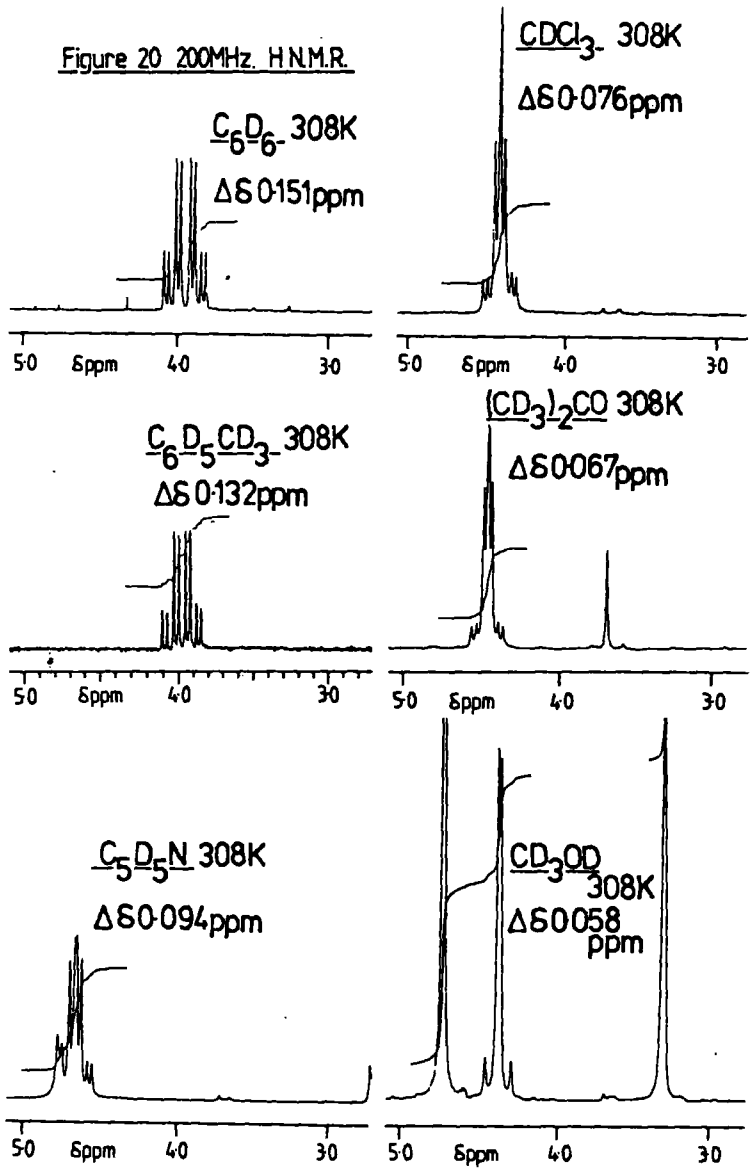


Figure 20 200MHz. H.N.M.R.



The possibility that the amide NH may form an intramolecular hydrogen bond with the lactone ether oxygen in non-polar solvents, at concentrations used in the N.M.R. experiments was considered. A Fourier Transform Infrared study in carbon tetrachloride and d_6-benzene showed that for (44f) at concentrations below 10^{-2}M only a single, sharp band is observed at 3435cm^{-1}. This corresponded to the free N-H stretch: no other bands were observed in this region over the concentration range 10^{-2} to 10^{-5}M. At higher concentrations a band appeared at 3380cm^{-1} which grew as a function of increasing concentration and was assigned to an intermolecular hydrogen bonded NH. The crystal structure analysis had revealed hydrogen bonding between the amide NH of one molecule and the carbonyl of another. Similar interactions, therefore, appear to occur at higher concentrations in solution. At concentrations greater than 10^{-2}M, the resonance signals for <u>both</u> H_S and H_R move to higher frequency (Figure 19). This implies that, on average, both the diastereotopic methylene protons spend more time in a magnetically deshielding environment. The phenyl ring or amide carbonyl group of a second camphanamide molecule approaching in a suitable orientation for intermolecular NH---O=C hydrogen bonding is possibly responsible. The line broadening observed in 0.1M solution is a result of a reduction in the rate of molecular tumbling in solution caused by aggregation of solute and is further evidence for molecular association via hydrogen bonding at high concentrations.

2.2.3 Molecular Mechanics Calculations

Using a model of a camphanamide constructed from fragments taken from the Cambridge Crystallographic Data base,[182] molecular mechanics energy calculations were performed on (44f). (Figure 21) illustrates the variation of molecular potential energy with changes in the C(10)-N-C(11)-C(12) and N-C(11)-C(12)-C(13) torsion angles. The contour lines are in energy units of kcals $mole^{-1}$. Comparison between the predicted torsion angles for the energy minima A and B and the observed crystallographic data for conformers A and B shows good agreement. (Figure 22) is the corresponding potential energy cross section along XY showing that A is a lower energy conformer than B. The calculated energy difference is 1.3kJ$mole^{-1}$. {The local energy minima are calculated to be within 4kJ$mole^{-1}$ of the absolute energies for the observed crystal conformations[183]}. It is well established[183] that any conformation in the crystalline state is likely to be important in solution.

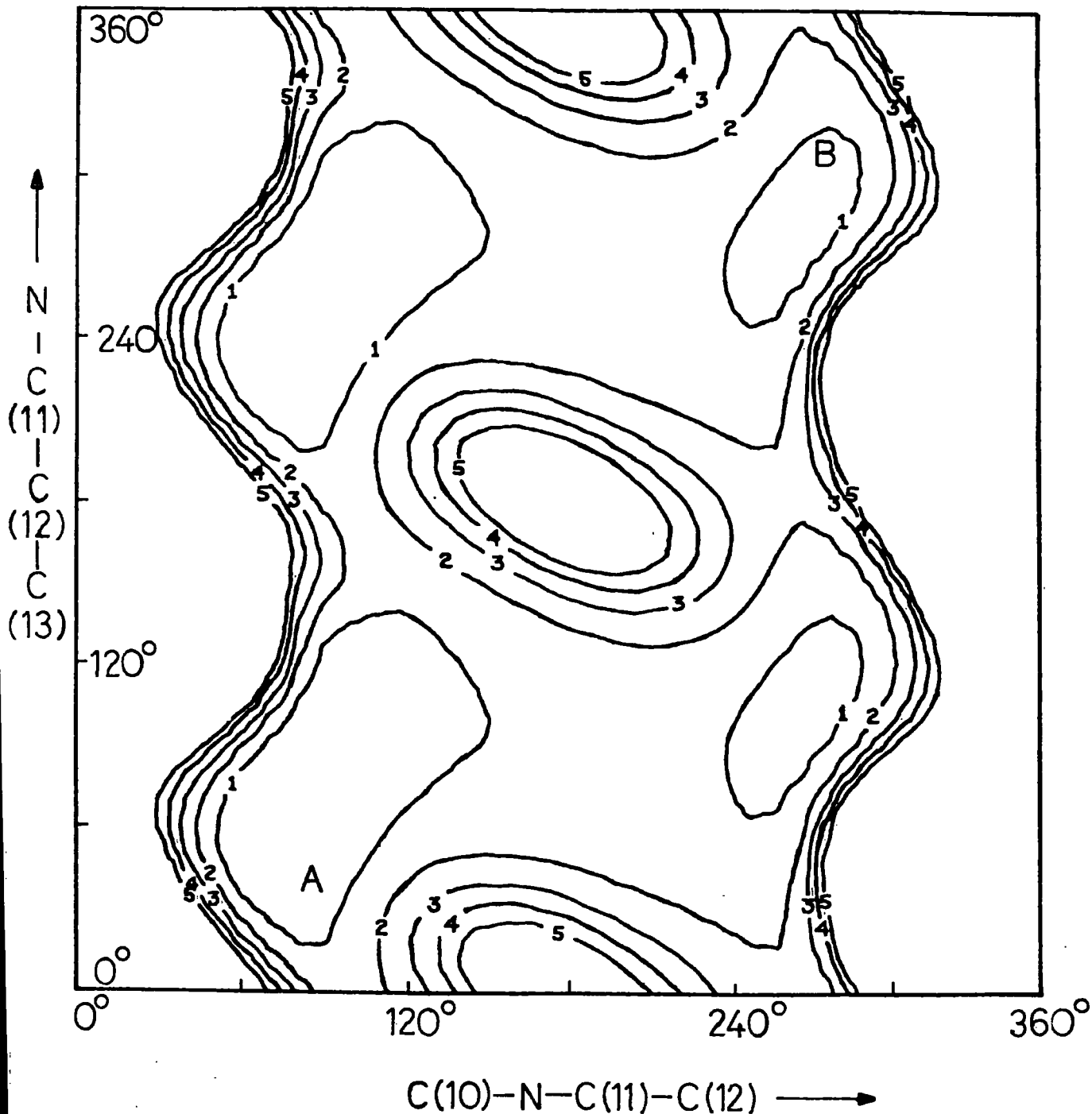
Molecule A should therefore represent the lower energy conformation in solution. In this energetically preferred conformation the pro-S hydrogen is closer, on average, to the amide carbonyl than the pro-R hydrogen. As temperature is lowered the differential shielding is more pronounced as conformer A is populated in preference to conformer B.

2.2.4 Nuclear Overhauser Effect Difference Spectra

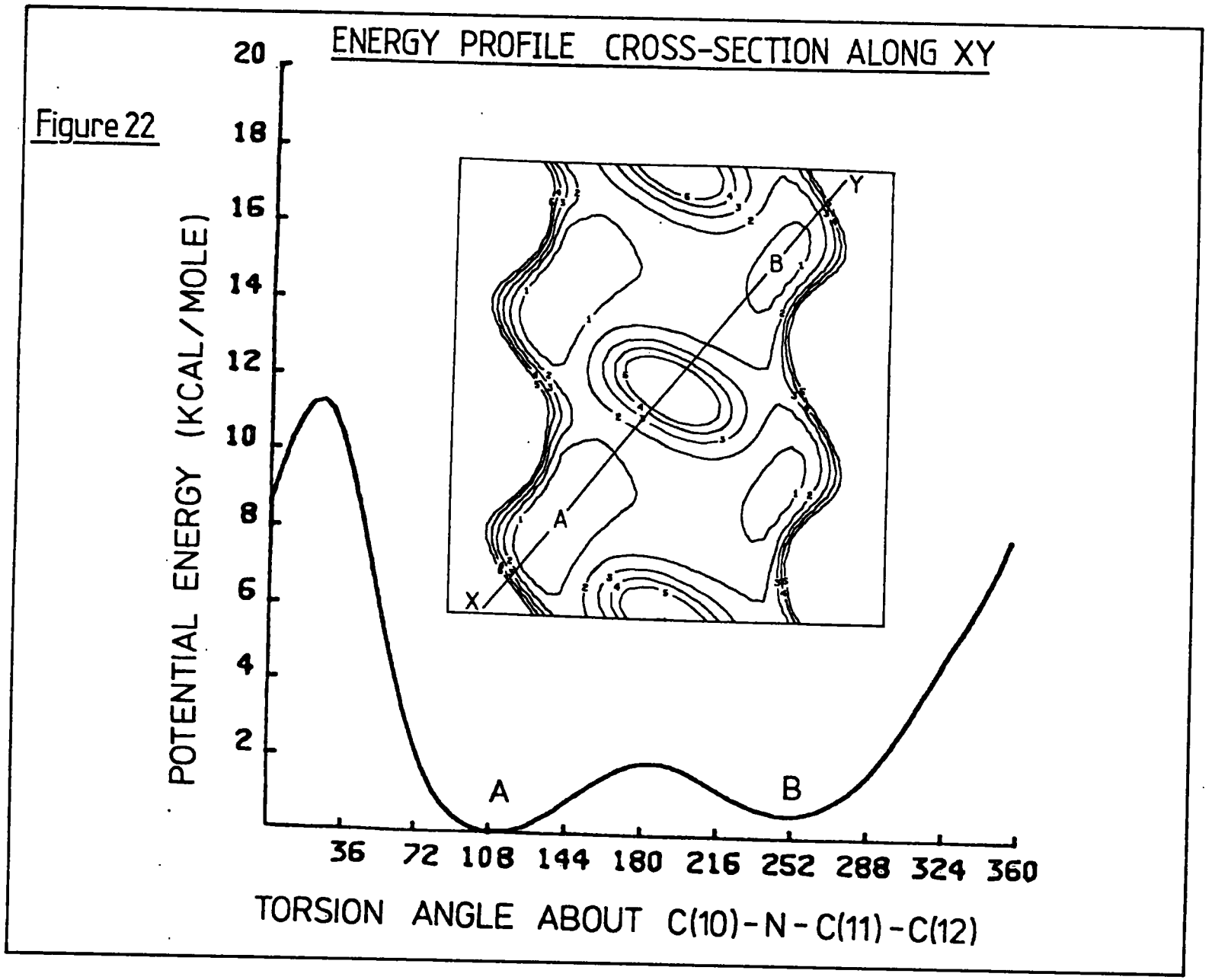
Inspection of the solid-state conformers A and B reveals that in A H_R is close to the nitrogen bound hydrogen whilst in B H_S is close to the NH. Thus in principle Nuclear Overhauser

Figure 21

Potential Energy Surface for Rotation About C(10)-N-C(11)-C(12) and N-C(11)-C(12)-C(13)



Energy Contours in k cals mole^{-1}


ENERGY PROFILE CROSS-SECTION ALONG XY
Figure 22
POTENTIAL ENERGY (KCAL/MOLE)
20
18
16
14
12
10
8
6
4
2
A
B
X
Y
36 72 108 144 180 216 252 288 324 360
TORSION ANGLE ABOUT C(10)-N-C(11)-C(12)

Effect Difference spectra recorded for gated irradiation of the NH proton should show non-zero enhancement for H_S and H_R. In addition, if conformer A is populated at the expense of conformer B, as predicted on energetic criteria, then H_S would be expected to experience a greater NOE enhancement than H_R.

NOE Difference spectra recorded for gated irradiation of the NH proton show no enhancements for H_S and H_R in d_8-benzene or d_8-toluene at temperatures from 298K down to 203K. At 193K in d_8-toluene a 12% enhancement is observed for both H_S and H_R. [E_{AB} = 1.3kJmole^{-1} corresponds to T = 156K for exclusive population of A]. Although the NOE experiments offer no supportive evidence, the proposed rationale for induction of anisochronicity by the carbonyl competently explains all the observed N.M.R. data and is in accord with the crystal structure and molecular mechanics calculations.

2.3 Molecular Conformations in Other Compounds

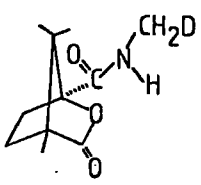
2.3.1 Camphanamides

Since H_S consistently resonates to high frequency in all studied camphanamides[137,184] the theory proposed as an explanation for diastereotopic methylene proton non-equivalence can be extended with reasonable confidence to describe geminal proton anisochronism in related compounds.

The conformation found for camphanamides could be viewed in a different way. If the overriding consideration is the formation of the NH-carbonyl hydrogen bonds then the two conformations A and B result from the enforced reorientation of the N-substituents of adjacent molecules by mutual steric and/or electronic repulsion. (Figure 23) shows projections

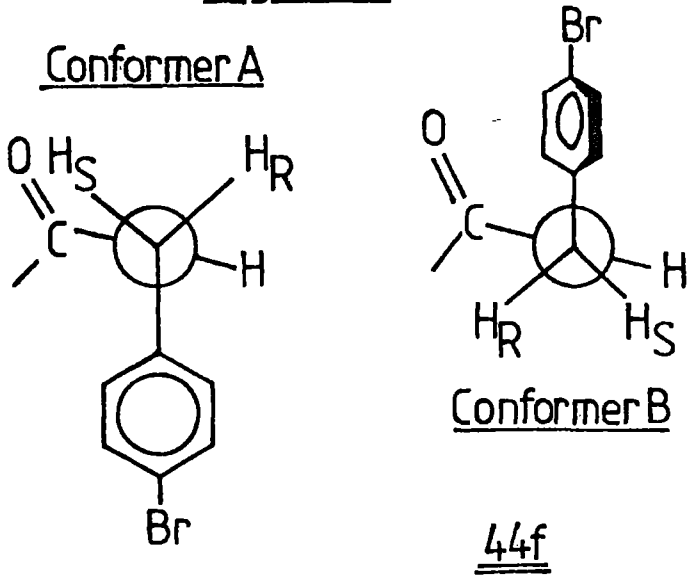
along the C(11)-N bond for A and B. The observed chemical shift non-equivalence is a direct reflection of the energy difference between conformations in solution. It is important to note that even if both conformations are equally populated (i.e. ϕ_i terms equal in equation 1) then in principle $\Delta\delta$ is not zero because the individual chemical shifts in these conformations (the δ_i terms) are not equal. In practice when the R group in (44) is deuterium, ^2H, then the energy difference between the two conformations is extremely small and the individual chemical shift terms are nearly the same. Hence $\Delta\delta$ does tend to zero. Non-equivalence is not observed for α-deuterated methylcamphanamides, (45), at 193K in d_8-toluene at 360MHz. Addition of 7.5 mole% of the L.S.R. Eu(fod)$_3$ to a solution of (45) in carbon tetrachloride causes severe line broadening and does not resolve the diastereotopic proton signals.

45



N-deuteromethyl-camphanamide

Figure 23

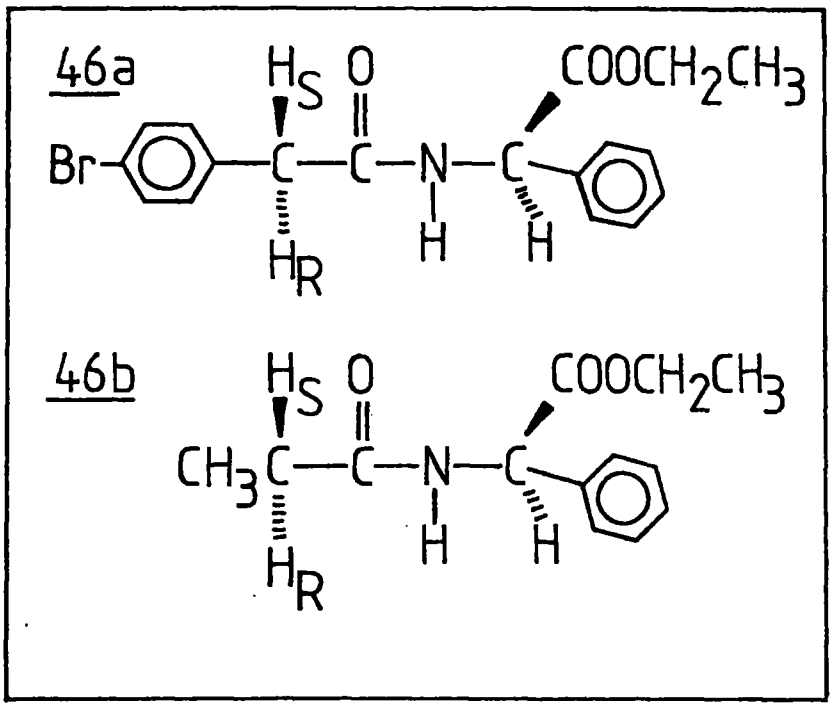


44f

Projection along C_{11}-N

2.3.2 Variation of Chemical Shift Non-equivalence with Structure

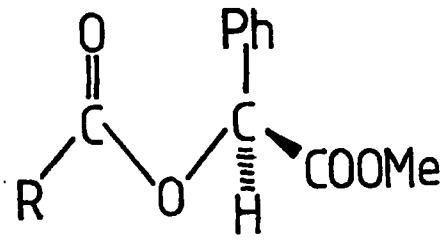
Chemical shift non-equivalence in geminal diastereotopic methylene protons in camphanamides is due to the anisotropic amide carbonyl β to the CH_2 group. It was reasoned that if the amide link was reversed so that the carbonyl group was α to the CH_2 group then $\Delta\delta$ might increase. With this in mind the ethanamides (46) were investigated.



In (R)-N-(phenylethylethanoyl)-p-bromophenylethanamide, (46a), at 250MHz in d_6-benzene, non-equivalence of 0.05 ppm was observed for the methylene protons whilst in (R)-N-(phenylethylethanoyl)-ethanamide, (46b), under these conditions non-equivalence was not observed. This demonstrates that a reversal in the amide link substantially reduces $\Delta\delta$.

2.3.3 Diastereotopic Methylene Protons in Mandelates

In the camphanamides studied the NHCO unit is planar, if the COO unit in esters, such as mandelates, is also planar then the mechanism for induction of chemical shift non-equivalence in camphanamides may also be invoked for mandelates. The chemical shifts and the magnitude and sense of non-equivalence of the diastereotopic methylene protons in a series of mandelates, (47), derived from (S)-methyl mandelate and the appropriate acid, are shown in Table 16.



47 a) $R=CH_2CH_2NO_2$
b) $R=CH_2CH_2COCH_3$
c) $R=CH_2D$
d) $R=CH_2Ph$
e) R=CHDCHDPh
f) $R=p\text{-}BrPhCH_2$

Table 16

Chemical Shift Non-equivalence in the Diastereotopic Methylene Protons in Mandelates[a] (47)

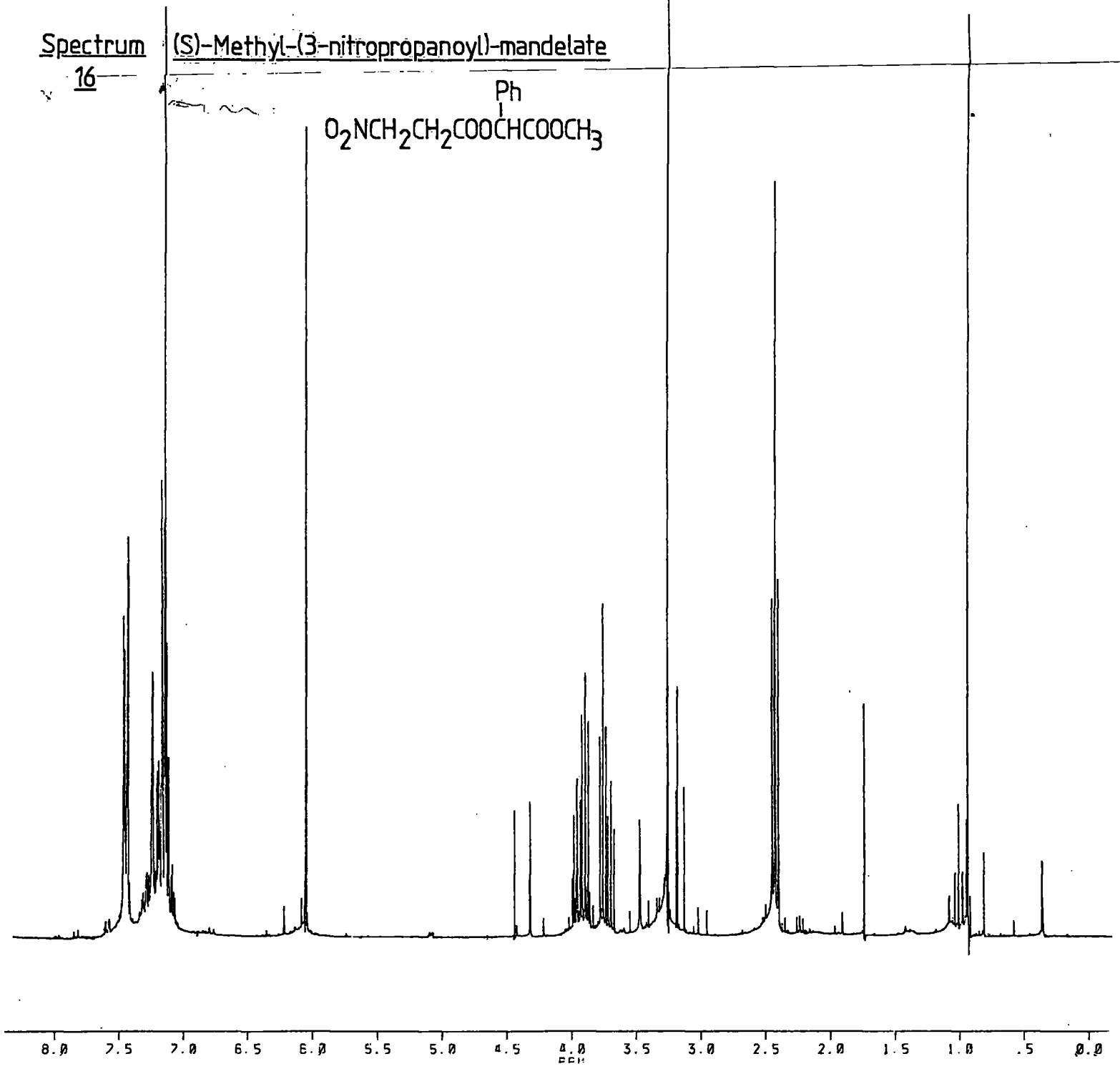
No	Compound	α-CH2		β-CH2		Δδα ppm	Δδβ	Model
		δ ppm	δ	δ ppm	δ			
1	47a	2.49	2.46	3.93	3.74	0.03	0.19	XX
2	47b	2.32	2.15	2.62	2.59	0.17	0.03	XIX
3	47c	1.85		----		0	----	
4	47d	3.68	3.53	----		0.15	----	XX
5	47e	2.61		2.89		----	----	XIX
6	47f	3.32	3.23	----		0.09	----	XX

a) Recorded at 250MHz in d_6-benzene at 298K.

The first entry, for the 3-nitropropanoyl-mandelate, spectrum 16, is unusual in that the chemical shift non-equivalence of the methylene protons β to the carbonyl group is greater than that for the α methylene protons. In all other mandelates, (e.g. spectrum 17), the α-CH_2 protons exhibit greater non-equivalence than the β-CH_2 protons. A second clue to molecular conformation is given by entry 17 in Table 13 for (R,S) 2-methyl-3-phenylmandelate. Spectrum 18 illustrates clearly that the methyl group in the (R,S) diastereoisomer resonates to higher frequency than in the (S,S) diastereoisomer and that one of the diastereotopic protons of the CH_2 group is considerably shifted, (0.3ppm), to higher frequency in the (S,S) diastereoisomer. (Figure 24), (XIII and XIV), shows the conformations for (R,S) and (S,S) diastereoisomers respectively which are hereby proposed to account for this behaviour. (XV and XVI) are projections along the C(1)-C(2) bond. In (XV), the (R,S) diastereoisomer, the methyl group is much closer to the ester carbonyl function than in (XVI), the (S,S) diastereoisomer. (XVII and XVIII) are projections along the C(3)-C(1) bond. In (XVIII), the (S,S) diastereoisomer, the pro-R proton, H_R, is particularly close to the ester carbonyl whilst in (XVII), the (R,S) diastereoisomer, both geminal methylene protons are equally remote from the carbonyl group.

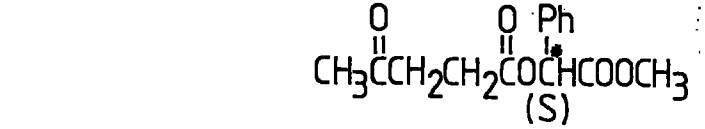
Extending this approach to a more general case where $PhCH_2CHCH_3$ is replaced by $R(CH_2)_n$ (Figure 25) then the two diastereomeric conformations now represent two low energy conformations for the diastereotopic methylene groups related by rotation about the C(1)-C(2) bond.

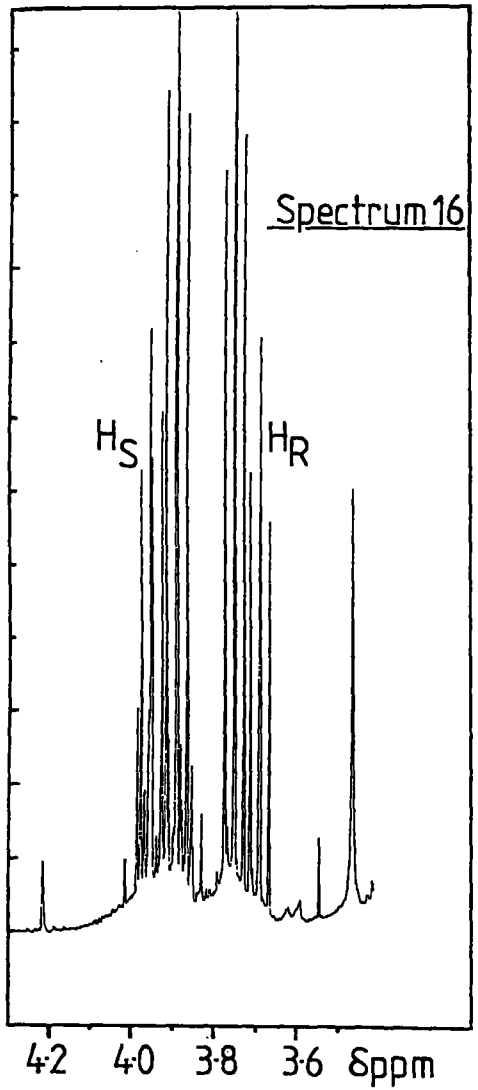
Spectrum 16 — (S)-Methyl-(3-nitropropanoyl)-mandelate

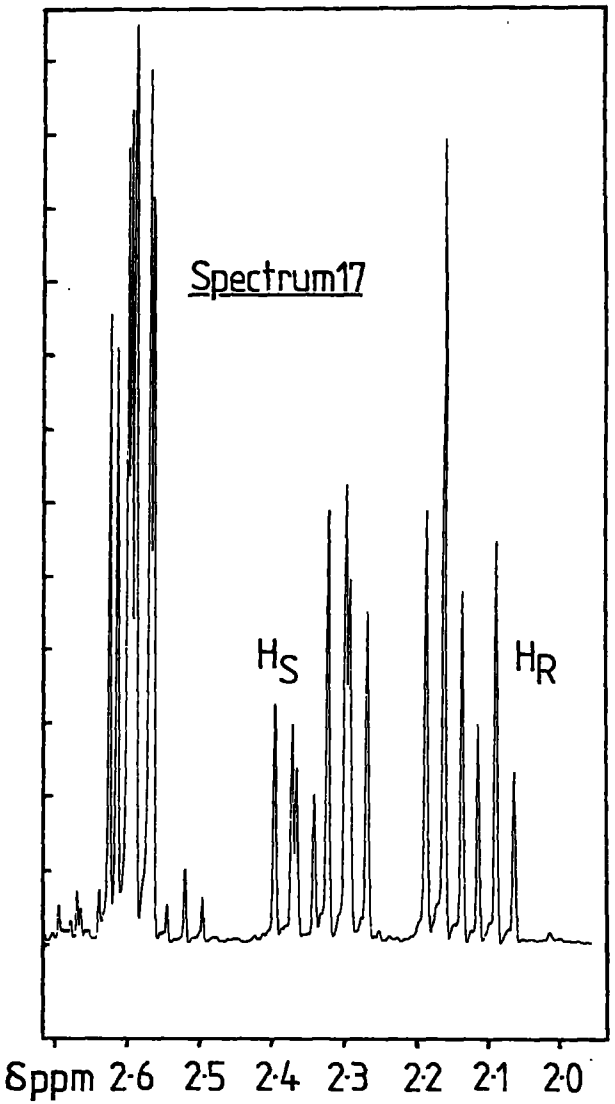


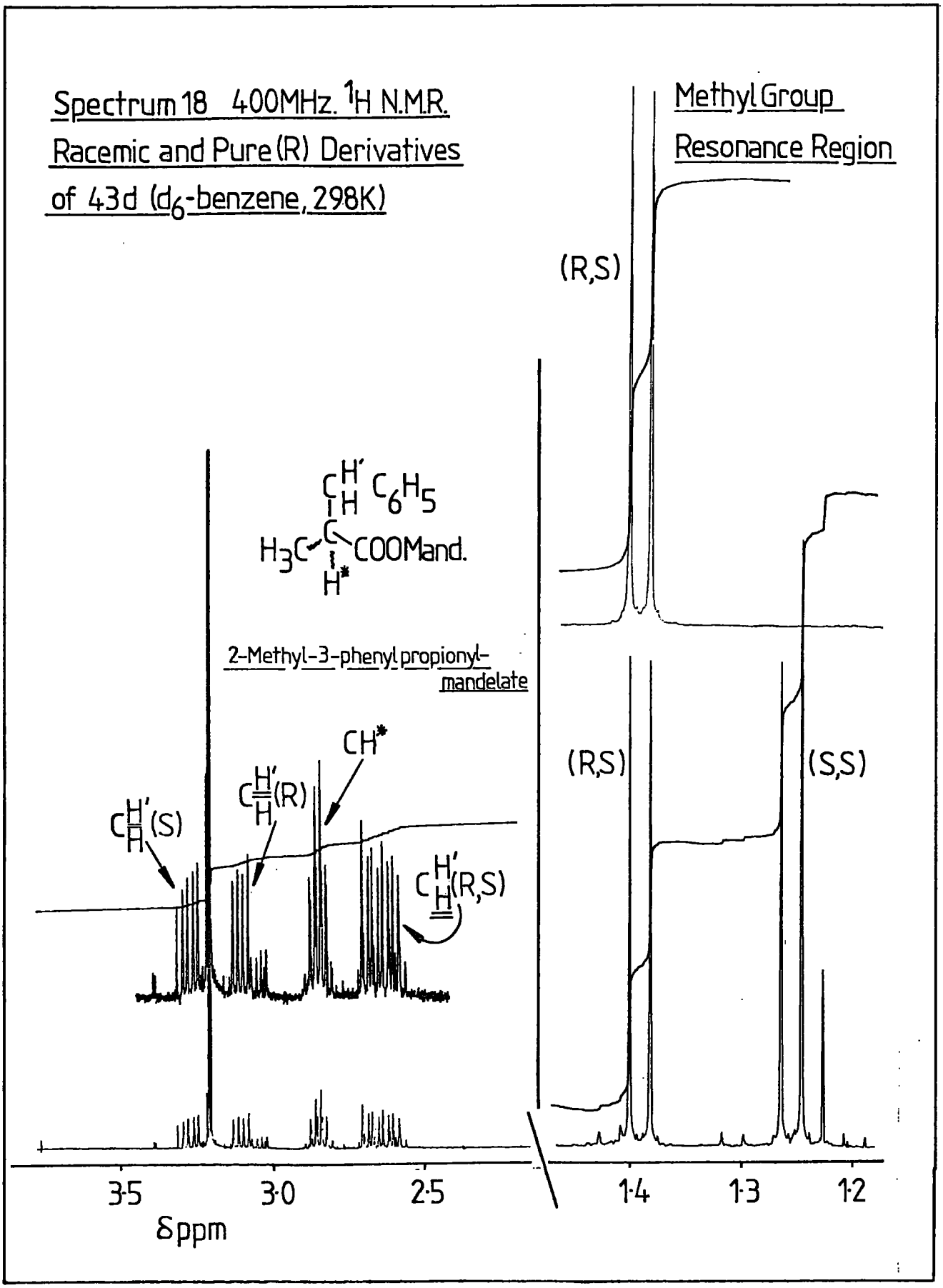
Spectrum 17

(S)-Methyl-(3-carbomethyl-propanoyl)-mandelate

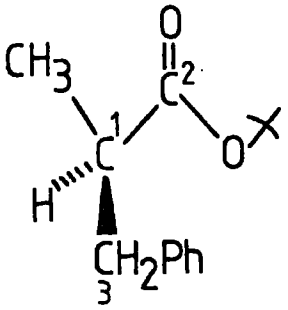



Spectrum 16
H_S
H_R
4·2
4·0
3·8
3·6
δppm

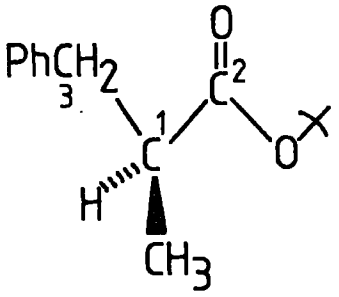

Spectrum17
H_S
H_R
δppm 2·6
2·5
2·4
2·3
2·2
2·1
2·0


Spectrum 18 400MHz. ^{1}H N.M.R.
Racemic and Pure (R) Derivatives
of 43d (d_6-benzene, 298K)
Methyl Group
Resonance Region
(R,S)
(R,S)
(S,S)
2-Methyl-3-phenyl propionyl-
mandelate
CH*
CH'H (S)
CH'H (R)
CH'H (R,S)
3·5
3·0
2·5
1·4
1·3
1·2
δppm

XIII



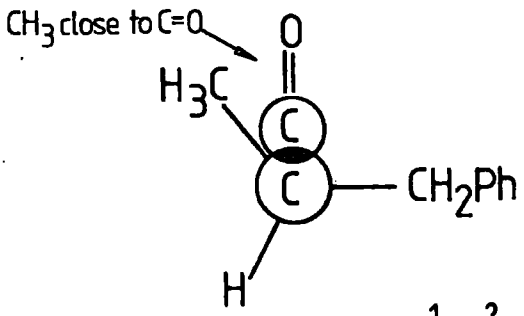
XIV



(R,S)Diastereoisomer (S,S) Diastereoisomer

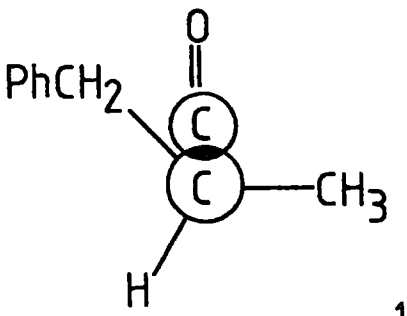
Figure 24

XV



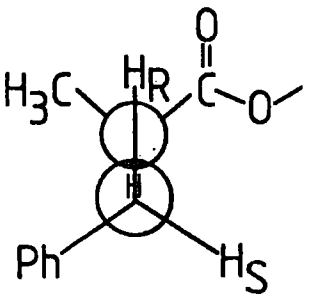
Projection along C^1-C^2

XVI



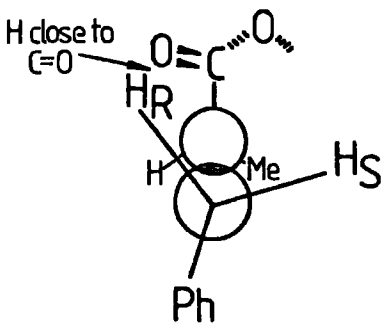
Projection along C^1-C^2

XVII



Projection along C^3-C^1

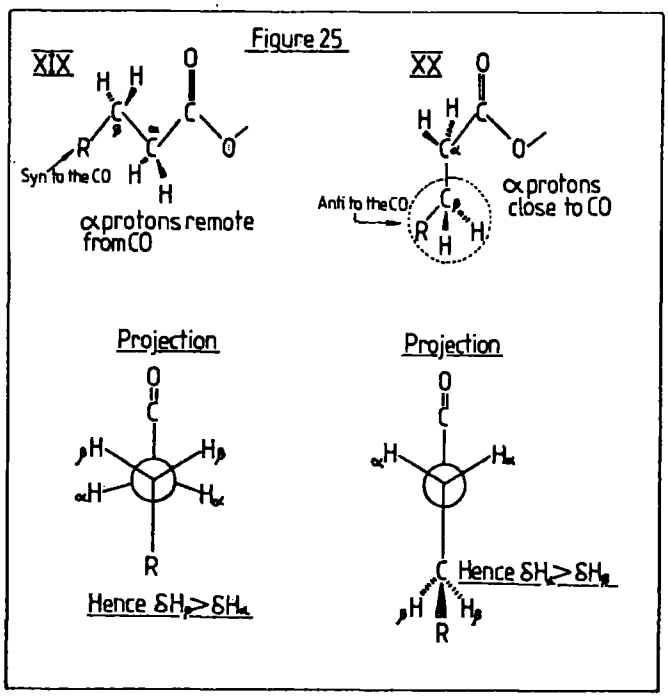
XVIII



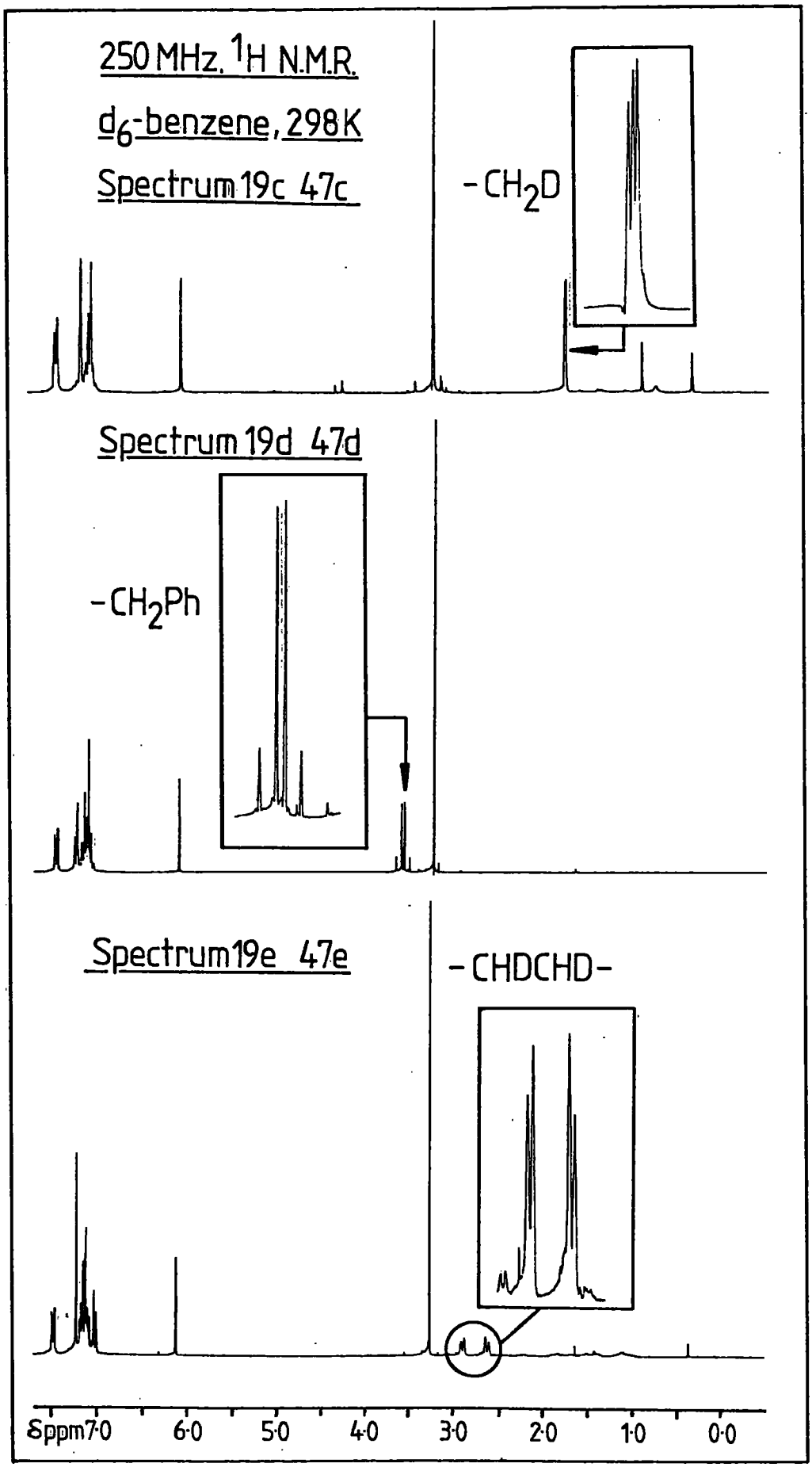
Projection along C^3-C^1

If the overriding consideration is that the R substituent should be syn rather than anti to the carbonyl group, then when n is odd (XIX) may be preferred, but when n is even (XX) may be preferentially populated. Now in (XIX) the β-methylene group is closer to the ester carbonyl than the α-methylene group and is consequently expected to resonate at higher frequency. When R = NO_2, then (XX) is the preferred conformation placing the α-methylene group closer to the carbonyl function than the β-methylene group.

Figure 25



Spectrum 19 illustrates 250MHz ^1H N.M.R. spectra for (47c, 47d and 47e), the insets show the diastereotopic methylene protons expanded. In spectrum 19c the CH_2 group appears as a triplet owing to coupling with ^2H. Deuterium decoupling results in collapse to a singlet. Note that for (47d) the methylene resonance is to high frequency in accordance with the model proposed in (XX), whilst in (47e) both resonances are at lower frequency in agreement with model (XIX). In this instance coupling with ^2H is not resolved.


250 MHz. 1H N.M.R.
d6-benzene, 298K
Spectrum 19c 47c
-CH2D
Spectrum 19d 47d
-CH2Ph
Spectrum 19e 47e
-CHDCHD-
δppm 7·0
6·0
5·0
4·0
3·0
2·0
1·0
0·0

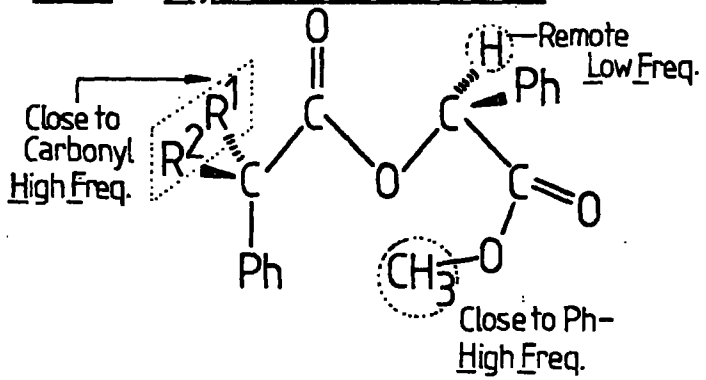
Returning to the (S)-methylmandelate derivatives of α-methoxyphenyl acetic acid, (43c), and 2-phenylpropionic acid, (43b), for which Mosher's[127] model incorrectly predicts opposite sense of non-equivalence for the acid substituents. The observed non-equivalence sense is correctly predicted, for (43b), by (XXI and XXII) in (Figure 26); where (XXI) corresponds to the (R,S) diastereoisomer with both acid substituents R_1 and R_2 close to the anisotopic carbonyl. The (S,S) diastereoisomer is represented by (XXII) in which both the acid substituents are remote from the carbonyl and hence are expected to resonate at a lower frequency.

In (43c) the model for the acid moiety remains unchanged from that proposed for (43b), but now the alcohol substituents must <u>also</u> rely on the carbonyl group to induce chemical shift non-equivalence. In this case, (XXIII and XXIV), both alcohol substituents exhibit the <u>same</u> sense of non-equivalence, rather than <u>opposite</u> senses as observed for (43b).

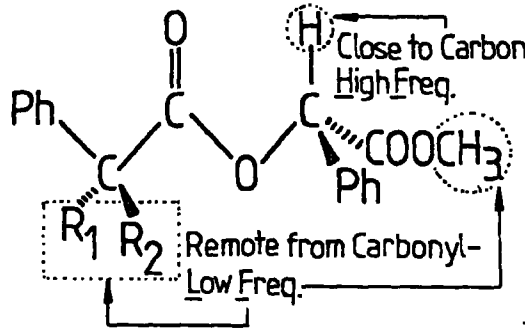
In relation to chiral methyl groups non-equivalence is not observed for the diastereomeric protons in α-deuterated ethanoylmandelate, (47c), at 193K in d_8-toluene at 360MHz. This result, in common with the related camphanamide derivative, (45), indicates that there is no preference for any rotameric conformation of the CH_2D group. Neither the camphanamide nor the mandelate molecule are sufficiently rigid to prevent free rotation of the CH_2D group and hence are extremely unlikely to affect a CHDT group.

Figure 26

XXI R,S Diastereoisomer



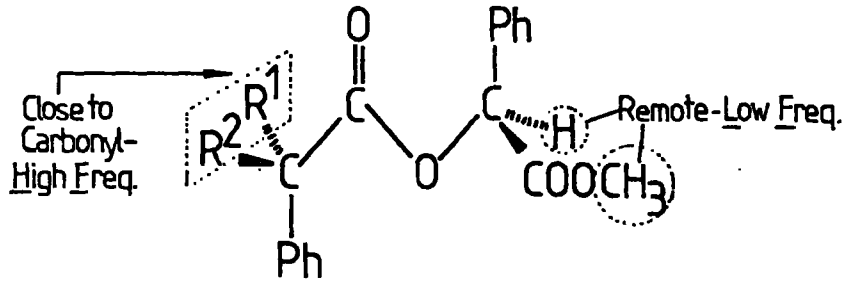
XXII S,S Diastereoisomer



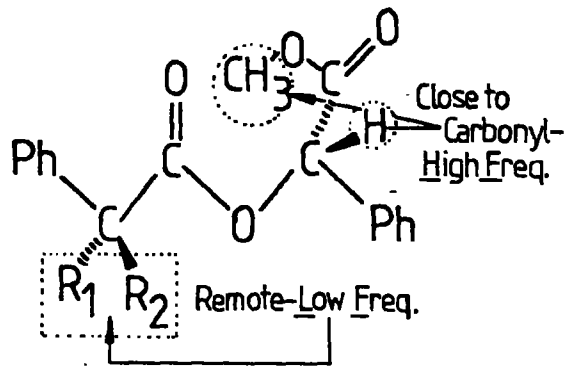
R_1, R_2 same
CH, COOMe opposite
} sense of non-equiv.

Ph > R_2 > R_1 Table 13 Entries 6-10

XXIV R,S Diastereoisomer



XXIII S,S Diastereoisomer



R_1, R_2 same
CH, COOMe same
} sense of non-equiv.

Table 13 Entries 1-5

2.4 Concluding Remarks

(S)-Methylmandelate is an effective Chiral Derivatising Agent for the assay of the enantiomeric composition of chiral acids. Derivatisation is straightforward and non-stereoselective. Since the completion of this work, Parker and Hodgson[3] have used (S)-methylmandelate to derivatise exo-2-norbornane-carboxylic acids obtained by hydrocyanation of norbornene, using a chiral palladium catalyst, followed by hydrolysis. Proton N.M.R. integration of the anisochronous bridge-head norbornyl protons ($\Delta\delta \approx 0.3$ppm) gives values in close agreement with those obtained by polarimetry. The method described permits the measurement of enantiomeric purities of 98% (i.e. corresponding to e.e. up to 96%). The conclusive study of the camphanamide system shows that chemical shift non-equivalence in diastereotopic methylene protons is caused by the amide carbonyl anisotropy. Using this model for the diastereomeric mandelate esters permits the assignment of absolute configuration to be made in cases where other models fail.

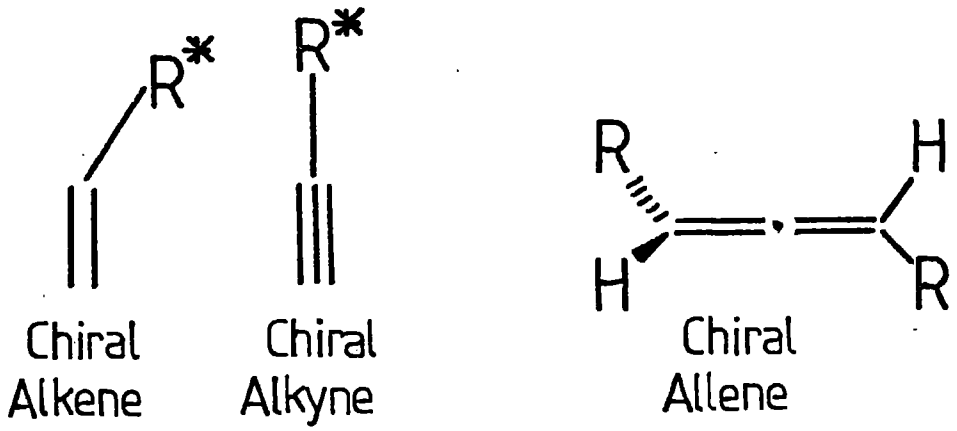
CHAPTER THREE

N.M.R. Assay of Enantiomeric Excess using Chiral Derivatising Agents-II

Platinum and palladium chiral phosphine complexes as C.D.A.s for chiral alkenes, alkynes and allenes.

3.1 General Comments

The term chiral alkene or alkyne is used to describe a molecule containing a double or triple bond respectively in addition to a chiral centre. Chirality in allenes depends on the location of the substituent groups at opposite ends of the π system, for example 1,3-disubstituted allenes are chiral.



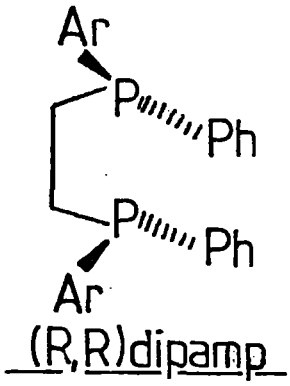
All the preliminary studies in this area were carried out using chiral alkenes. The original aim was to develop a Chiral

Derivatising Agent for non-functional alkenes which are not amenable to derivatisation by the established acid or amine C.D.A.s e.g. 3-methylcyclopentene.

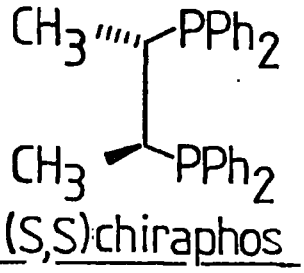
A C.D.A. suitable for chiral alkenes, alkynes or allenes must be readily available (or easily synthesised) as a pure enantiomer and must react quantitatively, but not enantioselectively, with both enantiomers of the chiral alkene. The reagent should have a reasonable shelf life, the derivatisation reaction must be as simple as possible and the resulting diastereomeric complexes should be stable and not prone to diastereoselective decomposition.

Ethene is readily displaced from certain transition metal complexes[185] by other alkenes, hence a straightforward derivatisation step might involve the displacement of ethene in the C.D.A. molecule by chiral alkene enantiomers. Provided that the ethene ligand is sufficiently labile then derivatisation

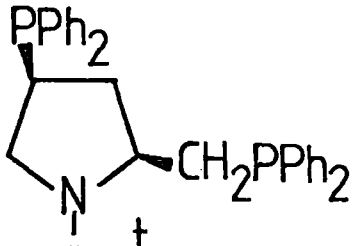
could occur "in situ" rather than requiring a separate reaction. The transition metals platinum,[186] palladium,[187] and rhodium[188] form stable alkene complexes. Some of these have been used as catalysts in hydrogenation[189] and carbon-carbon bond forming reactions.[190] Asymmetric catalytic hydrogenation[191] typically uses a rhodium complex in which the transition metal is bound to a chiral phosphine ligand. This can be either mono- or bidentate. In this connection well over one hundred chiral diphosphine ligands have been synthesised and many are commercially available, for example: (S,S)-bppm, (R,R)-dipamp and (S,S)-chiraphos.



(R,R)dipamp



(S,S)chiraphos



(S,S)bppm

The presence of chiral phosphine components enables phosphorus-31 N.M.R. to be used to study these systems. This has the advantage of larger chemical shift dispersion than

^{1}H N.M.R.,[192,193] offering improved resolution in situations where anisochronicity is likely to be small, for example when the chiral centre is remote from the double bond of the chiral alkene.

Platinum alkene complexes are generally more stable than their palladium analogues. Platinum has two spin isotopes:

Nuclear Spin Quantum No I = 0, Natural Abundance 67%.

Nuclear Spin Quantum No I = 1/2, Natural Abundance 33%.

Since the phosphorus and platinum nuclei ($I=\frac{1}{2}$) are spin coupled, each resonance in the ^{31}P N.M.R. spectrum of a platinum-phosphine complex [phosphorus-platinum ($I = 0$) coupling, 67% of the total signal intensity] has two accompanying satellites [phosphorus-platinum ($I = 1/2$) coupling, each satellite represents 16% of the total signal intensity]. The phosphorus-platinum coupling constant, measured as the separation of the corresponding satellite resonances, is extremely sensitive to both the magnetic and chemical environment of the phosphorus nuclei and provides an extra probe for the system.

With all these considerations in mind a platinum-chiral phosphine-ethene complex was designed which was envisaged as a suitable C.D.A. for chiral alkenes. Derivatisation would then involve displacement of ethene by the chiral alkene enantiomers. The resulting diastereomeric complexes are conveniently studied by ^{31}P and ^{195}Pt Fourier Transform (F.T.) N.M.R. Literature preparations for bis(phosphine)platinum(II)-ethene complexes are tedious involving several steps including a slow displacement of bound oxygen.[194,195,196]

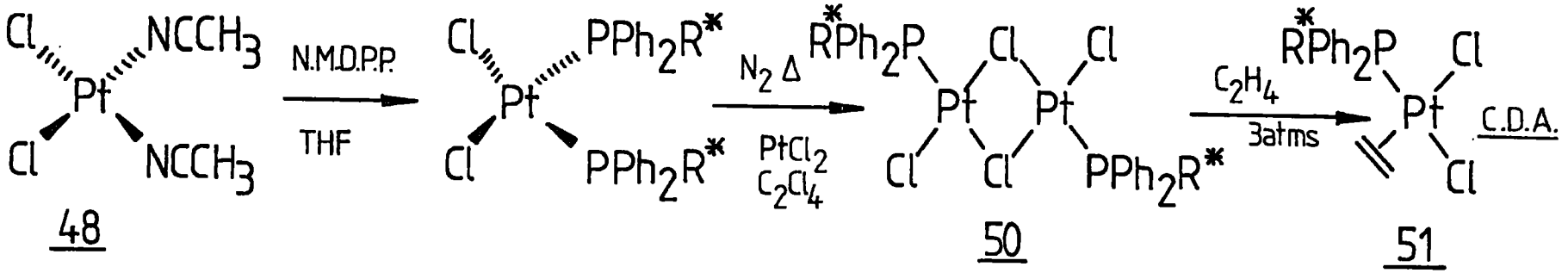
Early synthetic work is outlined in (Scheme 2). It was proposed to react bis-(acetonitriledichloro)platinum(II), (48), with neomenthyldiphenylphosphine (N.M.D.P.P.), (49), to yield the dichloro-diphosphino complex. Reaction with platinum(II) chloride gives the chloro-bridged dimer (50).[197] Fission in the presence of ethene gives the target dichloro(neomenthyl-diphenylphosphino)platinum(II)-ethene complex (51).

From the outset problems were encountered with the initial reaction, the exclusive product being the yellow trans-complex rather than the desired colourless cis-complex. Spectrum 20 shows the ^{31}P N.M.R. spectrum for the trans-complex recorded at 145MHz in d_6-benzene. The resonance occurs at 17.0 ppm relative to H_3PO_4 (85%), the phosphorus-platinum coupling constant, J_{P-Pt}, is 2480Hz. An alternative preparative route[198] involving reaction of N.M.D.P.P. with potassium tetrachloro-platinate(II) gives both the cis- and trans-complexes in 20% and 30% yields respectively, the major product (50%) being tetra(neomenthyldiphenylphosphino)-platinum(II)-tetrachloro-platinate salt. The ^1H N.M.R. spectrum of the complex mixture confirmed that both the cis and trans forms of the dichlorobis(neomenthyldiphenylphosphino)-platinum(II) complex were produced. An infrared study revealed Pt-Cl stretches at 353, 343 and 341 cm^{-1} in the trans-complex and 252, 250 and 248 cm^{-1} in the cis-complex, corresponding to chlorine trans to a second chlorine ligand or to a phosphine ligand respectively.

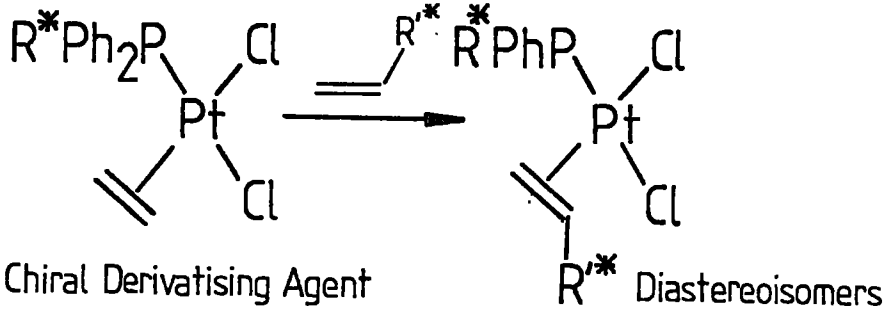
The trans-complex is the thermodynamically more stable product, as might be expected on the grounds of the increased

Scheme 2

Preparation



Derivatisation

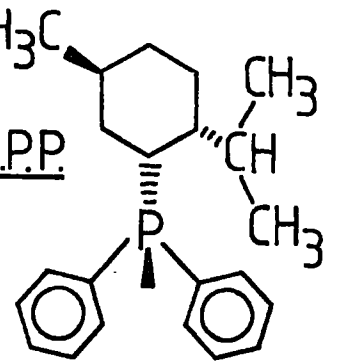


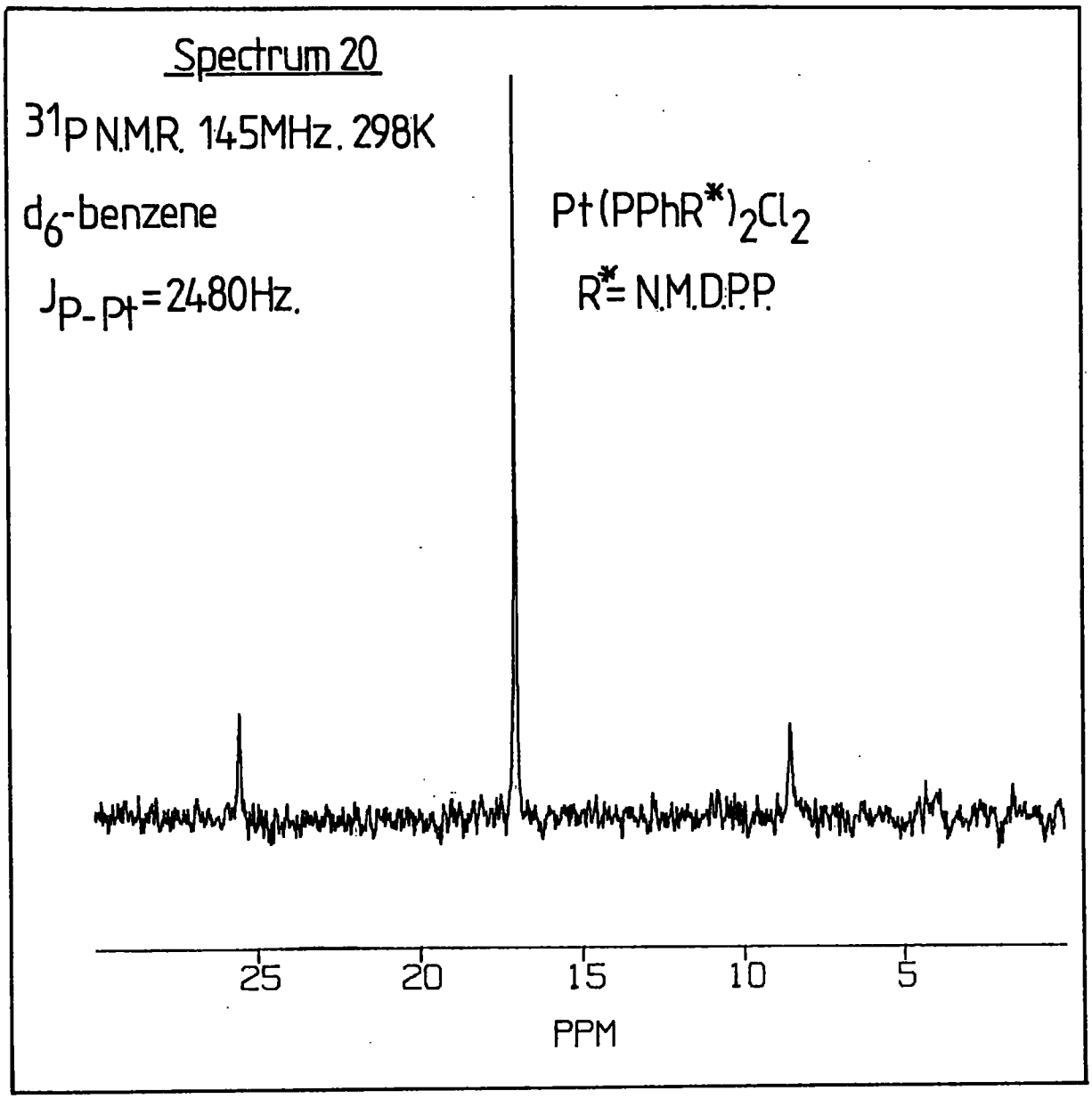
Chiral Phosphine

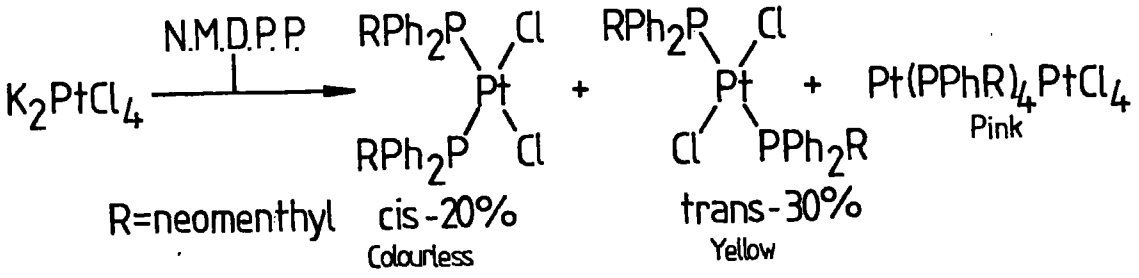
Neomenthyldiphenylphosphine

49

N.M.D.P.P.




Spectrum 20
^{31}P N.M.R. 145MHz. 298K
d_6-benzene
J_{P-Pt} = 2480Hz.
$Pt(PPhR^*)_2Cl_2$
R^* = N.M.D.P.P.
25
20
15
10
5
PPM


N.M.D.P.P.
K_2PtCl_4
RPh_2P
Cl
Pt
RPh_2P
Cl
+
RPh_2P
Cl
Pt
Cl
PPh_2R
+
$Pt(PPhR)_4PtCl_4$
Pink
R=neomenthyl
cis-20%
Colourless
trans-30%
Yellow

steric hindrance in the cis-complex. Conversion of the kinetic product to the thermodynamic product is rapid in the presence of excess phosphine. Dimerisation using both Smithes method[197] and a literature alternative[199] could be not accomplished. Attempts were also made to prepare the bis(neomenthyldiphenylphosphino)platinum(II) carbonate by reaction of the dichlorobis(phosphino)platinum(II) complex with silver carbonate.[200] Refluxing such carbonates in ethanol under an atmosphere of ethene has been reported[201] to yield the bis(neomenthyldiphenylphosphino)platinum-ethene complex. However, the dichlorobis(neomenthyldiphenylphosphino)platinum(II) complex failed to react with silver carbonate.

Clearly the use of a chiral chelating diphosphine avoids the problems encountered with formation of the trans-complex instead of the required cis-complex. In addition a C_2 symmetric phosphine is expected to exhibit a simplified ^{31}P N.M.R. spectrum.

The synthesis of a chiral chelating phosphino-platinum(0) ethene complex was reported in the literature at around this time,[202] and the ready displacement of ethene by small molecules such as carbon monoxide was noted. The chiral phosphine, 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane, (DIOP), is C_2 symmetric. The DIOP-platinum(0)- ethene complex appeared to be an ideal candidate for use as a C.D.A. for chiral alkenes.

3.2.1 Synthesis of DIOP-Platinum(0)-Ethene (52)[202]

The chiral phosphine DIOP is derived from diethyltartrate and is commercially available as (2R,3R) or (2S,3S)

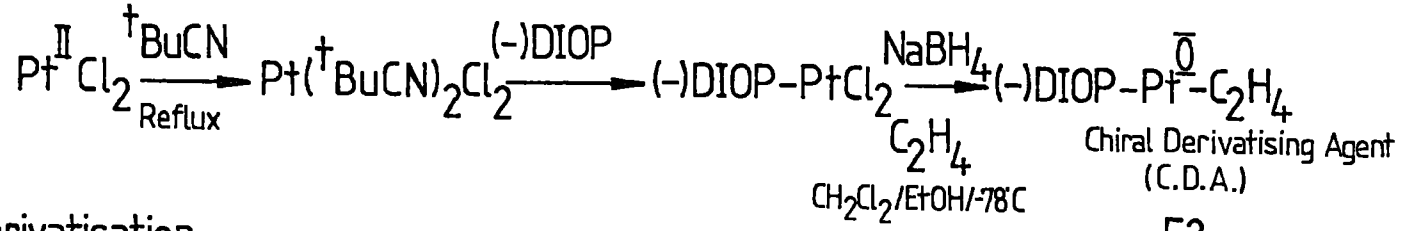
enantiomers of 98% purity. The synthesis of DIOP-platinum(0)-ethene is outlined in Scheme 3. Platinum(II) dichloride is heated at reflux in trimethylacetonitrile. Originally acetonitrile was used instead, but the bis(acetonitrile) complex reacts less rapidly with DIOP to give the dichloro-phosphino complex than does the bis(trimethyl-acetonitrile) complex. The reduction step at -78°C was found to work most efficiently with 2.3 equivalents of sodium borohydride. Use of more than 2.5 equivalents tended to result in over-reduction to platinum metal, whilst less than 2.0 equivalents led to incomplete reduction. The yield of DIOP-platinum(0)-ethene was also directly related to the time interval allowed between the reaction mixture reaching room temperature and its being "quenched" by addition of degassed ethanol. The complex (52) is stable for several months in air at room temperature.

In the ^{31}P N.M.R. spectrum of (52), the phosphorus atoms are isochronous, resonating at 13.7 ppm relative to 85% H_3PO_4 in d_6-benzene solution; the phosphorus-platinum coupling constant, J_{P-Pt}, is 3485Hz. The ^{195}Pt resonance occurs at -566 ppm relative to TMS on an absolute chemical shift scale.

3.2.2 Simple Derivatisation Reactions

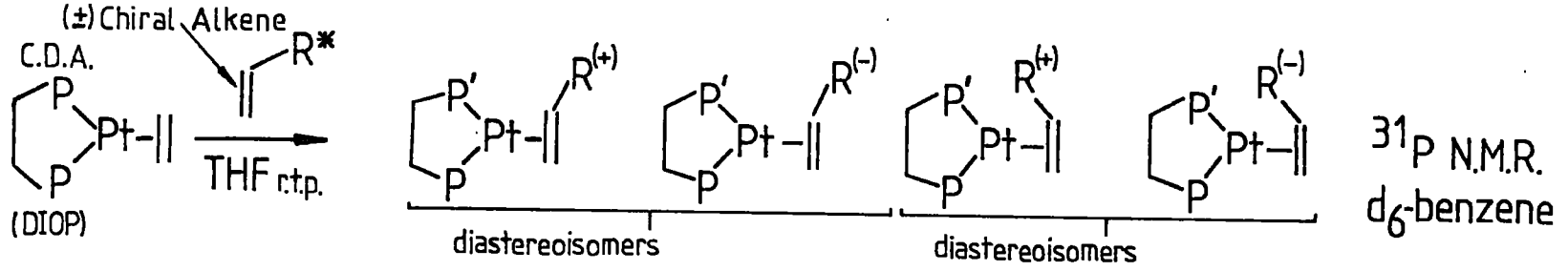
Having prepared the target C.D.A., (52), derivatisation with a few simple model substrates, (53), was attempted by stirring equimolar quantities of the complex and the substrate for 10 minutes in THF at room temperature. Displacement of ethene was often instantaneous with bubbles of gas being evolved in the solution containing the C.D.A. as soon as the substrate was injected. Evaporation of the THF and

Scheme 3
Preparation

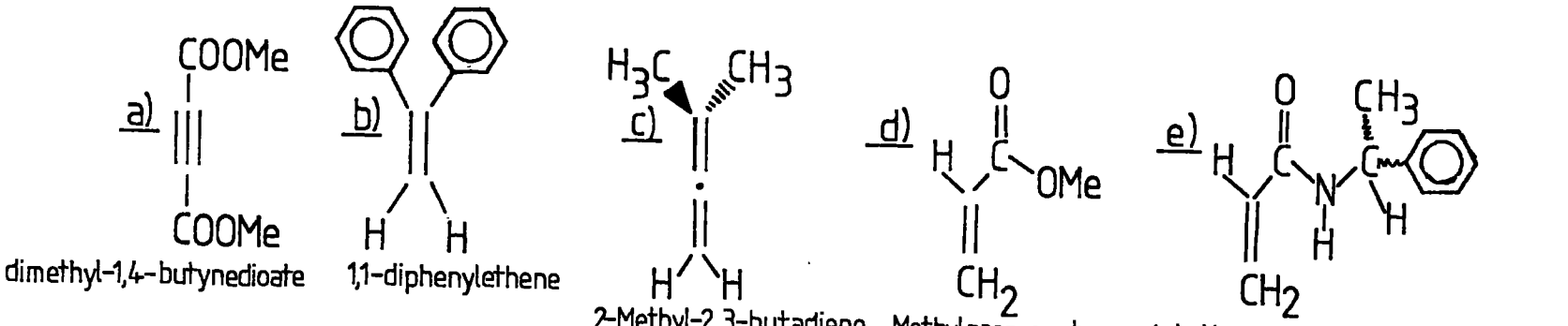


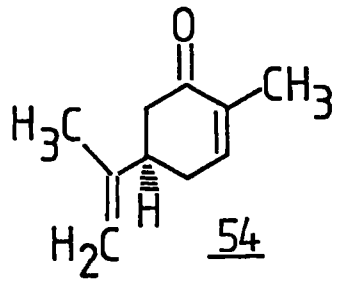
52

Derivatisation



Model Substrates 53

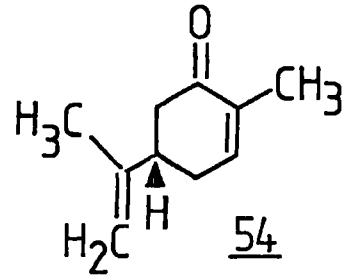




54

(-) Carvone

(R)-5-Isopropenyl-2-methyl-2-cyclohexenone

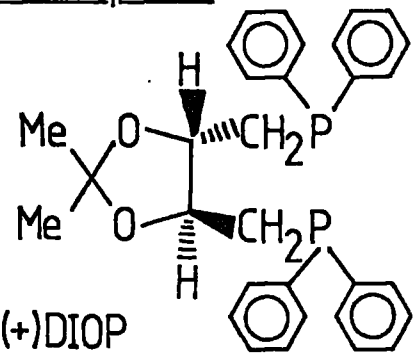


54

(+) Carvone

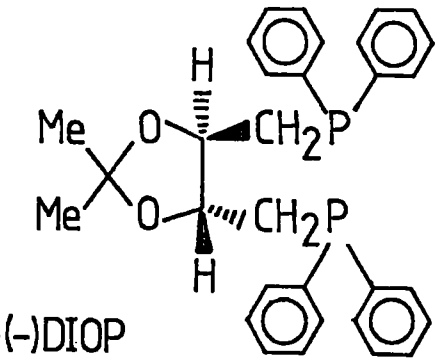
(S)-5-Isopropenyl-2-methyl-2-cyclohexenone

Chiral Phosphine



(S,S)-(+)DIOP

(+)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane



(R,R)-(-)DIOP

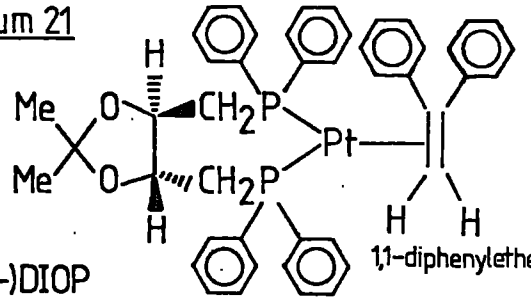
(-)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

dissolution of the residue in a suitable N.M.R. solvent permitted the direct study of the product.

With dimethyl-1,4-butynedioate (53a) as substrate the complex is C_2 symmetric and the phosphorus atoms in the DIOP ligand are equivalent, and hence isochronous. The ^{31}P N.M.R. resonance occurs at +5.9 ppm in d_6-benzene and the phosphorus-platinum coupling constant, J_{P-Pt}, is 3567Hz; the ^{195}Pt resonance occurs at -227 ppm relative to TMS.
Spectra 21, 22 and 23 were recorded observing the ^{31}P nucleus, at 101MHz in d_6-benzene, for substrates (53b), (53c) and (53d) respectively. In the case of (53b and c) the complexes formed with the C.D.A. are no longer C_2-symmetric; as a result the two phosphorus atoms are not chemically equivalent. They are consequently anisochronous and anisogamous, coupling with each other, and coupling differently with the platinum spin 1/2 nucleus. Typically the phosphorus-phosphorus coupling constant, J_{Pa-Pb}, is 60Hz. Proton N.M.R. confirms that in (53c) it was the more substituted double bond which was exclusively bound to the platinum centre.

Displacement of ethene by diphenylethene, (53b), was incomplete. Integration suggested that 70% reaction had occurred. This indicates that the double bond in (53b) is only just sufficiently electron poor to permit derivatisation. Non-functionalised alkenes such as cyclohexene or cyclopentene do not displace ethene from (52) even when present in ten fold excess. Only "electron poor" or sterically strained alkenes have a LUMO of the appropriate energy such that reaction with DIOP-platinum(0)-ethene occurs readily.

Spectrum 21



(R,R)-(-)DIOP

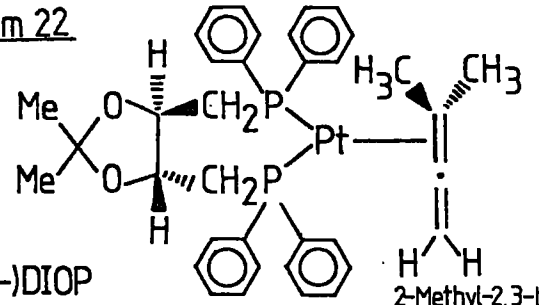
(-)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

1,1-diphenylethene

* (-)-DIOP-Pt-C_2H_4

‡ DIOP Oxide

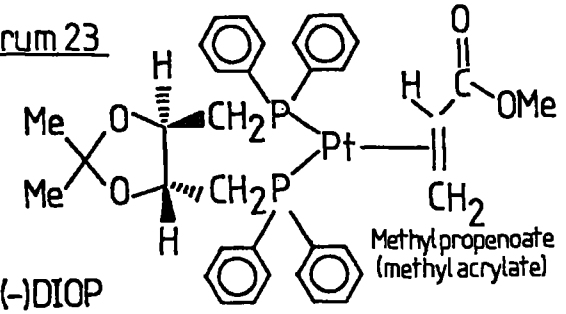
Spectrum 22



(R,R)-(-)DIOP
(-)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

2-Methyl-2,3-butadiene
(dimethyl allene)

Spectrum 23



Methyl propenoate
(methyl acrylate)

(R,R)-(-)DIOP
(-)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

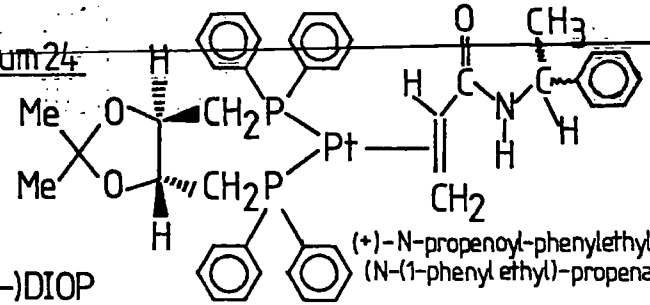
With methylacrylate (53d), as substrate the situation is complicated further by the chemical non-equivalence of the alkene *si* and *re* faces. Fortunately binding to the platinum in (52) is not face selective. In the spectrum 23 there are two pairs of two doublets corresponding to the mutually coupled phosphorus atoms P_aP_b and $P_a'P_b'$ for the *si* and *re* bound complexes. Phosphorus-31 N.M.R. data for all of these achiral substrate complexes are collected in Table 17.

3.2.3 DIOP-Platinum(O)-Ethene as a C.D.A.

The phosphorus-31 N.M.R. spectrum of (2R,3R)-DIOP-platinum-(R)-(+)-N-propenoylphenylethylamine, (53e), is shown in Spectrum 24. The general features of this spectrum, for derivatisation of a *single* acrylamide enantiomer, are similar to those observed for the corresponding achiral acrylate, (Spectrum 23). The substrate is bound to the platinum by either the *si* or *re* face. In each of these complexes the two phosphorus atoms are non-equivalent and couple with each other. Four sets of doublets plus their attendant ^{195}Pt satellites are observed. The anisogamy of the two phosphorus atoms in each complex is clearly illustrated by the very different appearance of the high and low frequency satellites.

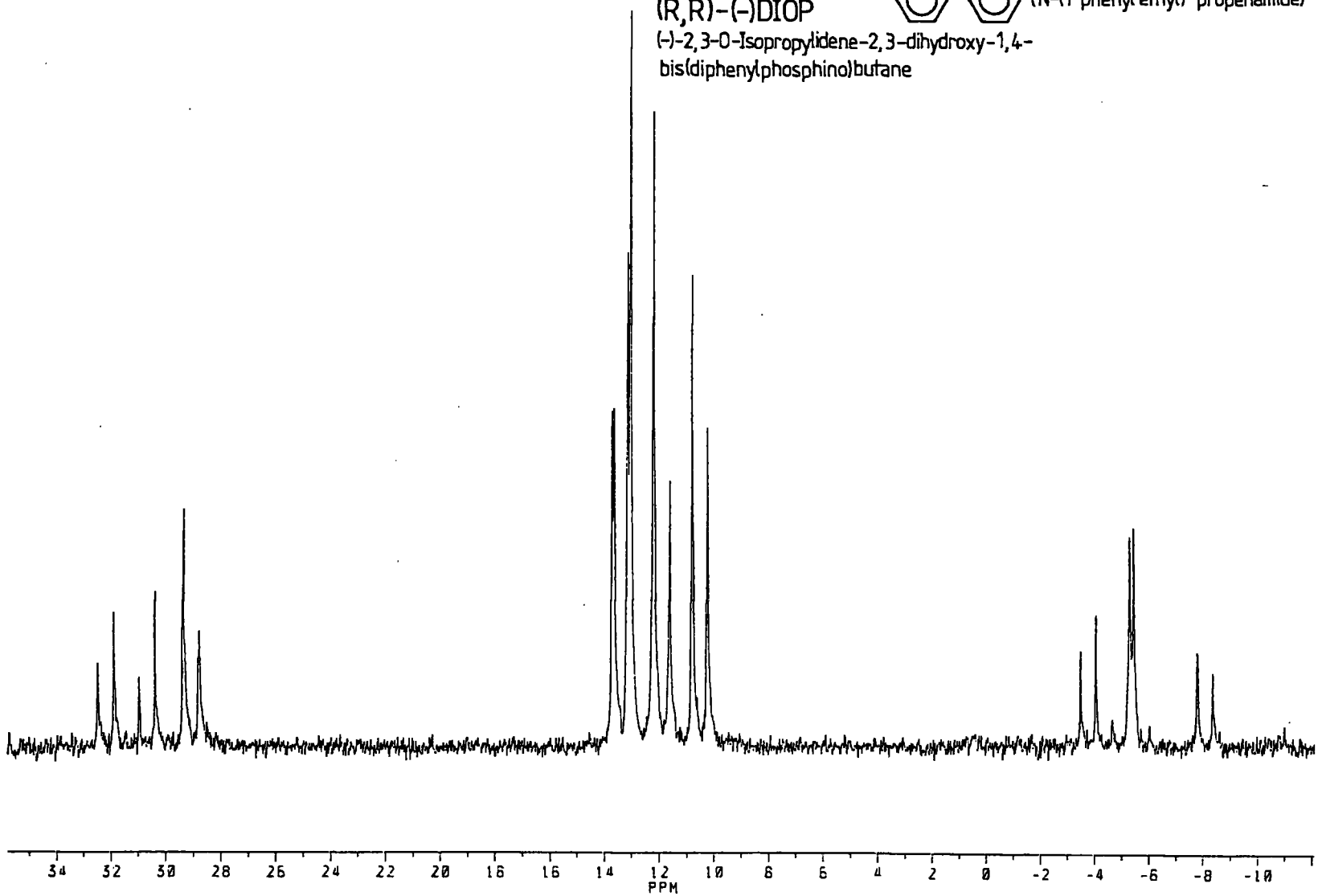
When the substrate is racemic then each of the two diastereomeric complexes behaves as described above giving rise to a total of eight doublets in the ^{31}P N.M.R. spectrum, (Spectrum 25). In principle comparison of the integration for any pair of diastereomeric resonances should yield the enantiomeric purity information. In many cases, however, the spectra are second order and peak intensities are distorted.

Spectrum 24

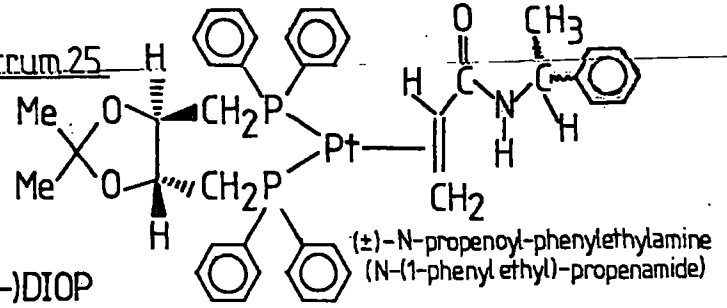


(+)-N-propenoyl-phenylethylamine
(N-(1-phenyl ethyl)-propenamide)

(R,R)-(-)DIOP
(-)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane



Spectrum 25



(±)-N-propenoyl-phenylethylamine
(N-(1-phenyl ethyl)-propenamide)

(R,R)-(-)DIOP
(-)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

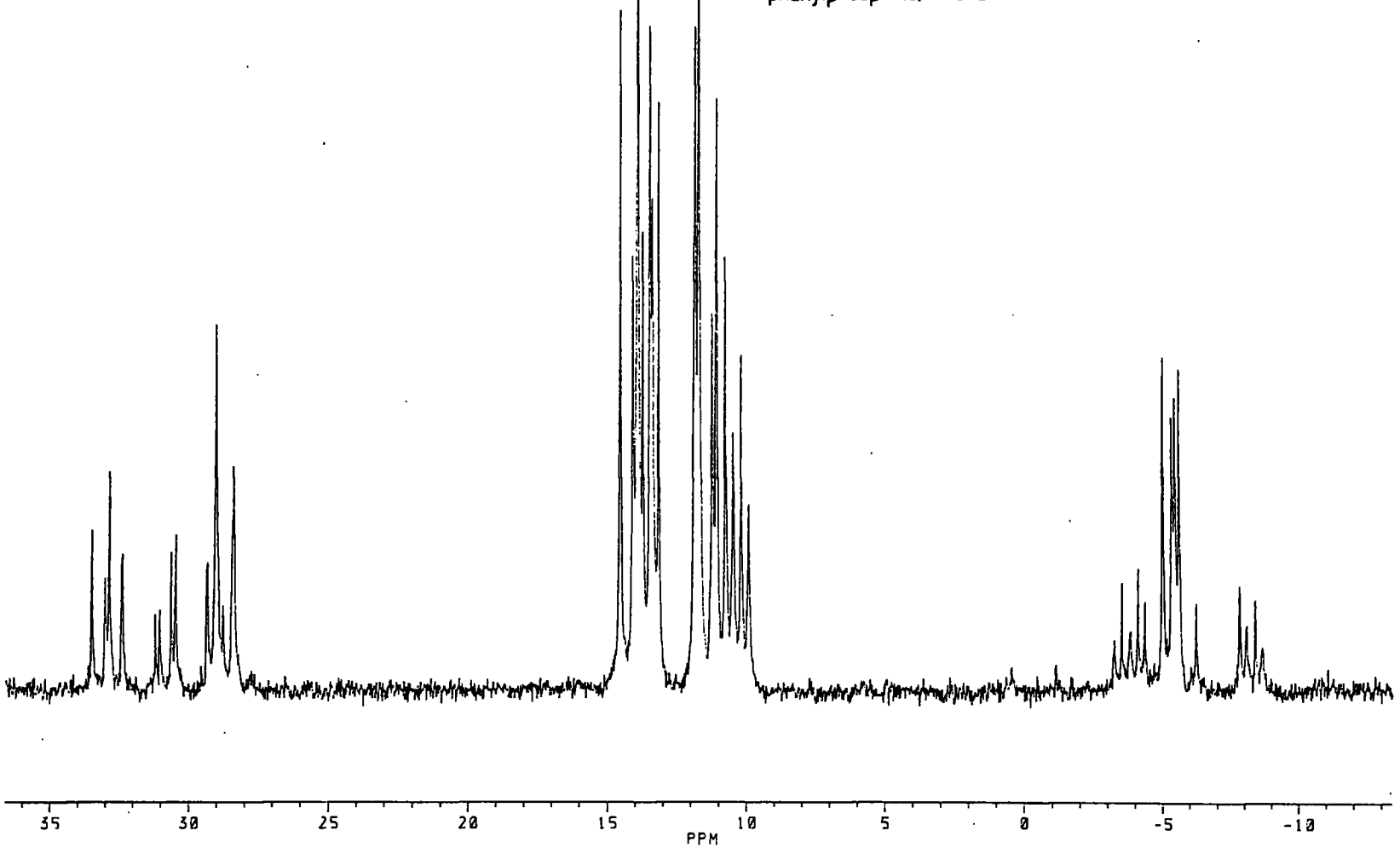


Table 17

N.M.R. Data for Platinum Achiral Alkene Complexes

Compound: (-)DIOP-Pt-Cl_2

δP =-1.50ppm J_{P-Pt} =3512Hz $\delta^{195}Pt$=+519ppm

Compound: (-)DIOP-Pt-Ethene

δP =13.70ppm J_{P-Pt} =3585Hz $\delta^{195}Pt$=-566ppm

Compound: (-)DIOP-Pt-dimethyl-1,4-Butyne-dioate

δP =+5.92ppm J_{P-Pt} =3567Hz $\delta^{195}Pt$=-227ppm

Compound: (-)DIOP-Pt-Br_2

δP =-3.19ppm J_{P-Pt} =3432Hz

Compound: (-)DIOP-Pt-Allyl acetate

δP =-2.56ppm J_{P-Pt} =3847Hz

Compound: (-)DIOP-Pt-norbornene

δP =14.04ppm J_{P-Pt} =3447Hz

Compound: (-)DIOP-Pt-1,1-Diphenylethene

δPa =11.16ppm J_{P-Pt} =3704Hz J_{Pa-Pb} =71Hz

δPb = 7.69ppm J_{P-Pt} =3360Hz J_{Pa-Pb} =71Hz

Compound: (-)DIOP-Pt-1,1-Dimethylallene

δPa =18.99ppm J_{Pa-Pt} =3463Hz J_{Pa-Pb} =54Hz

δPb = 6.65ppm J_{Pb-Pt} =2857Hz J_{Pa-Pb} =54Hz

Compound: (-)DIOP-Pt-Methylacrylate

δPa =13.79ppm J_{Pa-Pt} =3475Hz J_{Pa-Pb} =57Hz

δPb = 8.95ppm J_{Pb-Pt} =3862Hz J_{Pa-Pb} =57Hz

$\delta Pa'$ =12.37ppm $J_{Pa'-Pt}$ =3434Hz $J_{Pa'-Pb'}$ =61Hz

$\delta Pb'$ =10.76ppm $J_{Pb'-Pt}$ =3871Hz $J_{Pa'-Pb'}$ =61Hz

^{31}P N.M.R. spectra recorded at 101MHz in d_6-benzene at 298K. Chemical Shifts relative to 85% Phosphoric acid

^{195}Pt N.M.R. spectra recorded at 19MHz in d_6-benzene at 298K. Chemical Shifts relative to T.M.S.

Since each spectrum of this type contains 24 pairs of diastereomeric resonances it is usually possible to identify at least one pair of resonances which are not distorted and are able to give a reliable estimate of the enantiomeric composition. If only a racemic mixture of the substrate is available the complexity of these spectra can make peak assignment difficult, but if an enantiomerically pure, or enriched, sample is available then peak assignment is greatly facilitated.

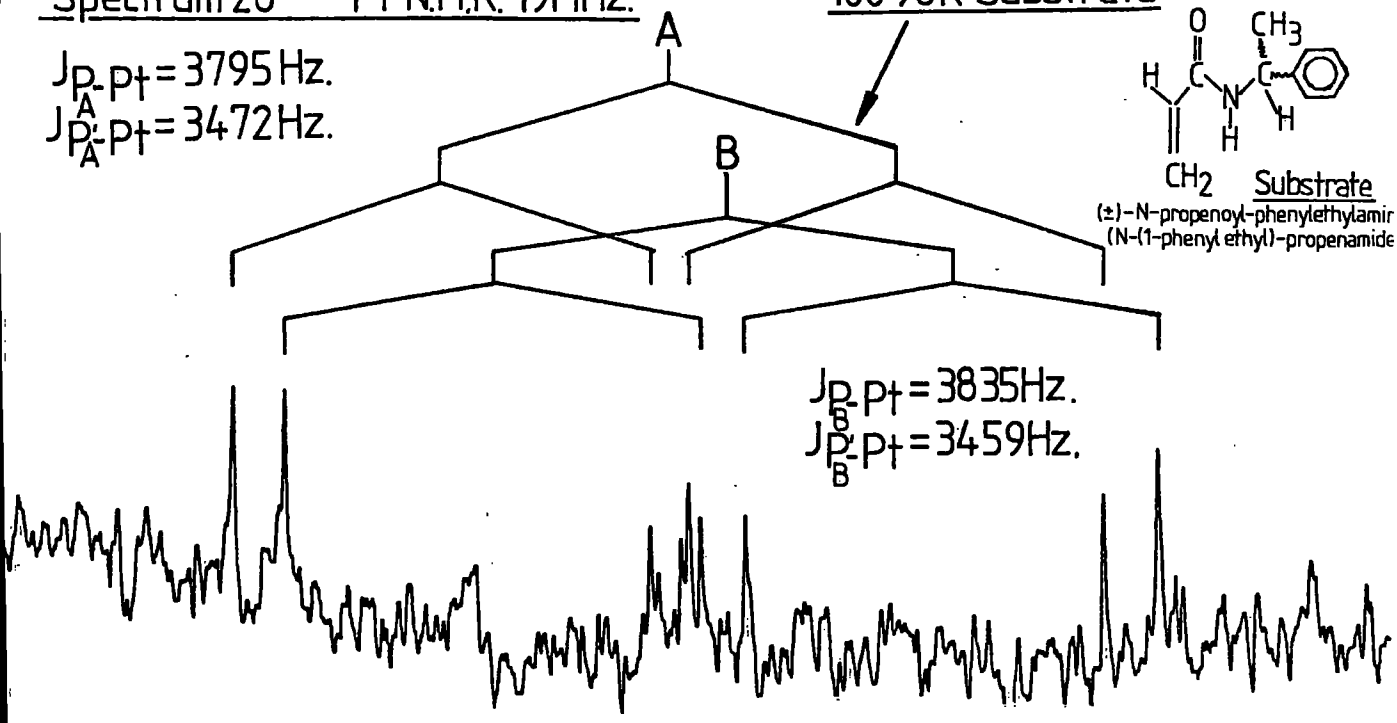
In comparison with the ^{31}P N.M.R. spectra (data shown in Table 18) those obtained observing the ^{195}Pt nucleus are very much simpler and hence more easily interpreted. Spectrum 26 illustrates ^{195}Pt N.M.R. spectra for chiral (a) and racemic (b) acrylamides (53e) derivatised with (2R,3R)-DIOP-platinum-ethene. In each of the four possible complexes in (b), [(+)-*si* bound, (+)-*re* bound, (-)-*si* bound and (-)-*re* bound], the platinum I = 1/2 nucleus is coupled with the two phosphorus atoms; four doublets are expected if the differential coupling with the non-equivalent phosphorus atoms in each species is not resolved. The major drawbacks with ^{195}Pt N.M.R. are the low natural abundance necessitating long spectral acquisition times and the need to use relatively low field instruments. The ^{195}Pt spectra reported in this work were recorded overnight (60,000 scans) at 19.2MHz (90MHz ^{1}H). All attempts to measure spectra at higher fields [e.g. 53MHz (250MHz ^{1}H)] failed; presumably due to the large anisotropy in non-C_2 symmetric platinum complexes which broadens the lines at high fields. In view of the results obtained, despite the simplicity of the spectra, ^{195}Pt cannot be proposed as a practical method for

Spectrum 26 ^{195}Pt N.M.R. 19MHz.

100%R Substrate

$J_{P_A\text{-}Pt} = 3795\,Hz.$

$J_{P'_A\text{-}Pt} = 3472\,Hz.$



Substrate

(±)-N-propenoyl-phenylethylamin
(N-(1-phenyl ethyl)-propenamide

$J_{P_B\text{-}Pt} = 3835\,Hz.$

$J_{P'_B\text{-}Pt} = 3459\,Hz.$

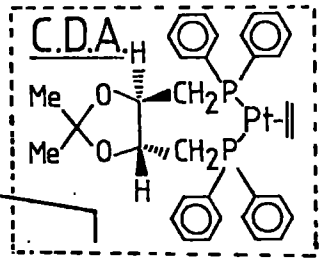
$J_{P_C\text{-}Pt} = 3845\,Hz.$

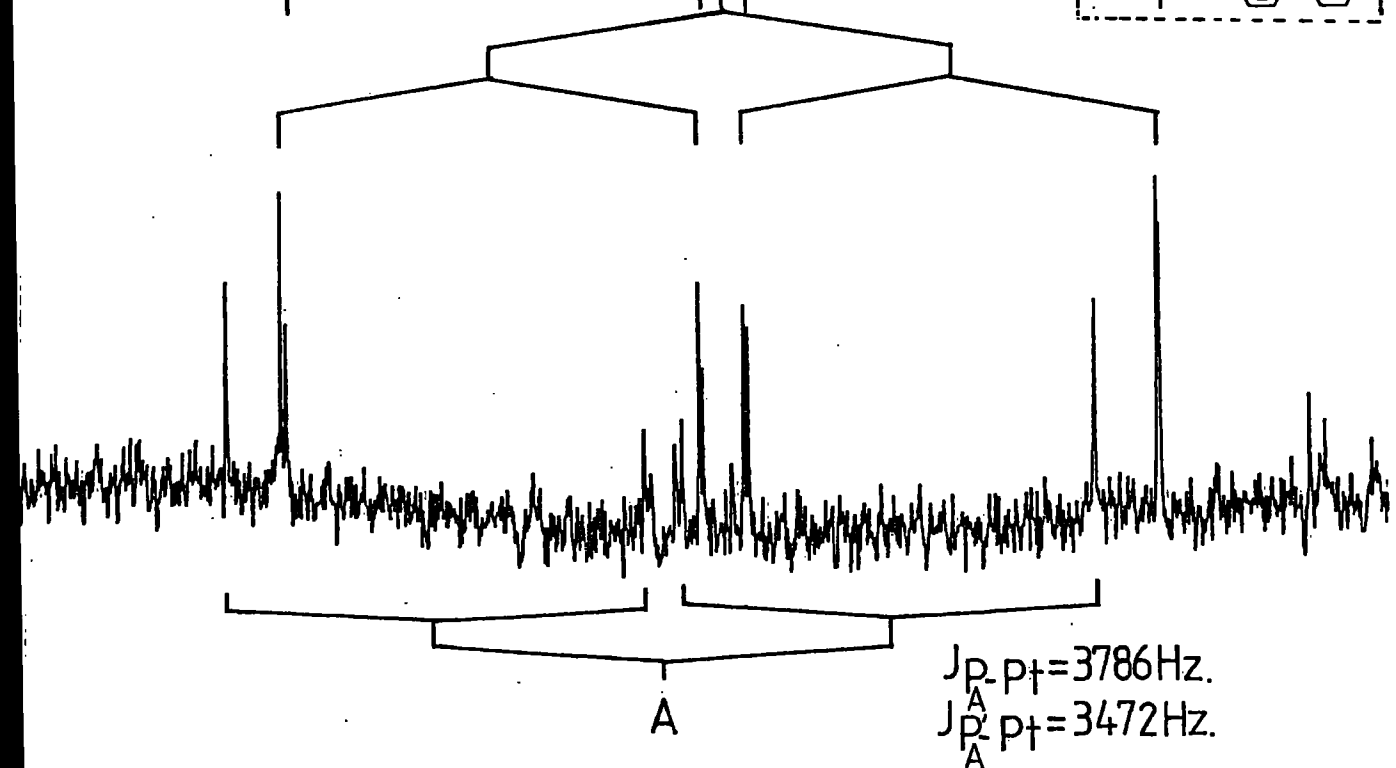
$J_{P'_C\text{-}Pt} = 3464\,Hz.$

$J_{P_D\text{-}Pt} = 3853\,Hz.$

$J_{P'_D\text{-}Pt} = 3479\,Hz.$

50%R 50%S Substrate





$J_{P_A\text{-}Pt} = 3786\,Hz.$

$J_{P'_A\text{-}Pt} = 3472\,Hz.$

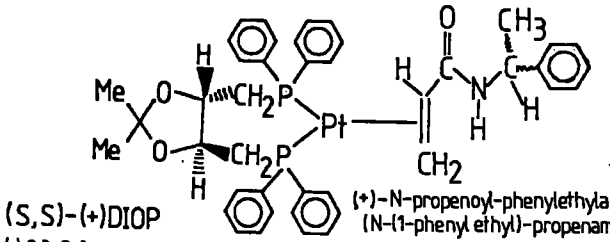
determination of enantiomeric composition. The signal to noise ratio is poor and resolution of diastereomeric resonances at low magnetic fields is insufficient to allow reliable integration.

Substituting the enantiomeric C.D.A. (2S,3S)-DIOP-platinum(0)-ethene, in place of the corresponding (2R,3R)-complex causes the predicted reversal in the sense of all resonances in the ^{31}P N.M.R. spectrum. This effect is clearly illustrated in Spectra 24 and 27 for 100%(R), (53e), with (2R,3R) and (2S,3S)-DIOP respectively.

In order to establish that derivatisation is non-stereoselective and that there is no facial selectivity in binding, a series of acrylamides (53e) of known enantiomeric composition were derivatised. The data in Table 19 show that the integrated enantiomeric compositions are within ±3% of the known values. Spectrum 28 is the ^{31}P N.M.R. spectrum for a 75%(R), 25%(S) substrate mixture derivatised with (2S,3S)-DIOP-platinum-ethene recorded in d_6-benzene at 101MHz. The peak at 23.5 ppm is due to DIOP oxide, the decomposition product. Spectra are usually acquired in d_6-benzene because its use maximises the observed non-equivalence for diastereomeric complexes. In the ^{1}H N.M.R. spectrum, dissolution of (52) in d_6-benzene causes the ethene proton to shift 0.58 ppm to higher frequency relative to the spectrum obtained in d_2-dichloromethane. This suggests that in benzene the C.D.A. may be solvated by solvent molecules "stacking" over the diphenyl-phosphine π system, placing the ethene protons in a more deshielded environment.

Spectrum 27

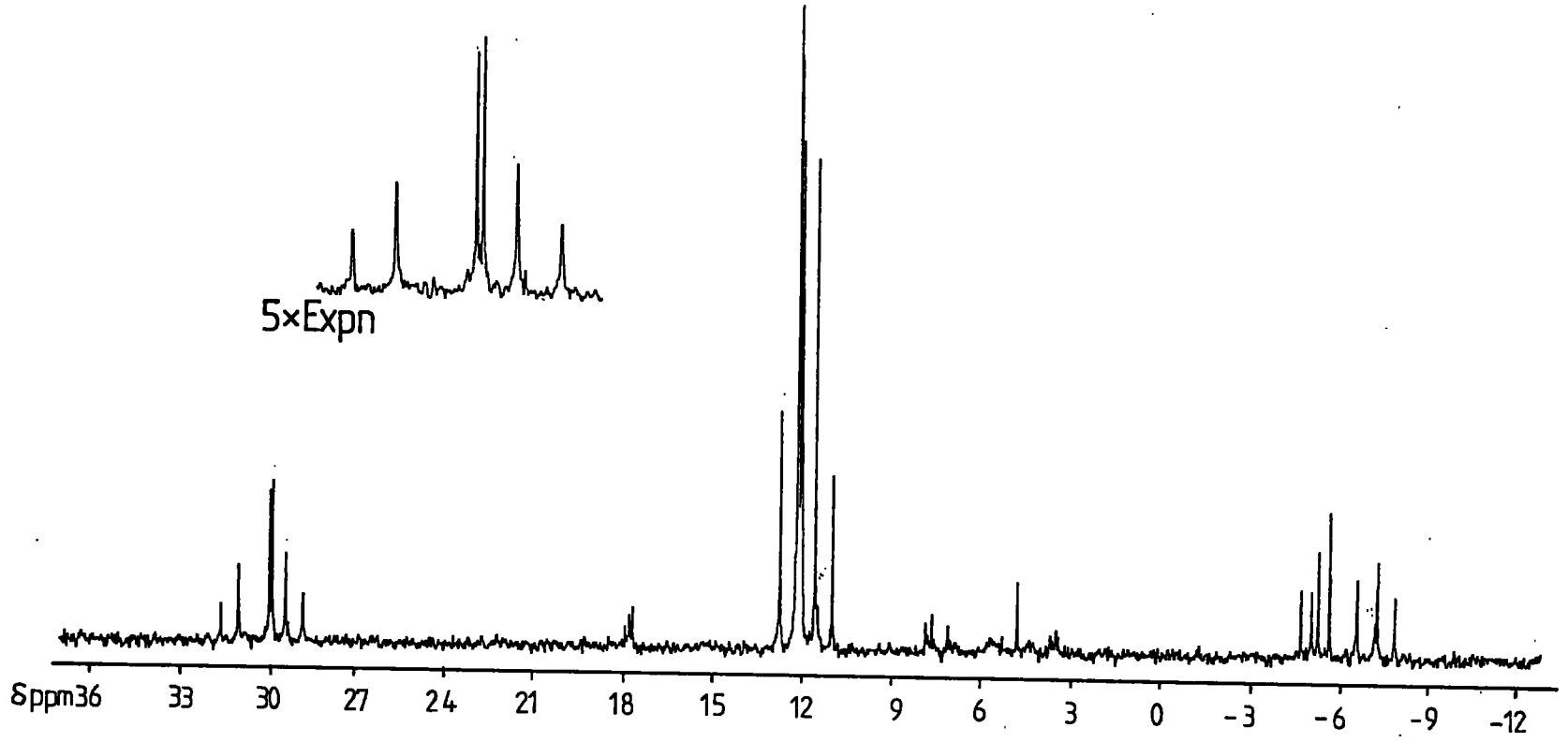
31P N.M.R. 36MHz.



(S,S)-(+)DIOP

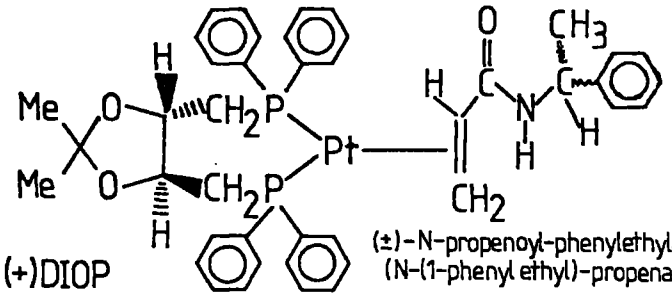
(+)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

(+)-N-propenoyl-phenylethylamine
(N-(1-phenyl ethyl)-propenamide)



Spectrum 28

75%(R)-(-),25%(S)-(+)



(S,S)-(+)DIOP

(+)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

(±)-N-propenoyl-phenylethylamine
(N-(1-phenyl ethyl)-propenamide)

Table 18

N.M.R. Data for Platinum Chiral Alkene Complexes

Compound: (-)DIOP-Pt-(±)-Acrylamide (53e)

	si/re constitutional isomers		diastereoisomers(±)
i)	δPa =12.8ppm	J_{Pa-Pt} =3801Hz	J_{Pa-Pb} =57Hz
ii)	δPb = 9.9ppm	J_{Pb-Pt} =3759Hz	J_{Pa-Pb} =57Hz
iii)	δPa' =12.7ppm	$J_{Pa'-Pt}$ =3512Hz	$J_{Pa'-Pb'}$ =61Hz
iv)	δPb' =11.3ppm	$J_{Pb'-Pt}$ =3477Hz	$J_{Pa'-Pb'}$ =61Hz
v)	δPa =13.6ppm	J_{Pa-Pt} =3838Hz	J_{Pa-Pb} =57Hz
vi)	δPb = 9.6ppm	J_{Pb-Pt} =3752Hz	J_{Pa-Pb} =57Hz
vii)	δPa' =13.3ppm	$J_{Pa'-Pt}$ =3470Hz	$J_{Pa'-Pb'}$ =64Hz
viii)	δPb' =10.8ppm	$J_{Pb'-Pt}$ =3500Hz	$J_{Pa'-Pb'}$ =64Hz

Compound: (-)DIOP-Pt-(±)-Carvone (54)

ix)	δPa =13.77ppm	J_{Pa-Pt} =3409Hz	J_{Pa-Pb} =65Hz
x)	δPb = 9.88ppm	J_{Pb-Pt} =3881Hz	J_{Pa-Pb} =65Hz
xi)	δPa' =12.50ppm	$J_{Pa'-Pt}$ =3537Hz	$J_{Pa'-Pb'}$ =65Hz
xii)	δPb' =10.75ppm	$J_{Pb'-Pt}$ =3938Hz	$J_{Pa'-Pb'}$ =65Hz

Compound: (-)DIOP-Pt-(±)-2-propenyl-α-methoxy-phenylethanoate

xiii)	δPa =14.68ppm	J_{Pa-Pt} =3887Hz	J_{Pa-Pb} =66Hz
xiv)	δPb =12.22ppm	J_{Pb-Pt} =3796Hz	J_{Pa-Pb} =66Hz
xv)	δPa' =13.80ppm	$J_{Pa'-Pt}$ =3774Hz	$J_{Pa'-Pb'}$ =68Hz
xvi)	δPb' =12.40ppm	$J_{Pb'-Pt}$ =3760Hz	$J_{Pa'-Pb'}$ =68Hz

Table 18 continued

Compound: (-)DIOP-Pt-(±)-trans-dimethyl-norbornene-2,3-dicarboxylate ester

si/re constitutional isomers — diastereoisomers(±)

xvii)	δPa =14.76ppm	J_{Pa-Pt} =3456Hz	J_{Pa-Pb} =67Hz	]
xviii)	δPb =12.70ppm	J_{Pb-Pt} =3376Hz	J_{Pa-Pb} =67Hz	]]
xix)	δPa' =14.54ppm	$J_{Pa'-Pt}$ =3439Hz	$J_{Pa'-Pb'}$ =68Hz	]
xx)	δPb' =12.03ppm	$J_{Pb'-Pt}$ =3367Hz	$J_{Pa'-Pb'}$ =68Hz	]]

Compound: (-)DIOP-Pt-(±)-1,2-cyclononadiene

xxi)	δPa =17.65ppm	J_{Pa-Pt} =3246Hz	J_{Pa-Pb} =72Hz	]
xxii)	δPb =10.27ppm	J_{Pb-Pt} =3246Hz	J_{Pa-Pb} =72Hz	]]
xxiii)	δPa' =17.30ppm	$J_{Pa'-Pt}$ =3060Hz	$J_{Pa'-Pb'}$ =71Hz	]
xxiv)	δPb' =10.98ppm	$J_{Pb'-Pt}$ =3060Hz	$J_{Pa'-Pb'}$ =71Hz	]]

Compound: (+)DIOP-Pt-(±)-1,3-di-^{n}butylallene

xxv)	δPa =17.14ppm	J_{Pa-Pt} =3235Hz	J_{Pa-Pb} =65Hz	]
xxvi)	δPb = 9.61ppm	J_{Pb-Pt} =3026Hz	J_{Pa-Pb} =65Hz	]]
xxvii)	δPa' =16.21ppm	$J_{Pa'-Pt}$ =3238Hz	$J_{Pa'-Pb'}$ =65Hz	]
xxviii)	δPb' = 9.83ppm	$J_{Pb'-Pt}$ =3026Hz	$J_{Pa'-Pb'}$ =65Hz	]]]
xxix)	δPa =17.62ppm	J_{Pa-Pt} =3252Hz	J_{Pa-Pb} =57Hz	]
xxx)	δPb = 6.01ppm	J_{Pb-Pt} =2942Hz	J_{Pa-Pb} =57Hz	]]
xxxi)	δPa'	Not Resolved		]
xxxii)	δPb' = 7.21ppm	$J_{Pb'-Pt}$ =2947Hz	$J_{Pa'-Pb'}$ =59Hz	]]

^{31}P N.M.R. Spectra recorded at 101MHz in d_6-benzene at 298K.

Chemical Shifts in ppm relative to 85% Phosphoric acid.

Table 19

Comparison Between Integrated and Prepared Compositions

Composition[a]	Integrated Composition
Compound: (-)-DIOP-Pt-(±)-Acrylamide. (53e)	
98% (R), 2% (S)-	96% (R), 4% (S)-
75% (R), 25% (S)-	73% (R), 27% (S)-
50% (R), 50% (S)-	52% (R), 48% (S)-
25% (R), 75% (S)-	24% (R), 76% (S)-
2% (R), 98% (S)-	3% (R), 97% (S)-
Compound: (-)-DIOP-Pt-(±)-5-Isopropenyl-2-methyl-2-cyclohexenone	
99% (R), 1% (S)-	97% (R), 3% (S)-
75% (R), 25% (S)-	72% (R), 28% (S)-
50% (R), 50% (S)-	50% (R), 50% (S)-
25% (R), 75% (S)-	76% (R), 24% (S)-
1% (R), 99% (S)-	2% (R), 98% (S)-

a) Compositions as prepared or as specified by suppliers.

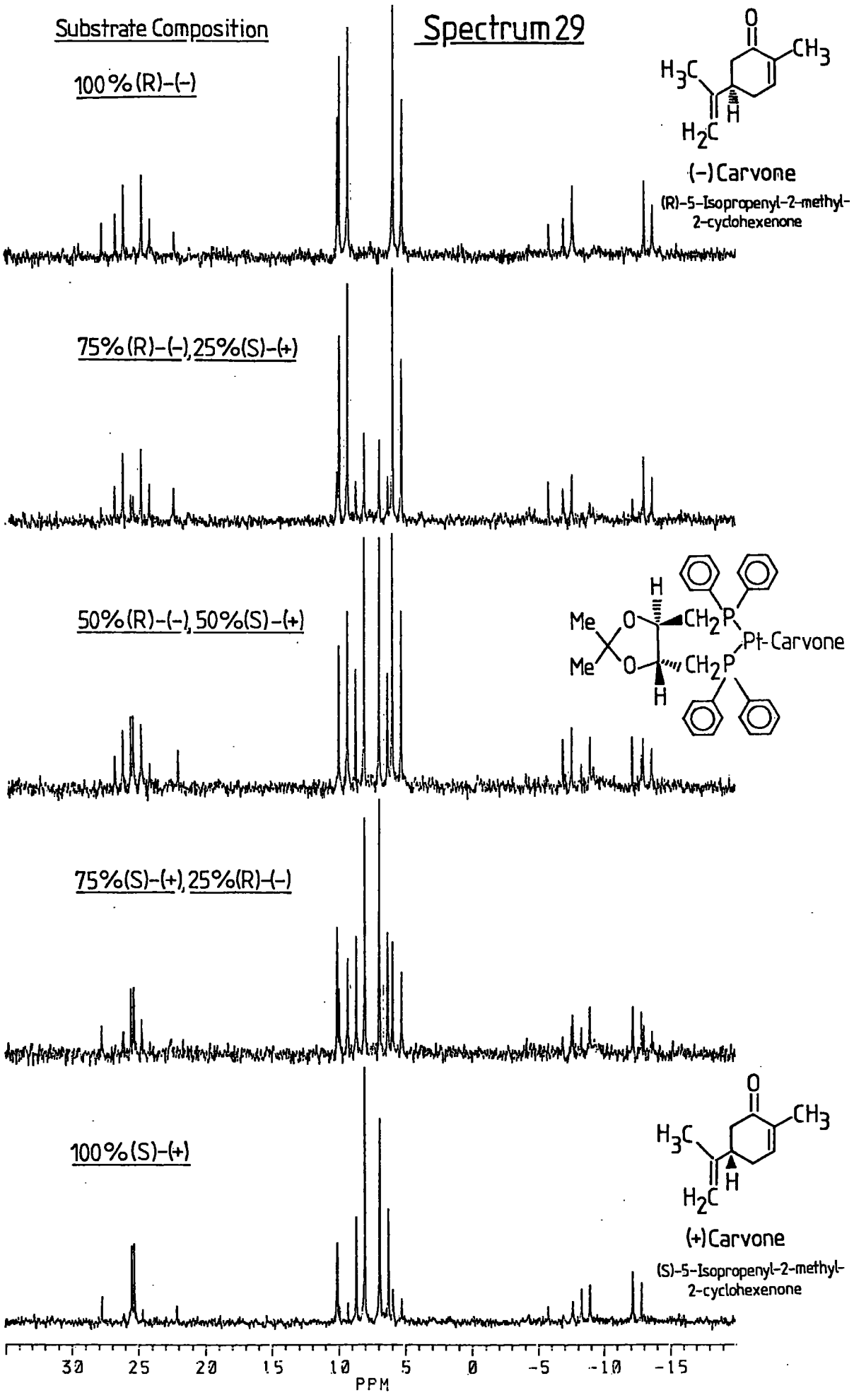
i) Acrylamides prepared from 98% (+) or (-) α-Methylbenzylamine and acryloyl chloride Supplied by Aldrich Chem. Co.

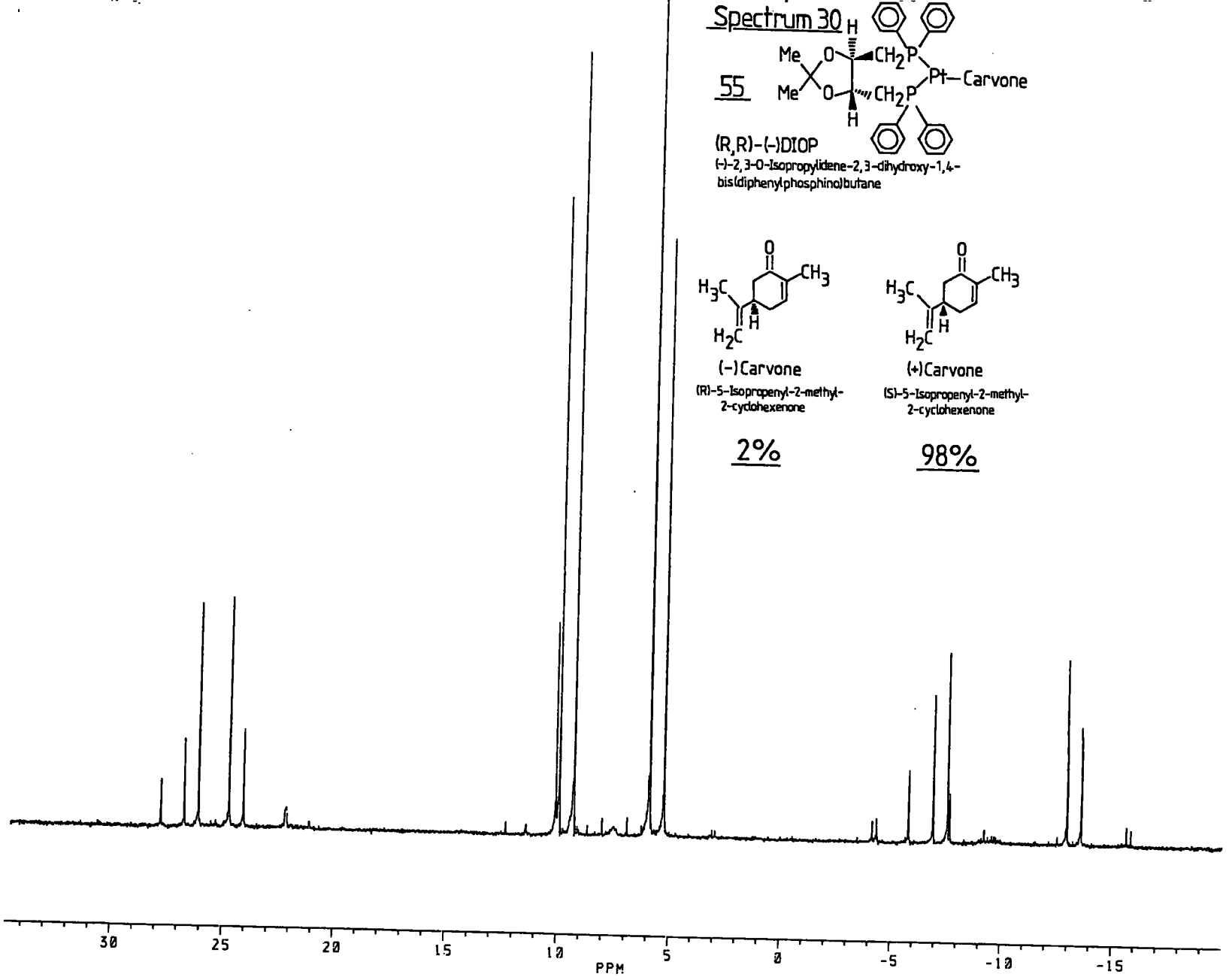
ii) 5-Isopropenyl-2-methyl-2-cyclohexenone (Carvone) 99% (S), 99% (R) Supplied by Fluka A.G.

Estimated error in preparation of mixtures ±2%.

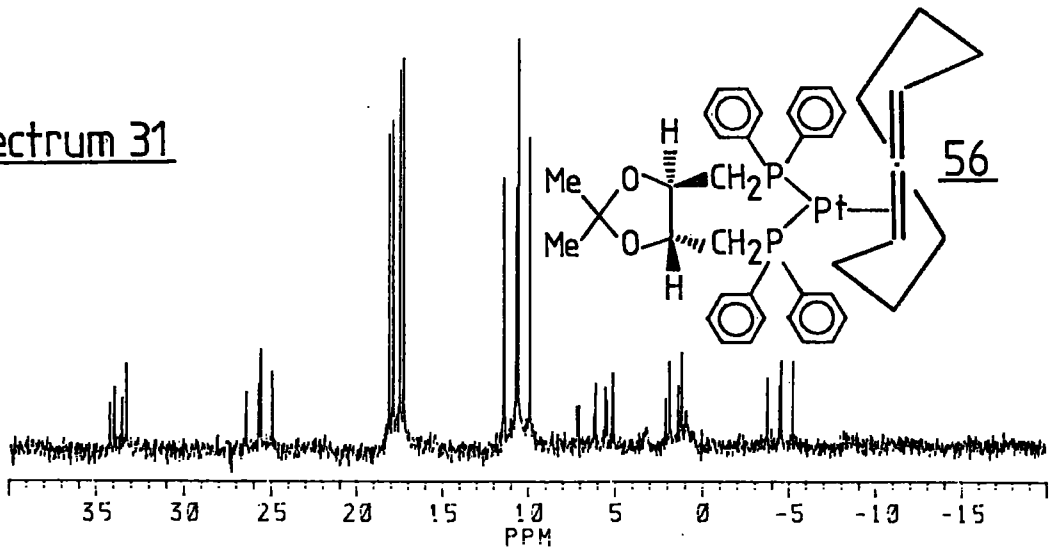
At this time separate derivatisation reactions were being carried out in THF. Direct derivatisations involving shaking equimolar quantities of the substrate and C.D.A. together in d_6-benzene in an N.M.R. tube were found to be equally successful with substrate (53e). In certain other cases, however, derivatisation was incomplete when this "in situ" approach was applied. Even when only a small proportion of the substrate is derivatised there is no evidence for enantio-selectivity in binding of the substrate. Spectrum 29 is a "stacked" plot of ^{31}P N.M.R. spectra acquired following direct derivatisation of 5-isopropenyl-2-methyl-2-cyclohexanone (carvone, 54) in mixtures of known enantiomeric composition. Binding of carvone occurs exclusively at the less hindered si-si face of the endocyclic double bond. The (±)-carvone mixtures were prepared from fresh commercial samples of (R) and (S) enantiomers specified by the suppliers (Fluka) to be 98% pure. Spectrum 30 was acquired for 5000 scans of a solution containing 10mg of the (2R,3R)-DIOP-platinum-(S)-carvone complex (55) and illustrates that the method is sufficiently sensitive to detect and permit measurement of the residual (R) enantiomer (2%). An aged sample (Koch-Light) of 97%(S)-carvone was derivatised and the enantiomeric composition determined to be 86%(S),14%(R).

A racemic mixture of the chiral cyclic allene 1,2-cyclononadiene, (56), was prepared by reduction of 9,9-dibromo-bicyclo[6.1.0.]nonane using methyllithium[203] and derivatised with (52). The ^{31}P N.M.R. spectrum is Spectrum 31. In each enantiomer only one face of the π system is available for binding to the transition metal. Approach of the metal to the


Substrate Composition
Spectrum 29
100% (R)-(-)
75% (R)-(-), 25% (S)-(+)
50% (R)-(-), 50% (S)-(+)
75% (S)-(+), 25% (R)-(-)
100% (S)-(+)
(-) Carvone
(R)-5-Isopropenyl-2-methyl-2-cyclohexenone
Pt-Carvone
(+) Carvone
(S)-5-Isopropenyl-2-methyl-2-cyclohexenone
30 25 20 15 10 5 0 -5 -10 -15
PPM


Spectrum 30
55
(R,R)-(-)DIOP
(-)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
Carvone
(-)Carvone
(R)-5-Isopropenyl-2-methyl-2-cyclohexenone
2%
(+)Carvone
(S)-5-Isopropenyl-2-methyl-2-cyclohexenone
98%
30
25
20
15
10
5
0
-5
-10
-15
PPM

Spectrum 31

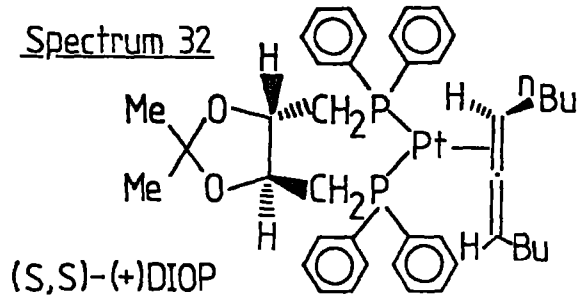


56

other face is obstructed by the ring, hence four doublets (plus associated satellites) are observed. Using a literature synthesis, involving the use of (-)-sparteine in conjunction with methyllithium at the reduction step,[204] a sample of enantiomerically enriched (56) was prepared and assayed to be 5%(S).

Samples of racemic, 33% enriched and 17% enriched 1,3-di-n-butylallene[205] (53f) were derivatised using (2S,3S)-DIOP-platinum-ethene. The spectrum obtained for the 33% enriched material is shown in Spectrum 32. Spectra for the racemic and 17% enriched allenes are identical i.e. the C.D.A. cannot be used to assay enantiomeric purity in this case. In Spectrum 32 the resonance signals for the two phosphorus atoms, (P_a and P_b) in the si-re bound complex exhibit different intensities to those corresponding to the two phosphorus atoms, (P_a' and P_b'),

Spectrum 32

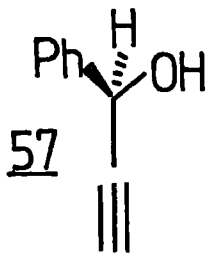


(S,S)-(+)DIOP

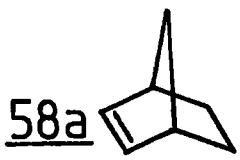
(+)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

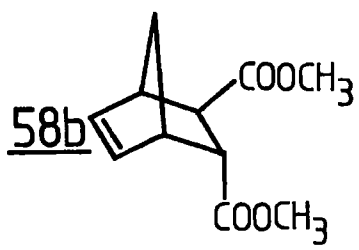
in the re-si bound complex. The unusual appearance of the spectrum is due to the clean separation of P_b and P_b' resonances whilst the P_a and P_a' resonances are almost co-incidental. In this case changing of the C.D.A. does not appear to result in reversal of the ^{31}P N.M.R. resonances. Another case in which enantioselectivity in binding occurs is observed with hydroxyphenylpropyne, (57), as a substrate, where one enantiomer is selectively bound. Thus the applicability of (52) appears to be limited to substrates in which the element of chirality is remote from the metal centre and which may not additionally bind to the metal via a second proximate polar group. This is in direct contrast to the silver-L.S.R. reagent for which the element of chirality must be close to the metal centre.

The strained alkene, norbornene, (58a), binds to the C.D.A. (52) to give one diastereisomer. The phosphorus-31 N.M.R. data (Table 17) are consistent with selective complexation of the exo-face of the double bond. The related racemic trans-dimethyl-norbornene-2,3-dicarboxylate ester (58b) gives two diastereoisomers on reaction with (52), in precisely 50:50 ratio. The C.D.A. does not react with (±)-limonene because the double bonds in the substrate are neither strained nor sufficiently electron deficient.



57


58a



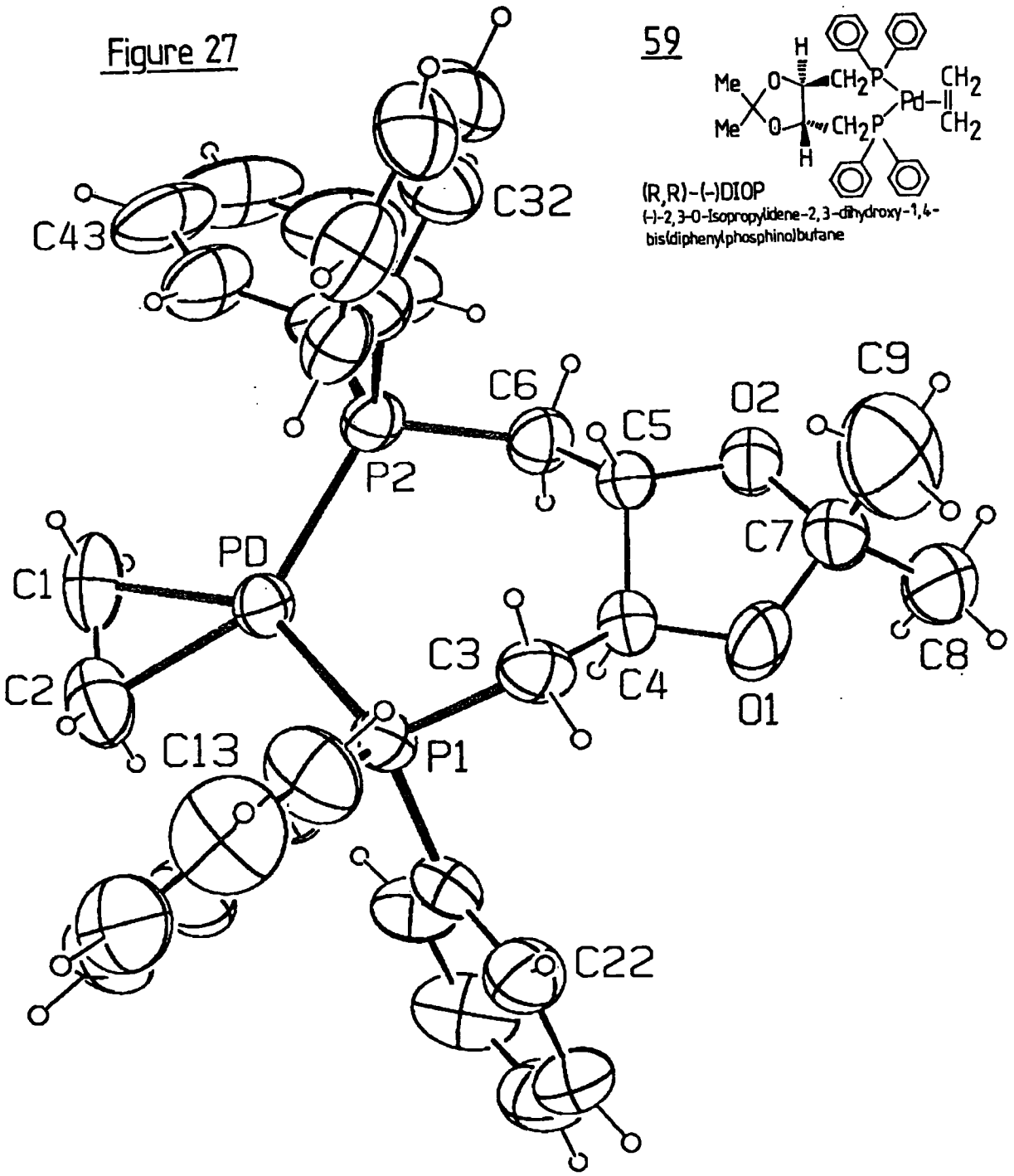
58b

The complex nature of the ^{31}P N.M.R. spectra and their seemingly inconsistent appearance for different substrates limits the use of the C.D.A. for the assignment of absolute configuration to cases where material of known enantiomeric enrichment is available. Once the assignments have been made then unknown mixtures can be assayed and absolute configuration assigned by internal comparison. Assignments of configuration will be consistent only for very closely related series of compounds.

3.3 DIOP-Palladium(O)-Ethene as a C.D.A.

In the course of studies directed towards elucidation of the mechanism of catalytic asymmetric hydrocyanation[3] coworkers sought a convenient precursor to palladium(O)-DIOP. Hodgson[206] was successful in preparing DIOP-palladium(O)-ethene, (59), by sodium borohydride reduction of the corresponding dichloride[207] in the presence of ethene at -40°C. The complex is reasonably stable in air, decomposing at 80°C, but is unstable in solution in the absence of ethene. Proton N.M.R. in d_6-benzene at 298K shows a broad signal corresponding to the ethene protons at 5.1 ppm ($w_{½}$=95Hz, 250MHz) which sharpens under higher partial pressures of ethene ($w_{½}$=48Hz with 10M excess of ethene). The ^{31}P resonance at 6.8ppm remains sharp throughout. This indicates that a fast dissociative alkene exchange mechanism operates in solution. Hodgson's[206] X-ray crystal structure determination is shown as an O.R.T.E.P. plot in (Figure 27). The carbon-carbon bond length in the co-ordinated ethene is 1.366(11), consistent with a weak palladium-ethene bond and in accord with the ease of dissociation of ethene in solution.

Figure 27

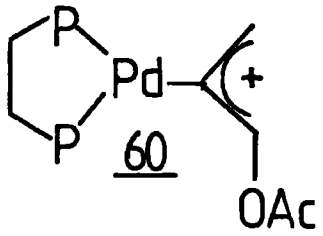


59

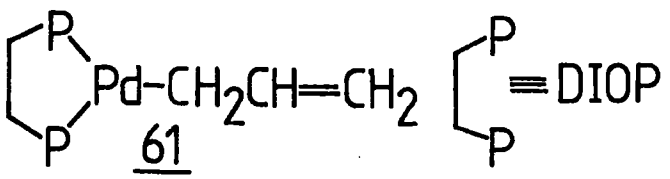
(R,R)-(-)DIOP
(-)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

(R,R)-(-)-DIOP-Palladium-Ethene

The ethene ligand is readily displaced by strained or electron poor η^2 donors such as norbornene and tetracyanoethene. Reaction with allylacetate gives the cationic palladium-η^3-allyl complex (60) whilst oxidative addition of allyl chloride gave not only the η^1 allyl chloride complex (61) but also DIOP-palladium(II) dichloride. The complex (59) will also abstract chlorine from chloroform or carbon tetrachloride to give the dichloride. N.M.R. Studies must, therefore, be carried out in d_2-dichloromethane or d_6-benzene.



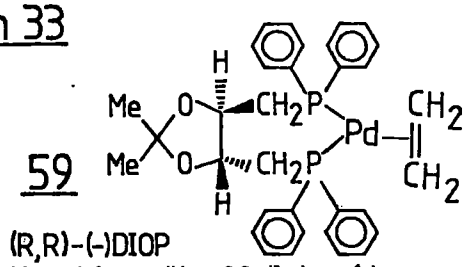
60



61

In view of the lack of success of the platinum C.D.A. (52) with non-functionalised alkenes and bearing in mind the apparent lability of the ethene in the corresponding palladium complex, (59), the use of the latter as a C.D.A. for chiral alkenes was investigated. In d_6-benzene solution in the absence of ethene the complex quickly decomposes to give DIOP oxide and the metal, hence derivatisation must be performed "in situ" directly before N.M.R. study. Spectrum 33 illustrates ^{31}P N.M.R. spectra acquired with 5-isopropenyl-2-methyl-2-cyclohexanone as substrate.

Spectrum 33

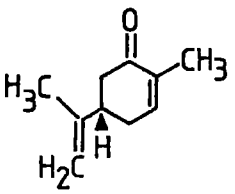


59

(R,R)-(-)DIOP

(-)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

100%(S)-(+)



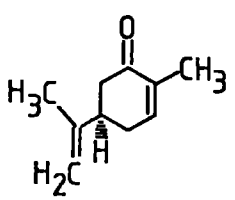
(+)Carvone

(S)-5-Isopropenyl-2-methyl-2-cyclohexenone

DIOP oxide

33%(S)-(+),67%(R)-(-)

100%(R)-(-)



(-)Carvone

(R)-5-Isopropenyl-2-methyl-2-cyclohexenone

35 30 25 20 15 10 5 0 -5 -10 -15

PPM

Table 20

N.M.R. Data for Palladium Alkene Complexes

Compound: $(DIOP)_2$-Pd	δP = -1.3ppm	
Compound: (DIOP)-$PdCl_2$	δP =+16.1ppm	
Compound: (DIOP)-Pd-ethene	δP = +6.8ppm	
Compound: (DIOP)-Pd-tetracyanoethene	δP = +9.2ppm	
Compound: (DIOP)-Pd-norbornene	δP = +6.2ppm	
Compound: (DIOP)-Pd-η^3-Allyl acetate	δP = +8.1ppm	
Compound: (DIOP)-Pd-η^1-Allyl chloride	δPa =+20.8ppm δPb = +2.0ppm	J_{Pa-Pb}=40Hz
Compound: (DIOP)-Pd-phenyliodide	δPa =+13.2ppm δPb = -3.2ppm	J_{Pa-Pb}=41Hz
Compound: (DIOP)-Pd-(±)-Carvone*	δPa = +8.5ppm δPb = +3.5ppm	J_{Pa-Pb}=47Hz
	δPa = +7.3ppm δPb = +4.3ppm	J_{Pa-Pb}=47Hz

1. ^{31}P N.M.R. Spectra recorded at 101MHz at 298K in d_2-dichloromethane except (*) in d_6-benzene.
2. Chemical Shifts in ppm relative to 85% Phosphoric acid.

Since palladium has no isotope with I = 1/2 the satellites, familiar in the spectra of platinum complexes, are not present in the spectra of the related palladium complexes, thus the useful phosphorus-platinum coupling constant "probe" is lost. With all other substrates (53) very broad ^{31}P N.M.R. resonance signals are observed indicative of dynamic processes in solution. The use of d_6-benzene limits the application of variable temperature techniques to slow these processes. D_8-toluene is a suitable alternative. Cyclopentene fails to react with (59) demonstrating that ethene is less susceptible to displacement by alkenes than originally anticipated. The ^{31}P N.M.R. data for all these palladium complexes is shown in Table 20.

In general the palladium complex offers no advantage over the platinum analogue, from the point of view of determination of e.e. The platinum complex (52) has proved to be a useful C.D.A. but is limited in its scope to strained or electron-poor alkenes. The spectra can be complicated and difficult to interpret. Nevertheless, once the assignments have been made the accuracy of enantiomeric purity determination is ±2% provided that resolution is sufficient to allow integration of diastereomeric resonances and that the spectra obtained are fully relaxed.

CHAPTER FOUR

N.M.R. Assay of Enantiomeric Excess using Chiral Solvating Agents-I

The development and application of chiral sulphoxides as Chiral Solvating Agents.

4.1 Chiral Solvating Agent Design

Chiral Solvating Agents permit "in situ" determination of enantiomeric purity without irreversible reaction with the sample. The enantiomeric composition of the solvating agent does not effect the measurement of the enantiomeric purity of the sample. The most widely used C.S.A.s are trifluoromethyl-arylcarbinols devised by Pirkle[151] and the alkyl-arylamines (section 1.7), both of these types of C.S.A.s operate effectively for only a limited range of solutes.

In an attempt to design a more generally applicable C.S.A. their mode of operation was considered. In order to be effective the chiral solute must be solvated by the C.S.A. in preference to the achiral diluting solvent. The diastereomeric C.S.A.-solute complexes so formed should then exhibit anisochronous chemical shifts.

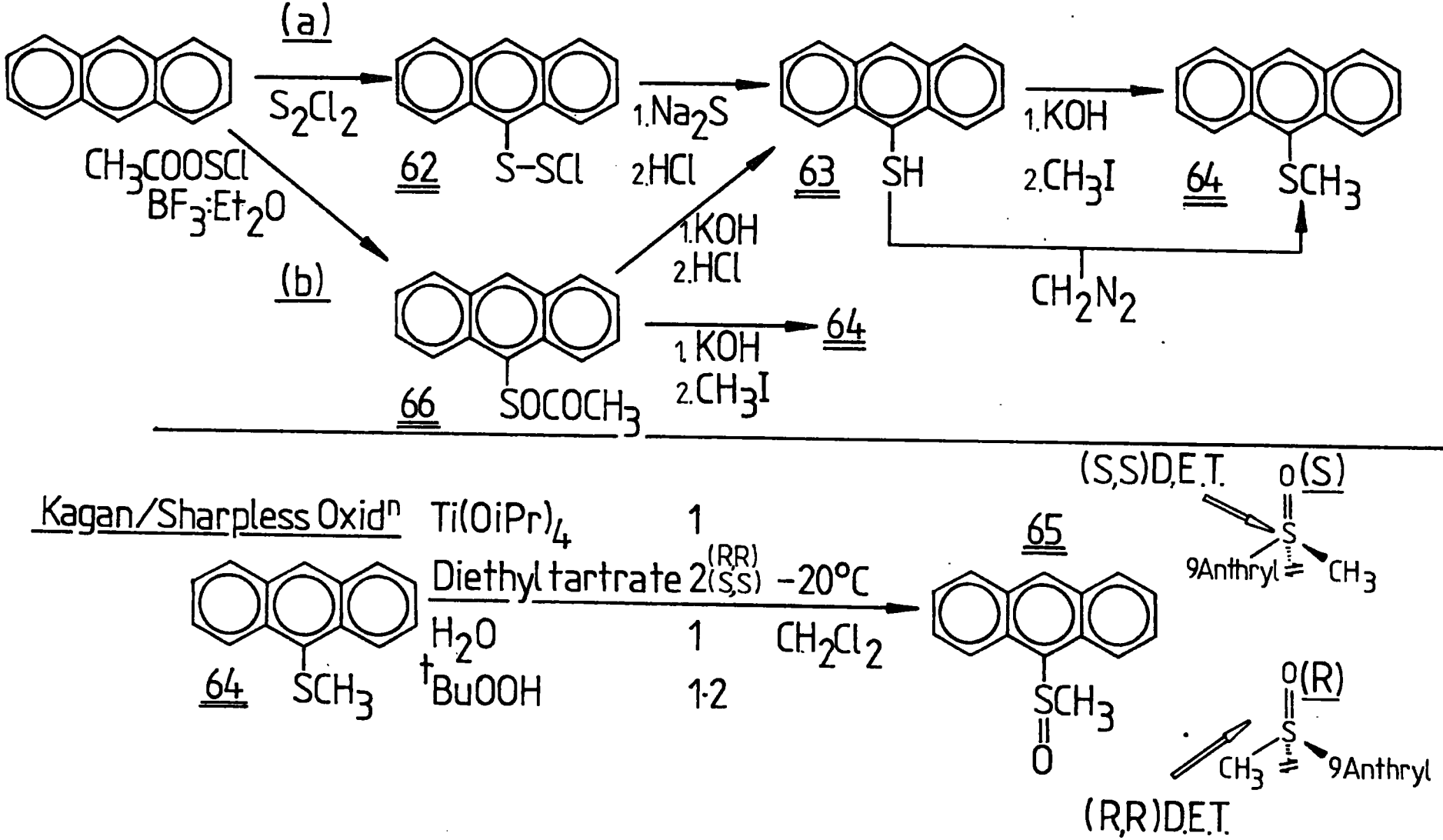
Dimethylsulphoxide is a polar solvent capable of solvating a large number of compounds and, in addition, the sulphur is a pro-chiral centre.[90] The groups around the sulphur atom are tetrahedrally disposed with the lone pair of electrons occupying one of the four sites. If each of the two methyl groups is replaced in turn by CD_3 then two enantiomers are obtained.[89] Chiral alcohols[208] and chiral amines[164] have both

been shown to be good C.S.A.s for racemic sulphoxides. The complementary nature of the C.S.A.-solute interaction implies that chiral sulphoxides should be effective C.S.A.s for racemic amines and alcohols. Conceptually the simplest chiral sulphoxide might be CD_3SOCH_3. However the model proposed by Pirkle[152] to explain the non-equivalence observed in sulphoxide substituents solvated by alkyl-arylcarbinols, (Figure 14), shows that this sulphoxide would be useless as a C.S.A. When the oxygen and sulphur lone pair of electrons are involved in formation of the required "chelate-like" complex then the induction of non-equivalence in the alcohol substituents would rely on the differential shielding effects of CH_3 and CD_3 groups. Clearly one of the sulphoxide substituents needs to be a group with considerable magnetic anisotropy such as an aryl group. Based on the experience Pirkle[209] acquired with the trifluoromethylcarbinols where induced non-equivalence increases in the aryl group sequence phenyl-< 2-naphthyl-< 9-anthryl-, 9-anthryl-methylsulphoxide (65) was proposed as a target C.S.A. molecule.

4.2 Synthesis of Chiral Sulphoxides

The early synthetic scheme for 9-anthrylmethylsulphoxide is outlined in Scheme 4a. Anthracene was treated with sulphur dichloride, S_2Cl_2,[210] giving 9-anthryldithiochloride, (62), which was converted to 9-anthrylthiol, (63), by subsequent reaction with sodium sulphide in methanol followed by acidification. The 9-anthrylmethylsulphide, (64), was then obtained by reaction of the thiol with concentrated base and methyliodide. Overall yields were disappointing (20%).

Scheme4


(a)
S_2Cl_2
62
S-SCl
1.Na_2S
2.HCl
63
SH
1.KOH
2.CH_3I
64
SCH_3
$CH_3COOSCl$
$BF_3:Et_2O$
(b)
66
$SOCOCH_3$
1.KOH
2.HCl
1. KOH
2.CH_3I
64
CH_2N_2
Kagan/Sharpless Oxidⁿ
$Ti(OiPr)_4$
1
Diethyl tartrate
2 (R,R) (S,S)
H_2O
1
^tBuOOH
1-2
-20°C
CH_2Cl_2
64
SCH_3
65
SCH_3
O
(S,S)D.E.T.
O(S)
9Anthryl
CH_3
O(R)
CH_3
9Anthryl
(R,R)D.E.T.

Consequently the preparative route to 9-anthrylthiol was completely revised to follow a more modern procedure,[211] (Scheme 4b). Anthracene is treated with methoxycarbonylsulphenyl chloride, $CH_3OCOSCl$, in the presence of $BF_3:Et_2O$. The yield of this pseudo Friedel-Crafts reaction was typically 75% and the product, 9-anthrylmethoxycarbonyl sulphide, (66), was readily purified by sublimation. 9-Anthrylmethyl sulphide, (64), was produced directly without isolation of the thiol by decarboxylation and treatment with methyl iodide. Alternatively the thiol, (63), was obtained by addition of concentrated base (decarboxylation) followed by re-acidification and the 9-anthrylmethyl sulphide was then produced by reaction of the thiol with diazomethane.[212] This final step was also used to prepare 2-naphthylmethyl sulphide from commercially available[213] 2-naphthylthiol. Thus 2-naphthyl- and 9-anthryl-methyl sulphides were readily available.

In 1980 Sharpless reported[214,215] the first practical method for asymmetric epoxidation. Using (+)- or (-)-diethyltartrate, titanium tetraisopropoxide and tert-butylhydroperoxide at -20°C, oxidation of allylic alcohols is typically 97% enantioselective. Oxidation involves transfer of oxygen from a bis(diethyltartrate)titanium complex to only one face of the double bond.[216] Face selectivity of oxidation is reversed when the enantiomeric diethyltartrate is used. Since these first reports the "Sharpless reagent" has been applied to the asymmetric oxidation of a number of compounds and is a firmly established procedure in asymmetric synthesis.

In 1984 Kagan and coworkers[217,218,219] reported the adaptation of the "Sharpless Reagent" for asymmetric oxidation

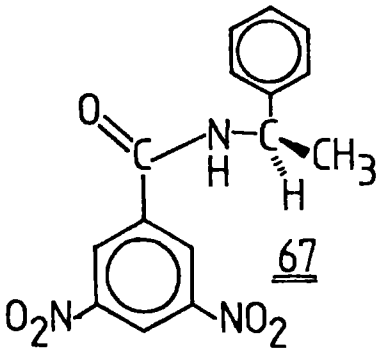
of sulphides to sulphoxides. Precisely one equivalent of water is added to the standard Sharpless reaction mixture and 1.2 rather than 1.0 equivalents of tert-butylhydroperoxide are used. Enantioselectivity of oxidation was reported to be as high as 98%. The reaction is sensitive to the quantity of water added, the enantiomeric excess obtained dropping sharply if more than 1.5, or less than 0.5 equivalents of water are used. In addition the enantiomeric excess of the product sulphoxide is significantly influenced by the temperature at which the reaction is performed, falling from 91% at -20°C to 62% at 0°C, for oxidation of p-tolylmethylsulphoxide.

Kagan obtained e.e. of 89%, 90% and 86% for oxidation of phenyl-, 2-naphthyl-, and 9-anthrylmethylsulphoxides respectively. The adapted "Sharpless reagent" was employed in the course of this research to oxidise the 2-naphthyl- and 9-anthrylmethylsulphides prepared as described earlier. The extreme sensitivity of the reaction to water requires that the apparatus and reagents must be especially dry. Tert-butyl-hydroperoxide, which is supplied as a 70% solution in water[220] must be extracted into dichloromethane and cautiously concentrated by distillation.[221] The precise concentration of the solution of $^{t}BuOOH$ in CH_2Cl_2 is determined by integration of the proton N.M.R. spectrum.[221] Reaction times at -20°C are usually 4-5 hours. The work-up procedure involves the decomposition of the diethyltartrate-titanium complex by addition of water followed by filtration of the precipitated titanium dioxide. The product mixture must be separated into components by column chromatography.

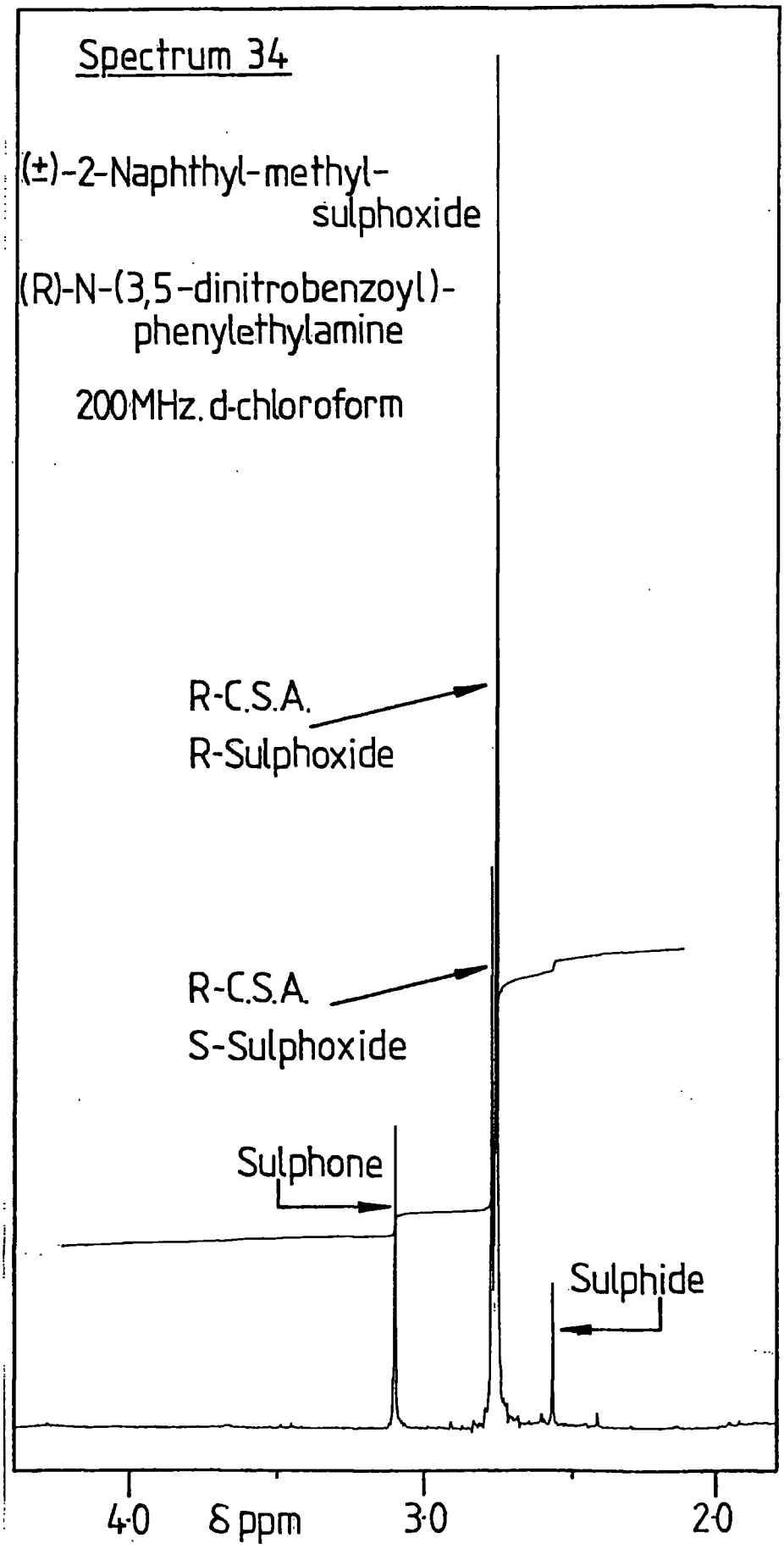
4.3 Enantiomeric Composition of Sulphoxides

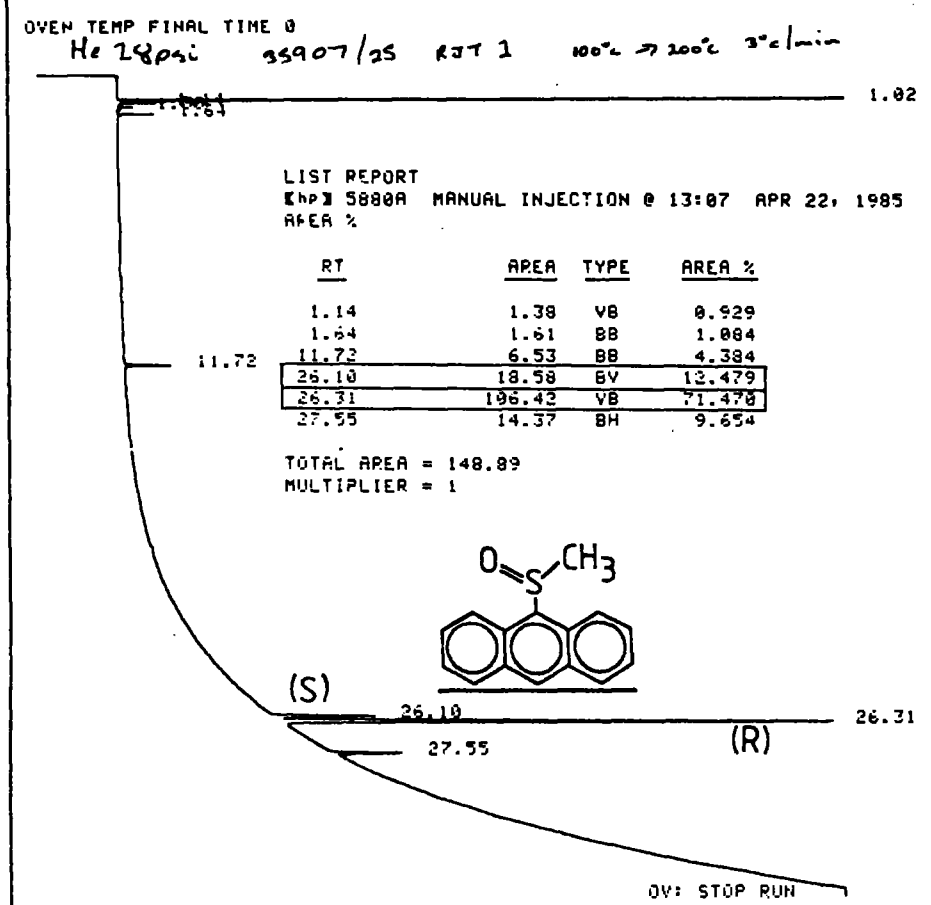
Enantiomerically enriched 2-naphthyl- and 9-anthryl-methylsulphoxides were obtained using (R,R)-diethyltartrate. Their enantiomeric purity was determined by two methods. The Gas Chromatograms, (Figure 28), were recorded for 2-naphthyl-methylsulphoxide and 9-anthrylmethylsulphoxide, (a and b respectively), using a column packed with C.S.P. Chirasil-Val, (6). They show that enantiomeric purity of 91.1% and 88.1% respectively, corresponding to enantiomeric excess of 82.2% and 76.2%, was achieved. Note that in (a) the column packing was Chirasil-(L)-Val and that in (b) the (D) type column was used, i.e. the (S) sulphoxide elutes first from the (D) column.

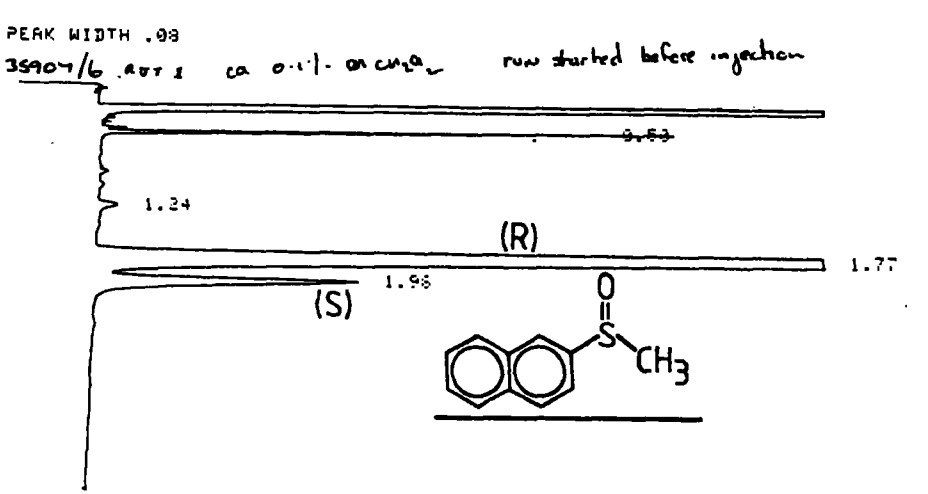
Kagan[167] has developed N-(3,5,-dinitrobenzoyl)-phenyl-ethylamine, (67), as a C.S.A. for chiral sulphoxides. Spectrum 34 shows the sulphoxide methyl group resonance region in the 200MHz ^1H N.M.R. spectrum in d-chloroform for a 1:1 mixture of the chiral 2-naphthylmethylsulphoxide and (R)-(-)-(67). Small quantities of unreacted sulphide and "over-oxidised" sulphone are present at 2.58 ppm and 3.12 ppm respectively. The resonance due to the (R)-C.S.A.-(S)-sulphoxide complex occurs 0.02 ppm to higher frequency than that for the (R)-C.S.A.-(R)-sulphoxide complex. Integration of these diastereomeric signals shows that the enantiomeric excess is 85±4%, this is in reasonable agreement with the G.C. result.



67


Spectrum 34
(±)-2-Naphthyl-methyl-sulphoxide
(R)-N-(3,5-dinitrobenzoyl)-phenylethylamine
200MHz. d-chloroform
R-C.S.A.
R-Sulphoxide
R-C.S.A.
S-Sulphoxide
Sulphone
Sulphide
4·0
δ ppm
3·0
2·0





[hp] 5880A MANUAL INJECTION @ 11:25 APR 17, 1985
AREA %

RT	AREA	TYPE	WIDTH	HEIGHT	BASELINE	AREA %
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0.00			THRESHOLD @ START RUN = 0			
0.00			PEAK WIDTH @ START RUN = 0.08			
0.00			RP: REJECT + 1E+06			
0.00			RP: SHOULDERS + ON			
0.30			RP: REJECT + 1			
0.50	25.07	BB	0.020	19.97	29.69	4.026
1.24	2.50	BB	-----	0.74	29.58	0.401
1.77	542.20	BV	0.075	113.19	29.43	87.074
1.98	52.92	VB	0.078	10.60	29.40	8.499

TOTAL AREA = 622.69

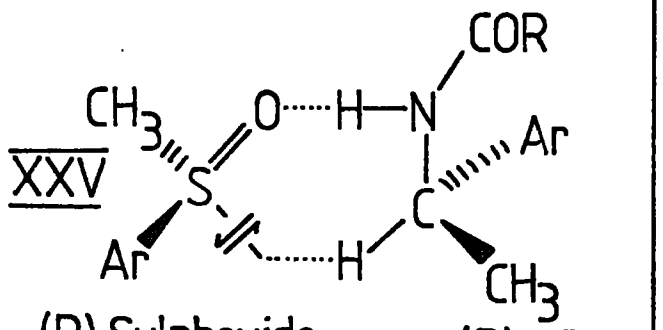
Figure 28 Gas Chromatograms for 2-Naphthyl- and 9 Anthryl-methyl-sulphoxides.

The interaction models[152] shown in (Figure 29) illustrate the possible mechanism of induction of the observed chemical shift non-equivalence. When the sulphur oxygen and lone pair of electrons are involved in hydrogen bonding to the amide NH and carbinyl hydrogen respectively in (XXV) and (XXVI), then the methyl group is differentially shielded by the amide phenyl ring in the (R,R) and (R,S) C.S.A.-sulphoxide complexes. An alternative model, (Figure 30), involving formation of the same "chelate-like" ring shows that π-π charge transfer is possible between the π-acidic nitrophenyl and π-basic sulphoxide phenyl rings in the (R,S) complex but <u>not</u> in the (R,R) complex. This extra stabilisation of one complex over the other may be the main reason that non-equivalence is observed in this instance.

4.4 Chiral Sulphoxides as C.S.A.s

The efficiency of 2-naphthyl-and 9-anthrylmethyl-sulphoxides as C.S.A.s for racemic alcohols (e.g. 1-phenyl-ethanol), racemic amines (e.g. 1-phenylethylamine) and racemic acids (e.g. M.T.P.A.) was tested in d-chloroform and d_6-benzene, non-polar solvents which are known to maximise chemical shift non-equivalence in diastereomeric species. The C.S.A./solute ratio[222] was varied from 1:1 up to 10:1, but in not one case was non-equivalence observed for any of either the solute or solvating agent resonances. It was surmised from this negative result that the essential C.S.A.-solute "chelate-like" complex is not formed in solution between the solute and the arylmethylsulphoxide. If this is the case, then an increase in the polarity of the C.S.A. molecule by replacement of the slightly electron releasing methyl group by an electron

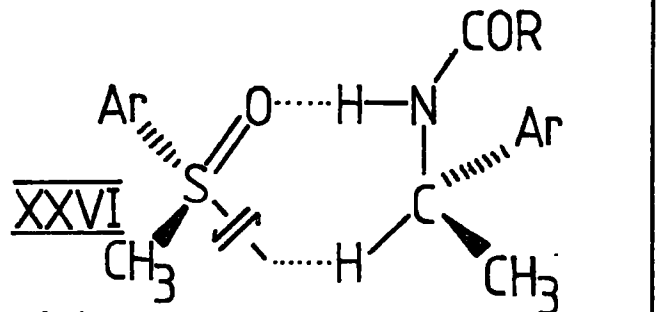
Figure 29



XXV

(R) Sulphoxide

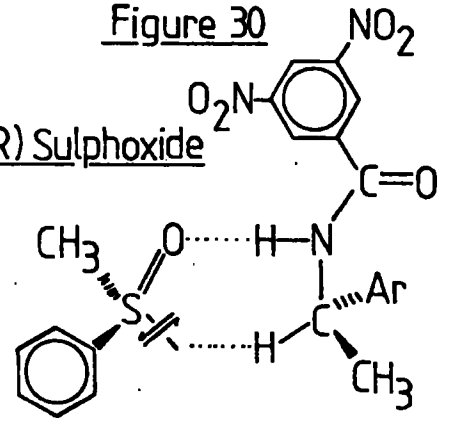
(R)-67



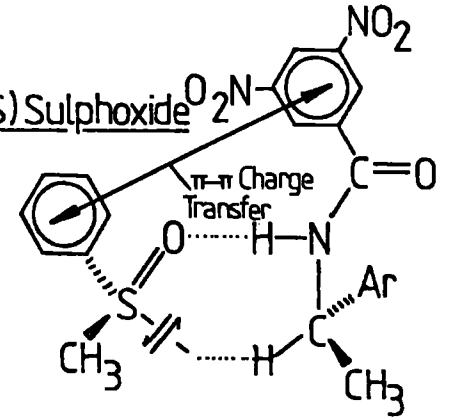
XXVI

(S) Sulphoxide

Figure 30



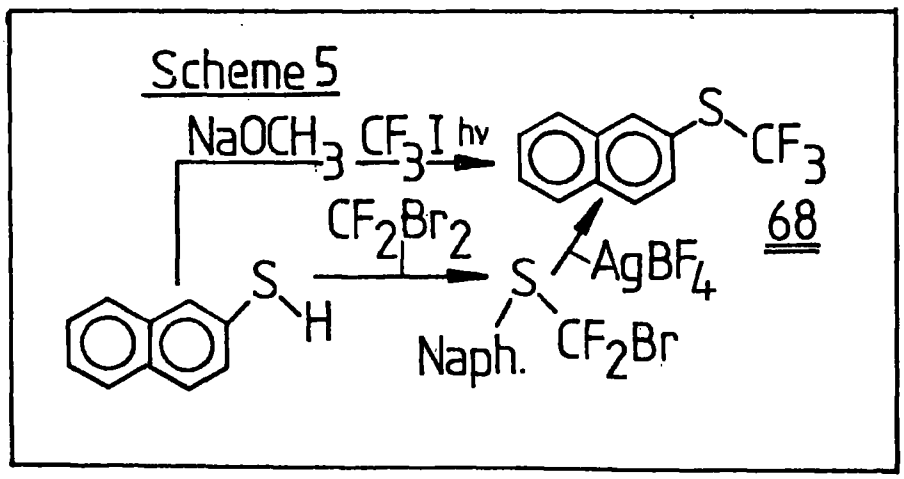
(R) Sulphoxide



(S) Sulphoxide

withdrawing trifluoromethyl group, for example, might increase the chance of chelate formation. In addition the presence of the CF_3 group would permit the acquisition of ^{19}F N.M.R. spectra, which are likely to be less congested than the ^{1}H spectra.

Attempts were made to prepare 2-naphthyltrifluoromethyl-sulphoxide, (68), from the 2-naphthylthiol by U.V.-irradiation in the presence of trifluoromethyliodide[223] and by reaction with sodium methoxide by treatment with trifluoromethyliodide at -50°C.[224] It was found, however, that the most effective method for introduction of a trifluoromethyl group into both 2-naphthyl- and 9-anthrylthiols involves their reaction with dibromodifluoromethane to give the corresponding difluorobromo-methylsulphide.[225] This is converted to the trifluoromethyl-sulphide by reaction with silver tetrafluoroborate. (Scheme 5). Despite numerous attempts to oxidise the trifluoromethyl-sulphides using Kagan's adapted "Sharpless reagent", the corresponding sulphoxides could not be obtained. Hence their behaviour as C.S.A.s remains unknown.



4.5 Future Work

The trifluoromethylarylsulphoxides are untried, however, it is possible that a key to a successful sulphoxide C.S.A. may lie in the structure of the N-(3,5-dinitrobenzoyl)-phenylethyl-amine reagent used in their assay. The additional π-π charge transfer between the π-acidic and π-basic rings, (Figure 30), may be a prerequisite if non-equivalence is to be observed. Consequently a 3,5-dinitrophenyl-methyl, (or trifluoromethyl), sulphoxide may constitute a sensible target for future work. Pirkle and Sikkenga[78] have observed preferential crystallisation of the (R)-trifluoromethylphenyl-carbinol-(R)-2,4,dinitrophenylmethylsulphoxide complex from a racemic mixture in CCl_4. The additional π-π charge transfer which is possible in the (R,R) complex is proposed as being responsible for this phenomenon. All sulphoxides are known to undergo racemisation at temperatures where inversion of configuration is rapid, p-nitrophenylmethylsulphoxide is noted particularly for this, {racemising at or above 86°C}. Thus the "shelf life" of such C.S.A. might be limited.

It is, perhaps, naive to think of a "universal C.S.A." as a possibility. Such a molecule would have to be able to interact with the enantiomers of a large number of compounds of widely differing functionalities and induce non-equivalence in all of them. In a more realistic outlook the researcher should be content to identify a series of C.S.A.s each of which works effectively for specific chiral compounds. An example of this type of more limited C.S.A. application is described in the next chapter.

CHAPTER FIVE

N.M.R. Assay of Enantiomeric Excess using Chiral Solvating Agents-II

The use of O-acetylmandelic acid as a Chiral Solvating Agent for amines and amino-alcohols

---

5.1 Introduction

The Mosher reagent, M.T.P.A., is firmly established as a Chiral Derivatising Agent. Very recently an extension of its use, as a Chiral Solvating Agent for amines, was reported.[177] Enantiomerically pure or enriched acid forms diastereomeric salts in solution with enantiomers of chiral amines, (section 1.7.3). The ions formed by proton transfer from the acid to the amine must form a close ion-pair in solution if chemical shift non-equivalence is to be observed. In numerous cases, however, the M.T.P.A. salts are insufficiently soluble in d_6-benzene or d-chloroform, [non-polar solvents which maximise non-equivalence], to permit their practical application. Salts such as these often dissolve readily in more polar solvents, but these tend to cause dissociation of the close ion-pairs into solvent-separated ion-pairs in which chemical shift non-equivalence is zero.

β-Amino-alcohols are an important class of pharmacologically active compounds. Many of them are α and β adreno-receptor agonists or antagonists for which a precise knowledge of the enantiomeric purity is critical. The proprietary drug "Propranolol", (73), for example, is a β-amino-alcohol in which

the (S) enantiomer behaves as a "β-Blocker", while the (R) enantiomer may function as a contraceptive. Related hydroxy-amines, which are marketed as drugs under the names "Salbutamol", (74) and "Labetalol", (76), present particular problems for enantiomeric assay due to their low solubility in non-polar solvents.[226]

Parker[137] has used (S)-O-acetylmandelic acid, (69), as a Chiral Derivatising Agent for alcohols in the same way that M.T.P.A. was applied to these compounds. Hence the reported use of M.T.P.A. as a Chiral Solvating Agent for amines[177] prompted an investigation of O-acetylmandelic acid in this application. Preliminary studies with phenylethylamine as the substrate have been reported.[153] Mandelic acid has been used as a C.S.A. for amines, but its scope is very limited by the poor solubility of the resulting diastereomeric salts.[226,227,143] It is, however, most useful when separation of diastereomeric mandelate salts can be achieved by crystallisation.[228] It is then possible to monitor the progress of the resolution by direct N.M.R. examination of the salt.[226]

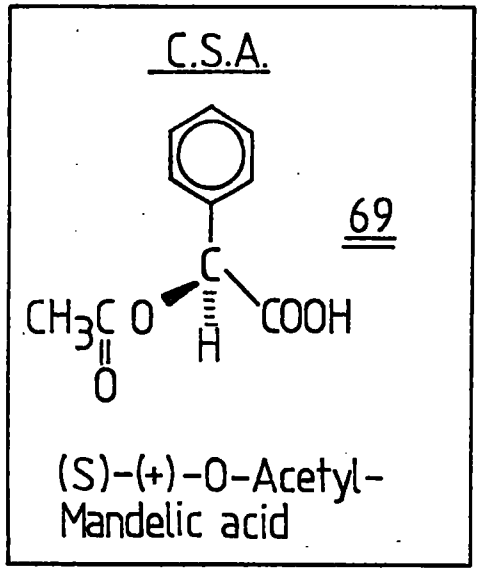
5.2 O-Acetylmandelic Acid as a C.S.A.

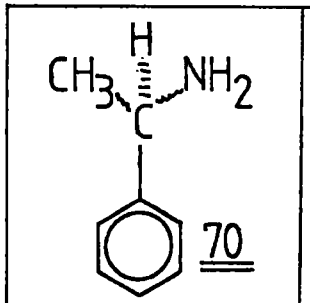
In a typical experiment the amine or amino-alcohol (0.05mmol) and (S) or (R)-O-acetylmandelic acid (0.06mmol) were dissolved in d-chloroform or d_6-benzene and the ^1H N.M.R. spectrum was recorded. Proton transfer was essentially complete in non-polar solvents such as these and in the resulting diastereomeric salts chemical shift non-equivalence was observed for one or more of the resonances proximate to the nitrogen. Although the spectra were usually recorded in

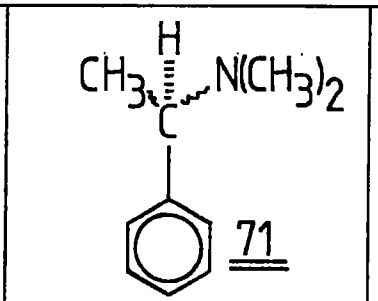
d_6-benzene, addition of d_5-pyridine was occasionally necessary to ensure that salts remained in solution. The compounds investigated, (70-80), are shown in (Scheme 6) and the corresponding N.M.R. data are reported in Table 21. Using mixtures of compounds (70), (71), (72), (77), (78), (79) and (80) of predetermined enantiomeric composition, an excellent agreement (±2%) between known composition and N.M.R. determined values was obtained. In a commercially available sample of (S)-(-)-α-phenylethylamine, (Aldrich), it was possible to detect and measure the percentage of the residual (R) enantiomer as 2% [$\delta(CDCl_3)$ 298K = 0. 18 ppm using (S)-O-acetylmandelic acid]. Thus the enantiomeric excess was determined to be 96%. Since the C.S.A. method is absolute, the reagent enantiomeric purity does not affect the determination of enantiomeric excess of the solute. The detection limit is set by the signal-to-noise ratio of the N.M.R. spectrometer used {see experimental}. The amine methyl proton resonance for mixtures of (R) and (S) cyclohexylamine, (72), in the presence of (S)-O-acetylmandelic acid is shown in (Figure 31). Spectrum 35 is a "stacked" plot for mixtures of (1S,2R) and (1R,2S)-N-methyl-ephedrine, (78), salts formed with (S)-O-acetylmandelic acid. Spectrum 36 shows the ^1H resonance for the methylene group α to the nitrogen in the N.M.R. spectrum of "Salbutamol" recorded at 250MHz in d_5-pyridine with simultaneous irradiation of the adjacent CH.

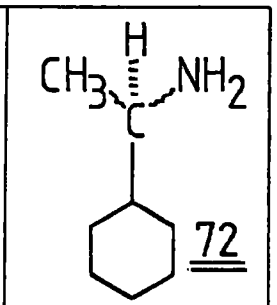
It is worth noting that in the case of (77) and (78) where there are two chiral centres, the enantiomeric pair (1S,2R) and (1R,2S) were studied. The other possible enantiomeric pair, (1R,2R) and (1S,2S) could be examined just as

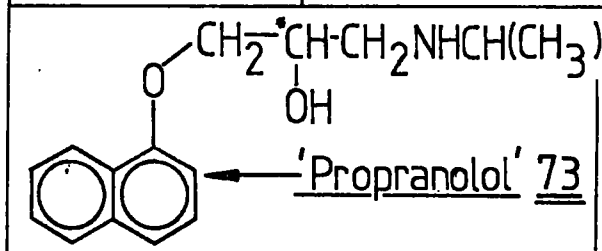
Scheme 6

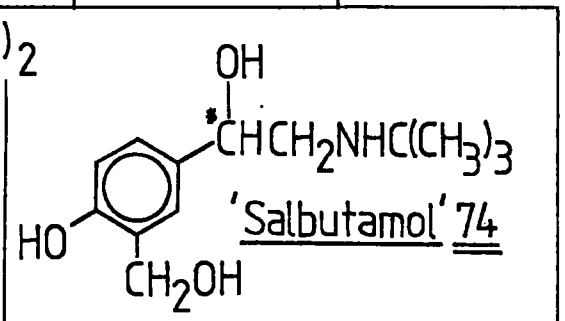

C.S.A.
69
(S)-(+)-O-Acetyl-
Mandelic acid

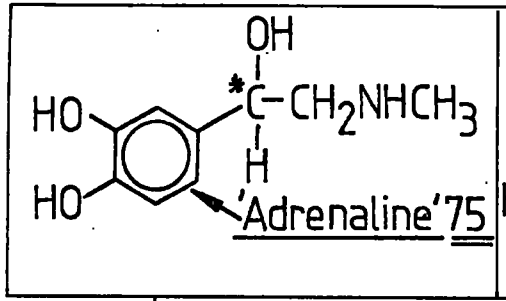

70

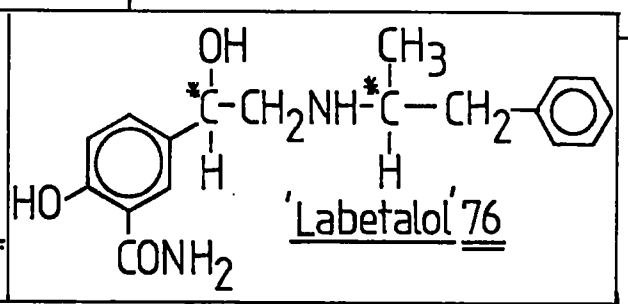

71

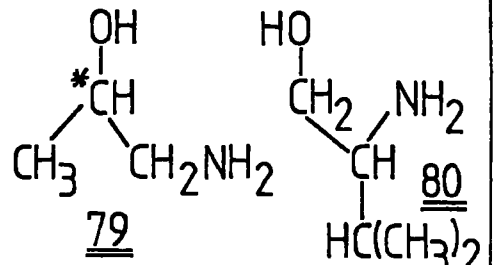

72


'Propranolol' 73

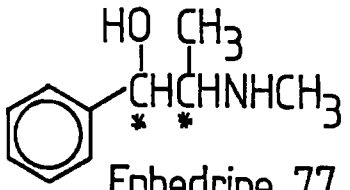

'Salbutamol' 74


'Adrenaline' 75


'Labetalol' 76


79

80
'Valinol'


Ephedrine 77

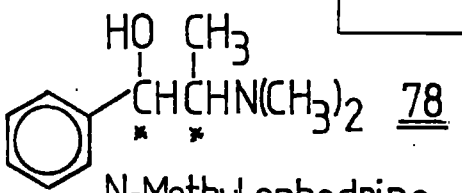

78
N-Methyl ephedrine

Table 21

Chemical Shift Non-equivalence for the (S)-O-Acetylmandelic Acid Salts of Racemic Chiral Amines and β-Amino-Alcohols.[a]

Compound	Resonance Observed	Δδ (ppm)	Solvent
70	CH_3	0.063	C_6D_6
	CH	0.075	C_6D_6
71	CH_3	0.058	C_6D_6
	CH	0.061	C_6D_6
72	CH_3	0.102	C_6D_6
	CH	0.142	C_6D_6
73[b,d]	CH	0.017	C_5D_5N/C_6D_6 (1:1)
74[c]	CH_2	0.017	C_5D_5N
75[d]	CH	0.018	C_6D_6
77[b]	NCH_3	0.060	$CDCl_3$
78	NCH_3	0.040	C_6D_6
79	CH_3	0.053	C_6D_6/C_5D_5N(2:1)
	CH	0.020	C_6D_6/C_5D_5N(2:1)
80	CH_3	0.021	C_6D_6/C_5D_5N(2:1)

a) Spectra were recorded at 298K and 250MHz.

b) Using (R)-O-acetylmandelic acid.

c) Simplified by simultaneous irradiation of the adjacent CH.

d) Simplified by simultaneous irradiation of adjacent CH_2.

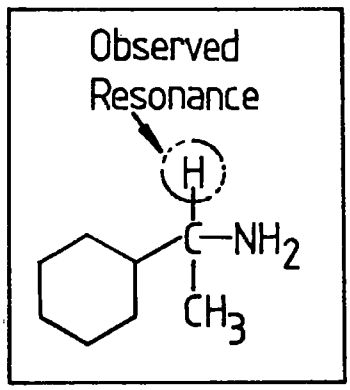
Figure 31

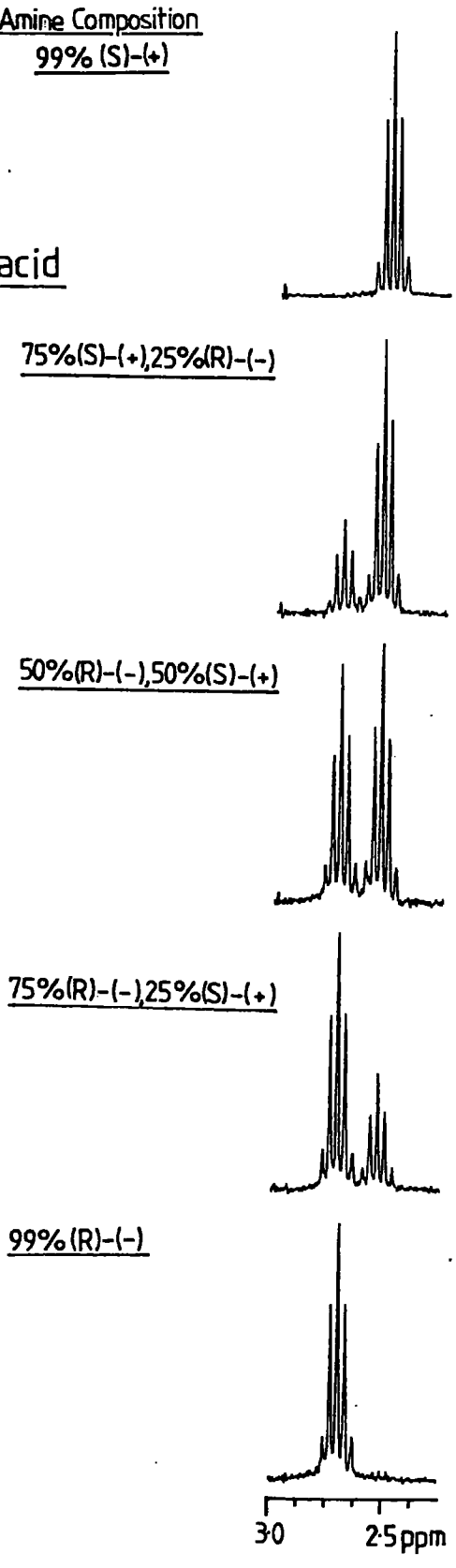
250MHz. ^{1}H N.M.R.

(±)-Cyclohexylamine

(S)-O-Acetyl mandelic acid

$CDCl_3$ 298K



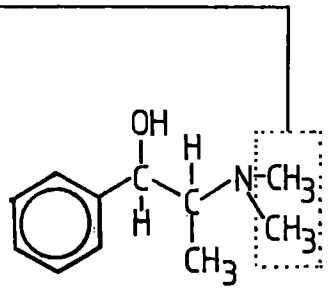


Spectrum 35

(S)-O-Acetyl mandelic acid/N methyl ephedrine

C_6D_6 , 250MHz., 298K

Composition



99%(1R,2S)

50%(1R,2S) 50%(1S,2R)

99%(1S,2R)

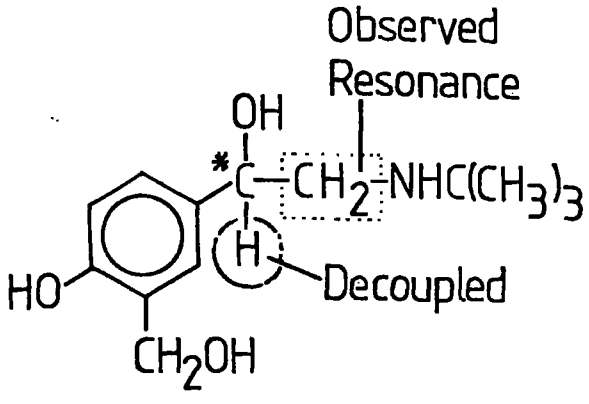
8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
PPM

Spectrum
36

(±)-'Salbutamol'

(R)-O-Acetyl mandelic acid

C_5D_5N, 250MHz, 298K



easily by the formation of diastereomeric salts with O-acetyl-mandelic acid. With the drug "Labetalol", (76), both racemates are present {i.e. the (RS/SR) and the (RR/SS)}. Since these two pairs are diastereomeric the ^{1}H N.M.R. spectrum of "Labetalol" in d_6-benzene/d_4-methanol (1:2, v/v) exhibits two doublets for the methyl resonance.[229] The non-equivalence induced by introduction of the (R)-C.S.A. is insufficient to permit integration of the (RRS,RSR) or (RRR,RSS) diastereoisomers.

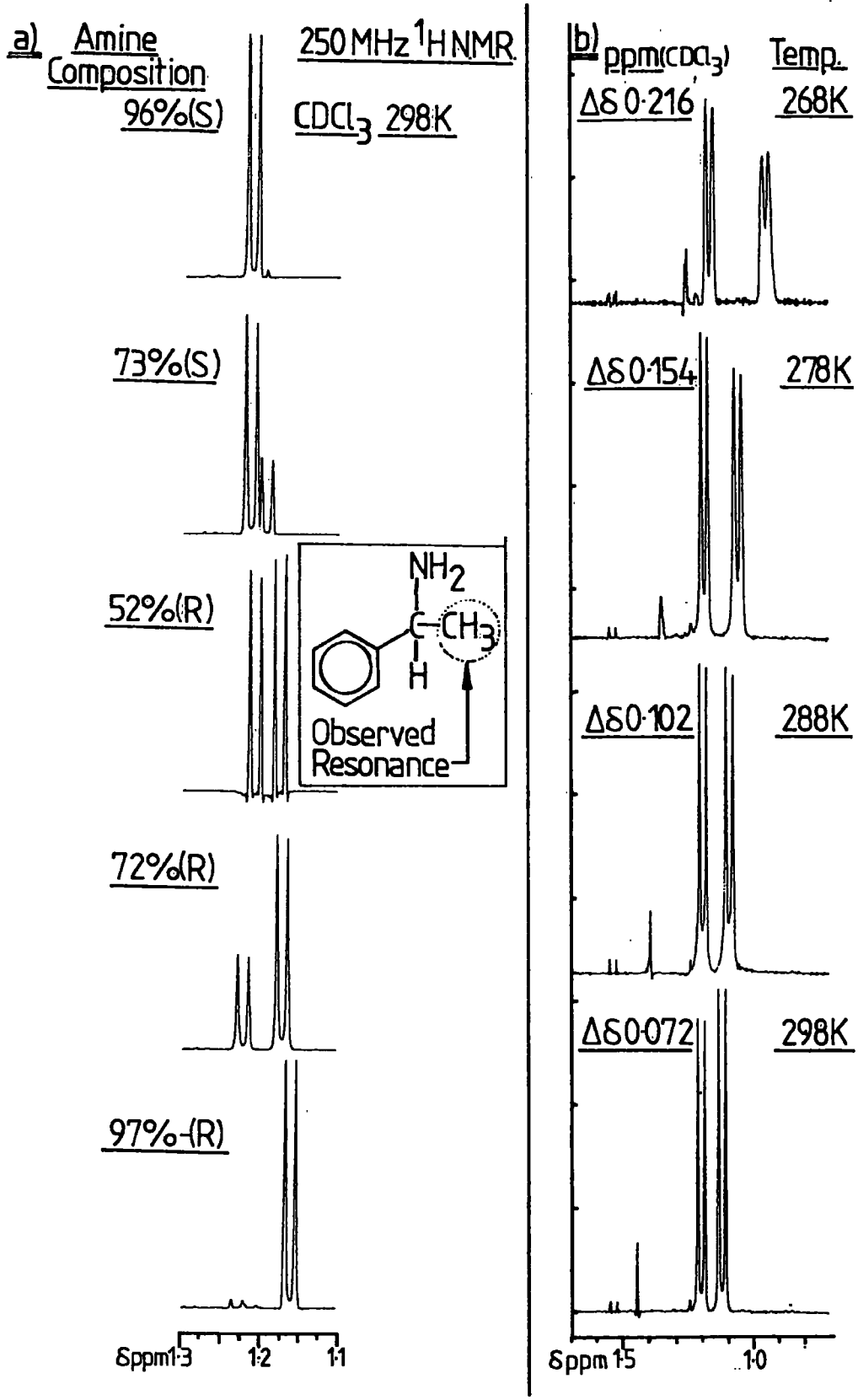
For a given solute the magnitude of chemical shift non-equivalence induced by O-acetylmandelic acid was greater than that observed using M.T.P.A. or mandelic acid. Further, the salts obtained were generally more soluble in non-polar solvents.

Observing the sense of non-equivalence of chemical shift for a range of known compositions, the configuration of the solute may be correlated with chemical shift. This information may then be used to assign solute absolute configuration within a related series of compounds, provided that these series are cautiously defined. For example, the sense of non-equivalence was the same for (70),(71), and (72) and for (77) and (78).

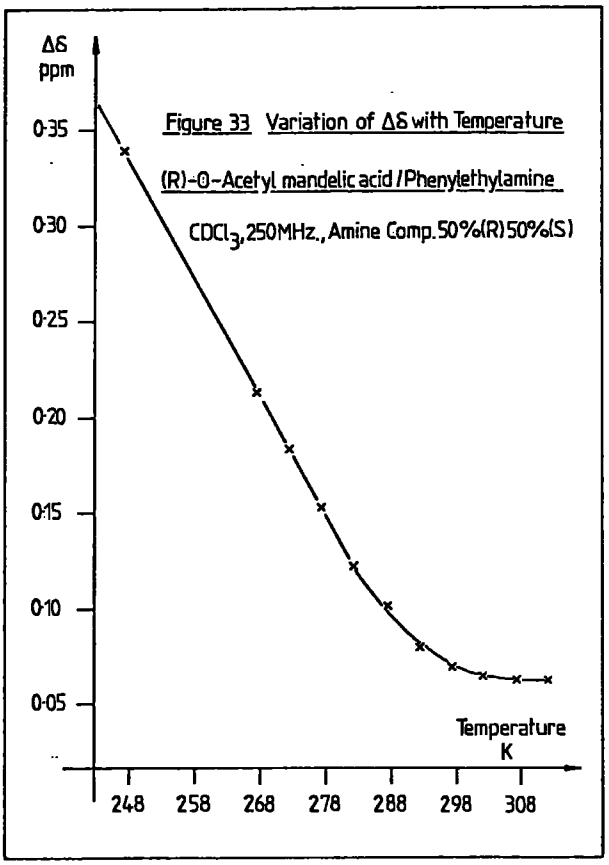
5.3 Factors Influencing the Magnitude of Non-equivalence

The magnitude of the observed chemical shift non-equivalence, $\Delta\delta$, is a complex function of solute and solvating agent structure, solvent, temperature and ,in certain cases, solute enantiomeric composition. The temperature variation has been examined more closely for (R)-O-acetylmandelic acid and phenylethylamine, (70), in $CDCl_3$. (Figure 32b) shows the appearance of the pair of methyl doublets in the amine as

Figure 32. Variation of Δδ with Solute Enantiomeric Composition and with Temperature [Phenylethylamine/(R)-O-Acetyl mandelic acid.]



temperature is altered. The data are illustrated graphically in (Figure 33).



There are two factors contributing to the observed temperature dependence. As the temperature is lowered there is preferential population of specific lower energy conformations. With (70), as temperature is lowered, the methyl doublet due to the (S)-phenylethylamine-(R)-C.S.A. salt shifts to lower frequency relative to all other resonances indicating that, on average, this group spends more time in a magnetically shielded environment. This behaviour is similar to that observed for the p-bromobenzylcamphanamide, (section 2.2.2), and accounts for the linear temperature dependence between 248 and 288K. Above 288K the non-equivalence tends to a limit corresponding to the intrinsic chemical shift non-equivalence of the two diastereomeric complexes. Mikolajczyk[153] has previously

reported that, for the same system, $\Delta\delta$ tended asymptotically to zero at temperatures greater than 134°C in hexachlorobutadiene. This was attributed to salt dissociation. Although solvent choice may be restricted, recording the N.M.R. spectrum at reduced temperatures is a useful technique for those systems where $\Delta\delta$ may be very small at room temperature. Many of the salts which are soluble in d_6-benzene are equally soluble in d_8-toluene, which offers greater temperature latitude.

The observed chemical shift non-equivalence for (70) with (R)-O-acetylmandelic acid is linearly dependent upon the enantiomeric composition of the amine. This behaviour is precisely mirrored in the (S)-O-acetylmandelic acid-phenylethyl amine system, Table 22 and (Figures 32a and 34), and has been reported previously.[153] It is consistent with a minimal degree of ion-pair aggregation in the concentration range studied

Figure 34 Variation of $\Delta\delta$ with Enantiomeric Composition

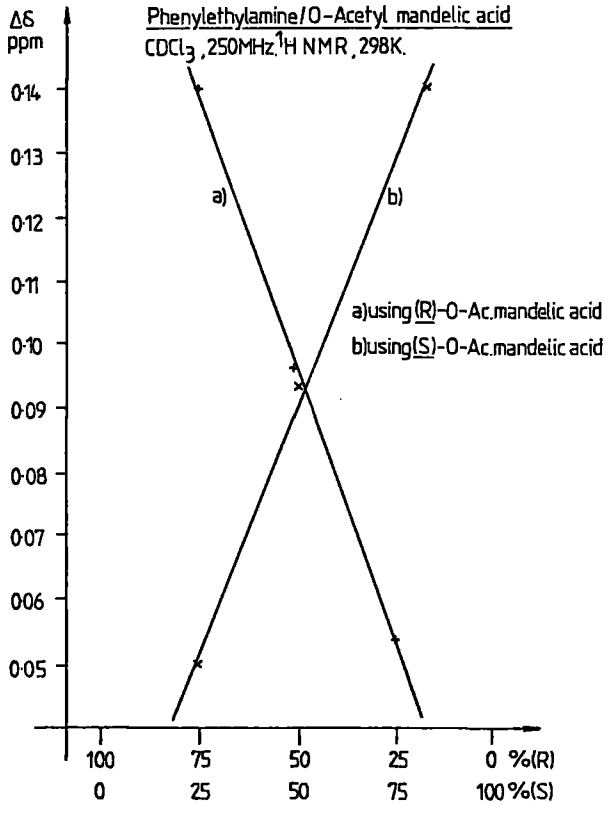


Table 22

Variation of Chemical Shift Non-equivalence with Enantiomeric Composition and Solvent for the O-Acetylmandelic Acid Salts of (70).

Enantiomeric Composition of (70)	Solvent (298K)	$\Delta\delta$ (ppm)
75%R, 25%S[a]	C_6D_6	0.130
	$CDCl_3$	0.140
50%R, 50%S[a]	C_6D_6	0.097
	$CDCl_3$	0.096
25%R, 75%S[a]	C_6D_6	0.066
	$CDCl_3$	0.054
75%R, 25%S[b]	$CDCl_3$	0.050
50%R, 50%S[b]	$CDCl_3$	0.094
25%R, 75%S[b]	$CDCl_3$	0.140

a) Using (R)-O-acetylmandelic acid.

b) Using (S)-O-acetylmandelic acid.

(0.002-0.1M) and may be attributed to the inequality of the dissociation constants for the diastereomeric complexes. This effect has only been observed with (70) as solvate. It may be associated with systems in which the intrinsic chemical shift non-equivalence makes a significant contribution to $\Delta\delta$ at ambient temperatures [i.e. systems exhibiting a non-linear $\Delta\delta$ temperature dependence, (Figure 33)]. Titrating (R)-O-acetyl-mandelic acid with (70) shows that the magnitude of non-equivalence increases as the mole ratio of acid increases upto 1:1, thereafter $\Delta\delta$ is invariant. This result confirms that a 1:1 complex is formed in solution. Non-equivalence,$\Delta\delta$, can be maximised by the appropriate choice of either (R) or (S) solvating agent enantiomer. Changing the chirality of the C.S.A. reverses the sense of non-equivalence of the solvate resonances and may be useful for the examination of partially obscured resonances.

5.4 Concluding Remarks

(S)- and (R)-O-Acetylmandelic acids are inexpensive, commercially available chiral solvating agents for the "in situ" determination of enantiomeric purity of chiral amines and amino-alcohols. They are more effective than M.T.P.A. or mandelic acid in this application, forming salts which are not only more generally soluble in non-polar solvents but also exhibit larger chemical shift non-equivalence for diastereomeric resonances.

EXPERIMENTAL

CHAPTER SIX

6.1 Instrumentation

6.1.1 Infrared Spectroscopy

I.R. spectra were recorded on a Perkin-Elmer 577 Infrared Spectrophotometer, a Perkin-Elmer 580A Infrared Spectrophotometer or on a Nicolet 60-SX F.T. Spectrophotometer.

Solid samples were recorded as KBr discs or nujol mulls between KBr plates and liquid samples were recorded as contact films between KBr plates.

6.1.2 N.M.R. Spectroscopy

Proton (^{1}H) N.M.R. spectra were recorded on a Varian EM360L Spectrometer, on an Hitachi-Perkin-Elmer R-24B Spectrometer both operating at 60MHz, or on a Bruker AC250 Spectrometer operating at 250MHz [signal:noise 850:1 ^{1}H,90° single pulse, 1% ethylbenzene] {the temperature was maintained at ±1°C using the Bruker temperature unit previously calibrated using 100% methanol} (University of Durham). Proton N.M.R. spectra were also recorded on a Varian Gemini 200 operating at 200MHz (U.D.I.R.L.), a Bruker WH360 operating at 360MHz (University of Edinburgh), a Bruker WH400 operating at 400MHz [signal:noise 760:1 ^{1}H,90° single pulse, 1% ethyl-benzene] (University of Warwick), a Jeol FX90 operating at 90MHz (City Polytechnic), a Varian XL200 operating at 200MHz and a Bruker AM250 operating at 250MHz (Glaxo Group Research).

Carbon (^{13}C) spectra were recorded on a Bruker CXP200 operating at 50MHz [MAR-CP solid state] (University of Durham) and a Bruker SY200 operating at 50MHz (University of Edinburgh).

Fluorine (^{19}F) spectra were recorded on a Bruker AC 250 operating at 235MHz (University of Durham).

Phosphorus (^{31}P) spectra were recorded on a Bruker AC250 operating at 101MHz (University of Durham), on a Bruker WH360 operating at 145MHz (University of Edinburgh) and on a Jeol FX90 operating at 36MHz (City Polytechnic)

Platinum (^{195}Pt) spectra were recorded on a Jeol FX90 operating at 19MHz (City Polytechnic).

N.M.R. solvents:

d_6-Benzene 99+ atom% D Aldrich 17597-8

d-Chloroform 99.8 atom% D Aldrich 15182-3

d_5-Pyridine 99 atom% D Aldrich 15232-3

d_4-Methanol 99.5 atom% D Aldrich 26982-4

d_2-Dichloromethane 99.6 atom% D Aldrich 26988-3

d_6-Acetone 99.5 atom% D Aldrich 15179-3

d_8-Toluene 99+ atom% D Aldrich 15199-8

N.M.R. References and Data Acquisition, (Brüker AC250) ^{1}H:TMS, ^{13}C:TMS, ^{19}F:$CFCl_3$, ^{31}P:85% H_3PO_4 and ^{195}Pt:TMS on an absolute chemical shift scale. Data were recorded for 16k points and integrals were measured for spectra obtained without mathematical data manipulation. ^{1}H: PW=1.0 corresponding to a flip angle of 25°, RD=1.0s, S/N (90° single pulse, 1% ethylbenzene) 850:1. ^{31}P: PW=5.0 corresponding to a flip angle of 45° [90°pulse=4.3μs], RD=1.5s, S/N (90° single pulse, ethylbenzene) 123:1.

6.1.3 Mass Spectrometry

Mass spectra of solid samples or liquids were recorded on an A.E.I.M.S.9 spectrometer or a VG 7070E spectrometer with

electron impact, chemical ionisation, negative ion and fast atom bombardment modes. 2,2'-Dithioethanol was used as the matrix for FAB spectra.

6.1.4 Elemental Analysis

Carbon, hydrogen and nitrogen analyses were obtained using a Perkin-Elmer 240 Elemental Analyser or a Carlo Erba Model 1106 analyser. Analysis for halogens and sulphur was obtained using a Perkin-Elmer Atomic Absorbption Spectrophotometer.

Melting points were determined on a Reichert-Kofler block at atmospheric pressure and are uncorrected.

6.1.5 Chromatography

Gas liquid chromatography (G.L.C.) analysis was carried out using a Hewlett Packard 5890A Gas Chromatograph fitted with a 25m fused silica column with Chirasil-Val coating.

Column chromatography was performed using Merck Kieselgel 60H and distilled solvents. Thin layer chromarography was performed using Merck DC-Alufoilen Kieselgel 60 F_{254}. Preparative thin layer chromatography was performed using 20*20cm plates coated with Merck Kieselgel 60 F_{254} (2mm).

6.1.6 Molecular Mechanics Calculations

Molecular mechanics conformational energy calculations were performed on the Glaxo Group Research molecular modelling system, running on a VAX 11-750 minicomputer coupled to Megatek and Sigma display terminals. The force-field calculations used standard Buckingham and single-term cosine potential functions[230] for the non-bonded and torsional energies,

respectively, and the electrostatic energy was calculated from a Coulombic potential using a distance-dependent dielectric term.[231] The associated non-bonded and torsional force-field parameters were set[232] to reproduce in "rigid-rotor" models (i.e. without full relaxation of molecular geometry), experimental torsional barriers in small molecules[233] and the observed distribution of θ, ϕ-angles in peptides and proteins.[234] A standard set of partial charges were placed on those atoms involved in potential hydrogen-bonding groups.

6.1.7 Optical Rotations

Optical rotations were measured for solutions in chloroform at the specified concentration. The optical path length of the cell was 10cm and the temperature at which measurements were made was 20°C. Illumination was provided by a sodium vapour lamp (589nm).

6.1.8 Reagents and Solvents

Reagents were used as supplied, without further purification, and solvents were dried by standard procedures.[212]

6.2 Experimental for Chapter Two

Representative procedures for preparation of esters and amides are given below:

6.2.1 Preparation of (S)-Methyl-(p-Bromophenylethanoyl)-mandelate (47f)

p-Dimethylaminopyridine (6.8mg, 0.045mmol) was added to a solution of (S)-methylmandelate (250mg, 1.5mmol) in dry

dichloromethane (10cm^3). The solution was cooled to -10°C and dicyclohexylcarbodiimide (200mg, 0.97mmol) was added, followed by p-bromophenylacetic acid (200mg, 0.93mmol). The mixture was stirred under nitrogen for 3h at -10°C, the precipitated dicyclohexylurea was filtered off and the solvent removed under reduced pressure, the resulting oil was taken up in dichloromethane and purified by chromatography on silica gel (40-60°C petroleum ether/ethylacetate, 1:1, v/v) to give a colourless oil (255mg, 70%) (Found: C, 55.8; H, 3.9. $C_{17}H_{15}O_4Br$ requires C, 56.0; H, 4.1%); δ_H (C_6D_6, 360MHz) 7.39 (2H,m,ArH), 7.16 (2H,m,ArH), 7.08-7.04 (3H,m,ArH), 6.77 (2H,m,ArH), 6.02 (1H,s,CH), 3.32 (1H,d,H_R), 3.23 (1H,d,J_{HS-HR} 15.6Hz,H_S) and 3.14ppm (3H,s,$COOCH_3$); m/e (E.I.) 364/362, 332/330, 305/303, 171/169, 149 and 118.

6.2.2 Preparation of (S)-Methyl(propanoyl)mandelate

Preparation as in 6.2.1 using propanoic acid (148mg, 2mmol) to give a liquid which distilled (100°C, 0.1mmHg) (200mg, 90%); $[\alpha]_{20}$ -137.2° (c=1.2, $CHCl_3$) {lit[235] $[\alpha]_{20}$ -135.5° (c=1.0, $CHCl_3$)}; δ_H (C_6D_6, 400MHz) 7.5-7.2 (5H,m,ArH), 6.09 (1H,s,CH), 3.17 (3H,s,$COOCH_3$), 2.53 (1H,dq,H_R), 2.41 (1H,dq,J_{HR-HS} 17.5Hz.,J_{vic} 7.5Hz,H_S) and 1.22ppm (3H,t,CH_3); m/e (E.I.) 222, 190, 166, 105 and 71.

6.2.3 Preparation of (S)-Methyl-(α-methoxyphenylethanoyl)-mandelate (43c)

Preparation as in 6.2.1 using (R)-(-) and/or (S)-(+)-α-methoxyphenylethanoic acid (166mg, 1.1mmol) to give (S)-methyl-(α-methoxyphenyl)mandelate (242mg, 70%); δ_H (C_6D_6, 200MHz) 7.62 (2H,m,ArH), 7.32 (2H,m,ArH), 7.02 (6H,m,ArH), 5.93 (1H,s,CH),

4.87 (1H,s,CH), 3.27 (3H,s,CH_3) and 3.10ppm (3H,s,CH_3).

6.2.4 Preparation of (S)-Methyl-(2-phenylpropanoyl)mandelate (43b)

Preparation as in 6.2.1 using (R)-(-) and/or (S)-(+)-2-phenylpropanoic acid (100mg, 0.67mmol) to give (S)-methyl-(2-phenylpropanoyl)-mandelate (140mg, 70%); δ_H (C_6D_6, 250MHz) 7.50 (10H,m,ArH), 6.14 (1H,s,CH), 3.78 (1H,qt,CH), 3.21 (3H,s,CH_3) and 1.54ppm (3H,d,CH_3).

6.2.5 Preparation of (S)-Methyl-(camphanoyl)mandelate (43e)

Preparation as in 6.2.1 using (1S,4R) and/or (1R,4S)-camphanic acid (67mg, 0.34mmol) to give (S)-methyl-(camphanoyl)-mandelate (83mg, 70%); δ_H (C_6D_6, 250MHz) 7.55-7.05 (5H,m,ArH), 6.09 (1H,s,CH), 3.25 (3H,s,CH_3), 2.10 (1H,m,CH), 1.83 (1H,m,CH), 1.38 (2H,m,CH_2), 1.11, 1.01 (6H,s+s,$C(CH_3)_2$) and 0.97ppm (3H,s,CCH_3).

6.2.6 Preparation of (S)-Methyl-(3-phenylbutanoyl)mandelate (43a)

Preparation as in 6.2.1 using 3-phenylbutanoic acid (152mg, 0.93mmol) to give a colourless oil (218mg, 75%); δ_H (C_6D_6, 250MHz) 7.34-6.97 (10H,m,ArH), 6.03 (1H,s,CH), 5.97 (1H,s,CH), 3.36-3.23 (1H,m,CH), 3.16 (3H,s,CH_3), 2.68-2.39 (2H,m,CH_2) and 1.35ppm (3H,d,CH_3).

6.2.7 Preparation of (S)-Methyl-(α-Methoxy-α-trifluoromethyl-phenylethanoyl)-mandelate (28)

Preparation as in 6.2.1 using α-methoxy-α-trifluoro-methylphenylethanoic acid (M.T.P.A.) (234mg, 1mmol) to give a colourless oil (230mg, 60%); δ_H (C_6D_6, 250MHz) 7.09-7.01 (2H,m,ArH), 6.65-6.13 (8H,m,ArH), 5.28 (1H,s,CH), 2.84,2.61 (3H,s+s,$\Delta\delta$ 0.23,CH_3) and 2.32ppm (3H,s,CH_3); δ_F (C_6D_6, 235MHz) -71.81,-72.32ppm (3F,s+s,$\Delta\delta$ 0.61,CF_3).

6.2.8 Preparation of (S)-Methyl-(2-methyl-3-phenylpropanoyl)-mandelate (43d)

Preparation as in 6.2.1 using 2-methyl-3-phenylpropanoic acid (164mg,1mmol) to give a colourless oil (203mg, 65%); δ_H (C_6D_6, 250MHz) 7.38-6.96 (10H,m,ArH), 6.03 (1H,s,CH), 3.07 (3H,s,CH_3), 3.03 (1H,q,H_R), 2.80 (1H,qn,CH), 2.53 (1H,qn,H_S) and 1.18ppm (3H,d,CH_3).

6.2.9 Preparation of (S)-Methyl-(3-nitropropanoyl)mandelate (47a)

Preparation as in 6.2.1 using 3-nitropropanoic acid (200mg, 1.7mmol) to give a pale yellow oil (340mg, 75%); δ_H (C_6D_6, 250MHz) 7.5-7.12 (5H,m,ArH), 6.08 (1H,s,CH), 4.00-3.89 (1H,m,CH), 3.79-3.68 (1H,m,CH), 3.29 (3H,s,CH_3) and 2.46ppm (2H,m,CH_2).

6.2.10 Preparation of (S)-Methyl-(3-carbomethylpropanoyl)-mandelate (47b)

Preparation as in 6.2.1 using 3-carbomethylpropanoic acid (55mg, 0.47mmol) to give a colourless oil (193mg, 73%); δ_H (C_6D_6, 250MHz) 7.45 (2H,m,ArH), 7.07 (3H,m,ArH), 6.11 (1H,s,CH), 3.17 (3H,s,OCH_3), 2.53 (2H,m,CH_2), 2.32-2.20 (1H,m,CH) and 1.64ppm (3H,s,CH_3).

6.2.11 Preparation of (S)-Methyl-(α-deuteroethanoyl)mandelate (47c)

Preparation as in 6.2.1 using α-deuteroethanoic acid[236] (24mg, 0.39mmol) to give a colourless solid (50.5mg, 62%); δ_H (C_6D_6, 250MHz) 7.54-7.48, 7.19-7.12 (5H,m,ArH), 6.12 (1H,s,CH), 3.27 (3H,s,CH_3) and 1.81-1.79 (2H,t,J_{H-D} 4.5Hz,CH_2).

6.2.12 Preparation of (1S,4R)-(-)-p-bromobenzylcamphanamide (44f)

p-Bromobenzylamine hydrochloride (227.3mg, 1.0mmol) was suspended in dry dichloromethane (7cm^3) and cooled to 0°C.

Triethylamine (150mg, 1.5mmol) was added followed by (1S,4R)-(-)-camphanoyl chloride (241mg, 1.1mmol). The mixture was stirred at 0°C for 3 hours. The solution was poured into sodium hydroxide solution (0.1M; 50cm^3) and the aqueous layer was extracted with dichloromethane (3*10cm^3). The combined organic layers were washed with hydrochloric acid (0.1M; 2*25cm^3) and water (2*30cm^3), dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure to give a colourless solid (220mg, 60%), which was be recrystallised from chloroform-carbontetrachloride (1:1) and hexane, m.p. 126-127°C (Found: C, 55.7; H, 3.6; N, 5.3. $C_{17}H_{20}NO_3Br$ requires: C, 55.7; H, 3.8; N, 5.5%); δ_H (C_6D_6, 360MHz) 7.19 (2H,m,ArH), 6.76 (2H,m,ArH), 6.74 (1H,br,NH), 4.12 (1H,dd,H_S), 3.96 (1H,dd,J_{HS-HR} 14.7Hz,H_R), 2.30 (1H,m,CH), 1.33 (1H,m,CH), 1.25 (1H,m,CH), 0.84, 0.83 (6H,s+s,$C(CH_3)_2$) and 0.69ppm (3H,s,CCH_3); δ_C (C_6D_6, 51MHz) 177.4 (C-10), 167.1 (C-5), 138.0 (C-15), 131.8 (C-16, C-14), 129.6 (C-17, C-13), 121.4 (C-12), 92.2 (C-1), 55.1 (C-4), 53.7 (C-7), 42.2 (C-11), 30.6 (C-2), 29.1 (C-3), 16.6 (C-8), 16.5 (C-9) and 9.7ppm (C-6); $\nu_{max.}$ (KBr) 3380 (s), 2960, 2920, 2860 (m), 1780 (s), 1675 (s), 1530 (s) and 1175cm^{-1} (m); m/e (E.I.) 367/365, 186/184, 149, 136, 109 and 83; crystal data for $C_{17}H_{20}BrNO_3$: M=366, monoclinic, space group C_2, a=25.454(6), b=6.507(3), c=21.947(7)A, β=112.4°, U=3362(2)A^3, D_c=1.45gcm^{-3}, F(000)=1504, μ(Mo-Kα)=24.3cm^{-1}. At convergence R=0.064 (R_w=0.086) for the 1903 observed reflections.

6.2.13 Preparation of (1S,4R)-(-)-Bromopropylcamphanamide (44c)

Preparation as in 6.2.12 using bromopropylamine hydrobromide (219mg, 1.0mmol) to give (1S,4R)-(-)-bromo-

propylcamphanamide (239mg, 75%) m.p. 114-115°C (Found: C, 48.3; H, 6.1; N, 4.2. $C_{13}H_{20}NO_3Br$ requires C, 48.9; H, 6.3; N, 4.4%); δ_H (C_6D_6, 360MHz) 5.95 (1H,br,NH), 3.00 (1H,sext,Hs), 2.88 (1H,sext,J_{HS-HR} 13.7Hz, Jvic 6.6Hz, HR), 2.79 (2H,t,CH_2Br), 2.27 (1H,m,CH), 1.57-1.17 (3H,m,CH_2CH), 0.85,0.82 (6H,s+s,$C(CH_3)_2$) and 0.68ppm (3H,s,CCH_3); m/e (E.I.) 319/317, 238, 224, 153, 109 and 83.

6.2.14 Preparation of (R)-N-(Phenylethylethanoyl)-p-bromophenylethanamide (46a)

p-Bromophenylethanoic acid (360mg, 1.67mmol) was dissolved in dry dichloromethane (2cm^3). Oxalyl chloride (0.2cm^3, 2.2mmol) was added and the reaction was initiated by the addition of one drop of DMF. The mixture was stirred for 15 minutes, excess oxalyl chloride was removed by repeated washing with dry dichloromethane (5*4cm^3). p-Bromophenylethanoyl chloride was thus obtained as a clear orange oil (3.25mg, 83%); δ_H ($CDCl_3$, 60MHz) 7.45 (2H,m,ArH), 7.1 (2H,m,ArH) and 4.05ppm (2H,s,CH_2).

(R)-(-)-α-Aminophenylethanoic acid ethylester hydrochloride (275mg, 1.28mmol) was dissolved in dry dichloromethane (3cm^3) and triethylamine (0.8cm^3, 5.73mmol) was added. The mixture was cooled to 0°C and p-bromophenylethanoyl chloride (325mg, 1.4mmol), dissolved in dry dichloromethane (3cm^3), was added. The solution was stirred for 2 hours. The precipitated triethylamine hydrochloride was filtered off and the filtrate was washed with hydrochloric acid (0.1M; 2*50cm^3), water (2*50cm^3) and dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure to give a white

solid, which was recrystallised from petroleum ether (100-120°C) (400mg, 83%), m.p. 114-116°C; δ_H (C_6D_6, 360MHz) 7.27-7.25 (2H,m,ArH), 7.15-6.96 (3H,m,ArH), 6.71-6.67 (2H,m,ArH), 6.22 (1H,br,NH), 5.71 (1H,d,CH), 3.86-3.68 (2H,m+m,CH_2), 2.95 (2H,s,Hs HR) and 0.72ppm (3H,t,CH_3); max. (KBr) 3300 (s), 3020 (m), 2960 (m), 1730 (s) and 1650 cm^{-1}(s); m/e (E.I.) 304/302, 171/169, 106, 90 and 77.

6.2.15 Preparation of (R)-N-Phenyl(ethylethanoyl)ethanamide (46b)

(R)-α-Aminophenylethanoic acid ethylester hydrochloride (487mg, 2.26mmol) was dissolved in dry dichloromethane (7cm^3) and triethylamine (1.5cm^3, 10.76mmol) was added. The mixture was cooled to 0°C and propanoyl chloride (0.21cm^3, 2.3mmol) was added and the mixture stirred for 3 hours. The precipitated triethylamine hydrochloride was filtered off and the filtrate washed with hydrochloric acid (0.1M; 2*50cm^3), water (2*40cm^3) and dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure leaving an orange oil, which was recrystallised from petroleum ether (80-100°C) (250mg, 47%), m.p. 85-87°C; δ_H (C_6D_6, 360MHz) 7.36,7.34 (2H,m,Ar), 7.10-6.95 (3H,m,ArH), 6.07 (1H,br,NH), 5.83 (1H,d,CH), 3.92-3.74 (2H,m+m,CH_2) and 1.80-1.65ppm (2H,m,Hs HR); ν_{max}. (KBr) 3300 (s), 3060 (m), 2980 (m), 1730 (s) and 1650cm^{-1} (s); m/e (E.I.) 235, 162, 106, 77 and 57.

6.3 Experimental for Chapter Three

6.3.1 Preparation of Bis(trimethylacetonitrile)dichloro-platinum(II)

Platinum(II) chloride (1.028g, 3.86mmol) was dissolved in trimethylacetonitrile (6cm^3, 54mmol) and the mixture heated to just below reflux temperature (100°C). After 5 hours all the platinum dichloride had reacted to give a yellow solution. Excess trimethylacetonitrile was removed by repeated addition of ethanol (5*4cm^3) followed by evaporation of solvent under reduced pressure. The product was obtained as a yellow powder (3.68mmol, 95%); (Found: C, 27.2; H, 3.8; N, 6.1. Calc. for $C_{10}H_{18}N_2Cl_2Pt$: C, 27.7; H, 4.2; N, 6.5%).

6.3.2 Preparation of Bis(neomenthyldiphenylphosphino)dichloro-platinum(II)

(A) Bis(trimethylacetonitrile)dichloro-platinum(II) (130mg, 0.3mmol) was dissolved in dried dichloromethane (4cm^3) under nitrogen. A solution containing neomenthyldiphenyl-phosphine (N.M.D.P.P.; 195mg, 0.6mmol) dissolved in dried dichloromethane (3cm^3) was injected and the mixture stirred for 30 minutes. Evaporation of solvent under reduced pressure gave the <u>trans</u> product exclusively (0.27mmol, 90%), decomp >120°C (Found: C, 58.1; H, 6.2; Cl, 7.7. Calc. for $C_{44}H_{58}P_2Cl_2Pt$: C, 57.9; H, 6.4; Cl, 7.8%); δ_H (CD_2Cl_2, 360MHz) 7.71-7.67 (8H,m,ArH), 7.43-7.31 (12H,m,ArH), 3.73-3.67 (2H,m,CHα), 2.74-2.69 (2H,m,CHβ), 2.62-2.59 (2H,m,CHβ<u>H</u>), 2.00-1.97 (2H,m,C<u>H</u>CH$_3$), 1.07 (6H,d,C(CH$_3$)$_2$), 0.97 (6H,d,C(CH$_3$)$_2$) and 0.63ppm (6H,m,CHC<u>H</u>$_3$); δ_P (C_6D_6, 145MHz) 17.03ppm (J_{P-Pt} 2480Hz); $\nu_{max.}$ (nujol/CsI) Pt-Cl 353, 343 and 341cm^{-1}.

(B) Neomenthyldiphenylphosphine (323mg, 1mmol) was dissolved in a mixture of ethanol (10cm^3) and dichloromethane (5cm^3). Potassium tetrachloroplatinate(II) (204mg, 0.5mmol) was dissolved in water (3cm^3) and added to the solution of the phosphine. The mixture was heated at reflux (80°C) for 3 hours and the precipitated [potassium tetraphosphine]$^{2+}$[tetrachloroplatinate(II)]$^{2-}$ salt was filtered off (836mg, 50%). Addition of methanol (1cm^3) precipitated the <u>trans</u> product (274mg, 30%) (as before), which was filtered off, and addition of ether (1.5cm^3) precipitated the <u>cis</u> product (183mg, 20%), (Found: C, 57.5; H, 6.2. Calc. for $C_{44}H_{58}P_2Cl_2Pt$: C, 57.9; H, 6.4%); δ_H (CD_2Cl_2, 360MHz) 7.93 (6H,m,ArH), 7.81 (6H,m,ArH), 7.41-7.31 (4H,m,ArH), 3.71-3.69 (2H,m,CHα), 2.71 (2H,m,CHβ), 2.68-2.58 (2H,m,CHβ<u>H</u>), 2.02-1.98 (2H,m,C<u>H</u>CH$_3$), 0.76 (6H,d,C(CH$_3$)$_2$), 0.64 (6H,d,C(CH$_3$)$_2$) and 0.58ppm (6H,d,C(CH$_3$)$_2$); $\nu_{max.}$ (nujol/CsI) Pt-Cl 252, 250 and 248cm^{-1}; m/e (FAB$^+$ 2,2'-dithioethanol) 879, 877, 843, 554 and 324.

6.3.3 <u>Preparation of 2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butanedichloroplatinum(II)</u>

Bis(trimethylacetonitrile)dichloroplatinum(II) (89mg, 0.21mmol) was dissolved in dried dichloromethane (3cm^3) under nitrogen. (R,R)-(-)- or (S,S)-(+)-DIOP (102mg, 0.21mmol) was dissolved in dried dichloromethane (3cm^3) under nitrogen and injected into the solution of the platinum complex which was instantly decolourised. After stirring for 15 minutes the volume of the solution was reduced and the product precipitated by addition of methanol (0.5cm^3). The filtered product was then washed with cold methanol (153mg, 95%), stable at 150°C (Found: Cl, 9.3. Calc. for $C_{31}H_{32}P_2O_2Cl_2Pt$: Cl, 9.3%);

δ_H ($CDCl_3$, 360MHz) 7.82-7.77 (4H,m,ArH), 7.68-7.62 (4H,m,ArH), 7.54-7.40 (12H,m,ArH), 3.92-3.88 (2H,m,J_{Pt-H} 10Hz,CH_2), 3.12-2.96 (2H,m,J_{Pt-H} 40Hz,CH_2), 2.65-2.56 (2H,m,CH-CH) and 1.13ppm (6H,s,$C(CH_3)_2$); δ_P (C_6D_6,101MHz) -1.5ppm (J_{P-Pt} 3512Hz); δ_{Pt} (C_6D_6, 19MHz) +519ppm {with reference to TMS}; m/e (FAB^+ 2,2'-dithioethanol) 730, 728, 693, 565, 488, 411, 380 and 303.

6.3.4 Preparation of 2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane platinum(0)-ethene (52)

(R,R)- or (S,S)- DIOP-platinum(II) dichloride (191mg, 0.25mmol) was dissolved in dried dichloromethane (4cm^3) and dried ethanol (4cm^3) and the solution cooled to -78°C. A stream of ethene was bubbled through the solution. Sodium borohydride (21.9mg, 0.58mmol, 2.3 equivalents) was dissolved in dried ethanol (4cm^3) and also cooled to -78°C before being slowly injected into the solution of the platinum complex. The mixture was stirred at -78°C under a stream of ethene for 1 hour then slowly allowed to warm to room temperature. At the first sign of darkening (usually c.-30°C) the solution was transfered into degassed, dried ethanol (30cm^3), after 15 minutes the product precipitated as off-white micro-crystals (137mg, 76%), decomp. >150°C (Found: C, 54.9; H, 4.9. Calc. for $C_{33}H_{36}P_2O_2Pt$: C, 54.9; H, 5.0%); δ_H (CD_2Cl_2, 360MHz) 7.74-7.66 (4H,m,ArH), 7.53-7.47 (4H,m,ArH), 7.44-7.30 (12H,m,ArH), 3.95-3.91 (2H,m,CH_2), 3.65-3.42 (2H,dtd,J_{vic} 15.8Hz, J_{Pt-H} 35Hz, J_{P-H} 14.8Hz,CH_2), 2.45-2.35 (2H,m,$H\alpha H\beta$), 2.06-2.01 (2H,m,J_{Pt-H} 57Hz,CH_2), 1.85-1.81 (2H,m,J_{Pt-H} 57Hz,CH_2) and 1.30ppm (6H,s,$C(CH_3)_2$); δ_P (C_6D_6, 36.3MHz) +13.7ppm (J_{P-Pt} 3585Hz); δ_{Pt} (C_6D_6, 19.2MHz) -566ppm; m/e (FAB^+ 2,2'-dithio-ethanol) 693, 565, 488, 411, 380 and 303.

6.3.5 Derivatisation Experiments with DIOP-Pt-Ethene (52)

DIOP-platinum(0)-ethene (15mg, 0.02mmol) was dissolved in dried THF (1.5cm^3) and the substrate (0.02mmol) injected directly, if a liquid, or as a solution in dried THF (1cm^3), if a solid. The mixture was stirred for 10 minutes and then the solvent was removed under reduced pressure, the residue was taken up in d_6-benzene and the N.M.R. spectrum recorded.

Alternatively, direct derivatisation was performed by shaking the substrate and the DIOP-platinum(0)-ethene complex together in d_6-benzene in an N.M.R. tube and the spectrum was then recorded directly.

(A) (-)DIOP-Pt-dimethyl-1,4-butynedioate (53a)

[Substrate: Aldrich D13,840-1] δ_H (C_6D_6, 90MHz) 7.81 (4H,m,ArH), 7.51 (4H,m,ArH), 6.98 (12H,m,ArH), 3.98 (2H,m,CH_2), 3.65 (2H,dtd,J_{vic} 14Hz, J_{Pt-H} 34Hz,J_{P-H} 14Hz,CH_2), 3.20 (6H,s,$COOCH_3$), 2.34 (2H,m,HαHβ) and 1.22ppm (6H,s,$C(CH_3)_2$); δ_P (C_6D_6, 101MHz) +5.92ppm (J_{P-Pt} 3567Hz); δ_{Pt} (C_6D_6, 19.2MHz) -227ppm.

(B) (-)DIOP-Pt-1,1-dimethylallene (53c)

[Substrate: Aldrich 11,093-0] δ_H (C_6D_6, 250MHz) 2.47 (6H,s,$C(CH_3)_2$) and 1.72ppm (2H,s,CH_2) δ_P (C_6D_6, 101MHz) Pa 18.99 (J_{Pa-Pt} 3463Hz, J_{Pa-Pb} 54Hz) and Pb 6.65ppm (J_{Pb-Pt} 2857Hz, J_{Pa-Pb} 54Hz).

(C) (-)DIOP-Pt-methylacrylate (53d)

[Substrate: Aldrich M2,730-1] δ_H (C_6D_6, 250MHz) 7.91-7.60 (4H,m,ArH), 7.51-7.24 (4H,m,ArH), 7.04 (12H,m,ArH),5.68 (1H,m,=CH), 5.34-5.23 (2H,m,=CH_2) 4.08-3.82 (2H,m,CH_2), 3.74-

3.54 (2H,m,CH_2), 3.28 (3H,d,OCH_3),2.54-2.46 (2H,m,$CH_\alpha H_\beta$), 1.31 (3H,s,CH_3) and 1.28ppm (3H,s,CH_3); δ_P (C_6D_6, 101MHz) Pa 13.79 (J_{Pa-Pt} 3475Hz, J_{Pa-Pb} 57Hz), Pb 8.95 (J_{Pb-Pt} 3862Hz, J_{Pa-Pb} 57Hz), Pa' 12.37 ($J_{Pa'-Pt}$ 3434Hz, $J_{Pa'-Pb'}$ 61Hz) and Pb' 10.76ppm ($J_{Pb'-Pt}$ 3871Hz, $J_{Pa'-Pb'}$ 61Hz); m/e (FAB^+ 2,2'-dithio-ethanol) 779, 690, 565, 488, 411 and 380.

(D) <u>(-)DIOP-Pt-allyl bromide</u>

[Substrate: Aldrich A2,958-5] δ_P -3.19ppm (J_{P-Pt} 3432Hz).

(E) <u>(-)DIOP-Pt-allyl acetate</u>

[Substrate: Aldrich 18,524-8] δ_P (C_6D_6, 101MHz) -2.56ppm (J_{P-Pt} 3847Hz).

(F) <u>(-)DIOP-Pt-norbornene</u>

[Substrate: Aldrich N3,240-7] δ_P (C_6D_6,101MHz) 14.04ppm (J_{P-Pt} 3447Hz).

(G) <u>(-)DIOP-Pt-1,1-diphenylethene (53b)</u>

[Substrate: Aldrich D20,680-6] δ_P (C_6D_6, 101MHz) Pa 11.16ppm (J_{P-Pt} 3704Hz, J_{Pa-Pb} 71Hz) and Pb 7.69ppm (J_{P-Pt} 3360Hz, J_{Pa-Pb} 71Hz).

(H) <u>(-)DIOP-Pt-(±)-acrylamide (53e)</u>

[Substrate: Phenylethylamine (1cm^3, 8.6mmol) was dissolved in dried dichloromethane and the solution cooled to 0°C. Triethylamine (1.25cm^3, 8.9mmol) was added and then acryloyl chloride (0.7cm^3, 8.6mmol) was slowly injected ensuring that the temperature remained at 0°C throughout. The mixture was stirred for 1 hour and then the precipitated

triethylamine hydrochloride was filtered off. The filtrate was washed with hydrochloric acid (0.1M; 3*25cm^3), and water (3*25cm^3), then dried over anhydrous magnesium sulphate. Removal of solvent under reduced pressure gave a colourless oil which crystallised in diethylether, (1.24g, 83%), m.p. 94-96°C (Found: C, 75.1; H, 7.0; N, 7.8. Calc. for $C_{11}H_{13}NO$: C, 75.4; H, 7.4; N, 8.0%); δ_H ($CDCl_3$, 250MHz) 7.34-7.26 (5H,m,ArH), 6.29 (1H,dd,$J_{H\alpha-Hx}$ 17Hz,$J_{H\alpha-H\beta}$ 2Hz,Hα), 6.09 (1H,dd,$J_{Hx-H\alpha}$ 17Hz,$J_{Hx-H\beta}$ 10Hz,Hx), 5.99 (1H,br,NH), 5.69 (1H,dd,$J_{H\beta-Hx}$ 10Hz,$J_{H\beta-H\alpha}$ 2Hz,Hβ), 5.21 (1H,qn,CH) and 1.53ppm (3H,d,J_{vic} 5Hz,CH_3); $\nu_{max.}$ (KBr) 3240 (br), 3050 (w), 2980 (w) and 1610cm^{-1} (s); m/e (E.I.) 175, 160, 120, 105, 77 and 55.]

{use of either (R)-(+)- or (S)-(-)- phenylethylamine gives the acrylamides with the corresponding configuration}

Platinum Complex

δ_P (C_6D_6, 101MHz) Pa 12.8 (J_{Pa-Pt} 3801Hz, J_{Pa-Pb} 57Hz), Pb 9.9 (J_{Pb-Pt} 3759Hz, J_{Pa-Pb} 57Hz), Pa' 12.7 ($J_{Pa'-Pt}$ 3512Hz., $J_{Pa'-Pb'}$ 61Hz), Pb' 11.3 ($J_{Pb'-Pt}$ 3477Hz, $J_{Pa'-Pb'}$ 61Hz),Pa 13.6 (J_{Pa-Pt} 3838Hz, J_{Pa-Pb} 57Hz), Pb 9.6 (J_{Pb-Pt} 3752Hz, J_{Pa-Pb} 57Hz), Pa' 13.3 ($J_{Pa'-Pt}$ 3470Hz, $J_{Pa'-Pb'}$ 64Hz) and Pb' 10.8ppm ($J_{Pb'-Pt}$ 3500Hz $J_{Pa'-Pb'}$ 64Hz);

δ_{Pt} (C_6D_6, 19.2MHz) Pta -405.7, -586.8 (J_{Pta-P} 3786Hz), Ptb -603.1, -784.3 (J_{Ptb-P} 3472Hz), Pta' -429.6, -611.0 ($J_{Pta'-P}$ 3845Hz), Ptb' -630.5, -811.9 ($J_{Ptb'-P}$ 3464Hz), Pta" -431.9, -612.5 ($J_{Pta"-P}$ 3853Hz) and Ptb" -632.4, -812.9ppm ($J_{Ptb"-P}$ 3479Hz).

(J) (-)DIOP-Pt-(±)-Carvone (54)

[Substrate: Fluka Chemika A.G. 22070-(+), 22060-(-)] δ_P (C_6D_6, 101MHz) Pa 13.77 (J_{Pa-Pt} 3409Hz, J_{Pa-Pb} 65Hz), Pb 9.88 (J_{Pb-Pt} 3881Hz, J_{Pa-Pb} 65Hz), Pa' 12.50 ($J_{Pa'-Pt}$ 3537Hz, $J_{Pa'-Pb'}$ 65Hz) and Pb' 10.75ppm ($J_{Pb'-Pt}$ 3938Hz, $J_{Pa'-Pb'}$ 65Hz).

(K) (-)DIOP-Pt-(±)-2-propenyl-α-methoxyphenylethanoate (53g)

[Substrate: Allyl alcohol (0.1cm^3, 1.5mmol) was dissolved in dried dichloromethane (20cm^3) under nitrogen. 4-Dimethyl-aminopyridine (D.M.A.P.; 5mg) and dicyclohexylcarbodiimide (D.C.C.; 302mg, 1.5mmol) were added to the solution which was then cooled to -5°C (ice/salt). (±)-Methoxyphenylacetic acid (265mg, 1.5mmol) was added and the mixture stirred at -5°C for 3 hours after which the precipitated dicyclohexylurea was filtered off. The solvent was removed under reduced pressure and the residue taken up in dichloromethane (3cm^3) and filtered a second time. Removal of solvent gave a colourless oil which was purified by preparative T.L.C. on silica (40-60°C petroleum ether:ethylacetate, 1:1, v/v)].

Platinum Complex

δ_P (C_6D_6, 101MHz) Pa 14.68 (J_{Pa-Pt} 3887Hz, J_{Pa-Pb} 66Hz), Pb 12.22 (J_{Pb-Pt} 3796Hz, J_{Pa-Pb} 66Hz), Pa' 13.80 ($J_{Pa'-Pt}$ 3774Hz, $J_{Pa'-Pb'}$ 68Hz) and Pb' 12.40ppm ($J_{Pb'-Pt}$ 3760Hz, $J_{Pa'-Pb'}$ 68Hz).

(L) (-)DIOP-Pt-(±)-trans-dimethylnorbornene-2,3-dicarboxylate (58b)

[Substrate: Methanol (1cm^3, 25mmol) and triethylamine (1cm^3, 7.2mmol) were mixed in dry dichloromethane (3cm^3) and

trans-3,6-endomethylene-1,2,3,6-tetrahydrophthaloyl chloride (Aldrich 11415-4) (0.5cm^3, 3mmol), dissolved in dry dichloromethane (2cm^3), was added dropwise to the solution at 0°C. The mixture was stirred for 2 hours and then the precipitated triethylamine hydrochloride was filtered off. The filtrate was washed with hydrochloric acid (0.1M; 2*5cm^3), potassium hydroxide solution (0.1M; 2*5cm^3), water (2*5cm^3) and dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure to give an oil (480mg, 77%); δ_H ($CDCl_3$, 60MHz) 6.10 (2H,m), 3.7 (3H,s,CH_3), 3.6 (3H,s,CH_3), 3.43-3.10 (3H,m), 2.6 (1H,m) and 1.3ppm (2H,m)].

Platinum Complex

δ_P (C_6D_6, 101MHz) Pa 14.76 (J_{Pa-Pt} 3456Hz, J_{Pa-Pb} 67Hz), Pb 12.70 (J_{Pb-Pt} 3376Hz, J_{Pa-Pb} 67Hz), Pa' 14.54 ($J_{Pa'-Pt}$ 3439Hz, $J_{Pa'-Pb'}$ 68Hz) and Pb' 12.03ppm ($J_{Pb'-Pt}$ 3367Hz, $J_{Pa'-Pb'}$ 68Hz).

(M) (-)DIOP-Pt-(±)-1,2-cyclononadiene (56)

[Substrate: Potassium tert-butoxide (8.7g, 77.67mmol) was suspended in dried hexane (20cm^3) under nitrogen. Cyclooctene (7.5cm^3, 60mmol) was injected and the stirring mixture cooled to -10°C. Bromoform (5.5cm^3, 63mmol) was added dropwise to the cooled solution over 1 hour and the mixture was stirred overnight at room temperature. Water (20cm^3) and hydrochloric acid (2M; 2cm^3) were added. The aqueous layer was separated and extracted with hexane (2*30cm^3), the combined organic layers were washed with water (2*40cm^3), dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure. The product {9,9 dibromobicyclo[6.1.0]-nonane}

distilled (102°C, 0.1mmHg) as a pale yellow oil (8.04g, 48%). 9,9 Dibromobicyclo[6.1.0]nonane (2cm^3, 11.4mmol) was dissolved in dried diethylether (15cm^3) and the solution cooled to -35°C. Methyllithium (15cm^3, 1.3M solution in diethylether, 19.5mmol), was added over 15 minutes and the mixture stirred for 30 minutes. Water (40cm^3) was injected cautiously and after stirring for a further 10 minutes the aqueous layer was separated and extracted with diethylether (2*30cm^3). The combined organic layers were washed with water (2*20cm^3), dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure giving the product {1,2-cyclononadiene} which distilled as a pale yellow oil (76°C, 19mmHg), (810mg,68%). Enantiomerically enriched product was obtained by introduction of (-) sparteine (2.6cm^3, 11.1mmol) at the reduction step. The work up procedure then included a hydrochloric acid wash (2*20cm^3).]

Platinum Complex

δ_P (C_6D_6, 101MHz) Pa 17.65 (J_{Pa-Pt} 3246Hz, J_{Pa-Pb} 72Hz), Pb 10.27 (J_{Pb-Pt} 3246Hz, J_{Pa-Pb} 72Hz), Pa' 17.30 ($J_{Pa'-Pt}$ 3060Hz, $J_{Pa'-Pb'}$ 71Hz) and Pb' 10.98ppm ($J_{Pb'-Pt}$ 3060Hz, $J_{Pa'-Pb'}$ 71Hz).

(N) (+)DIOP-Pt-(±)-1,3-di-n-butylallene (53f)

δ_P (C_6D_6, 101MHz) Pa 17.14 (J_{Pa-Pt} 3235Hz, J_{Pa-Pb} 65Hz), Pb 9.61 (J_{Pb-Pt} 3026Hz, J_{Pa-Pb} 65Hz), Pa' 16.21 ($J_{Pa'-Pt}$ 3238Hz, $J_{Pa'-Pb'}$ 65Hz), Pb' 9.83 ($J_{Pb'-Pt}$ 3026Hz, $J_{Pa'-Pb'}$ 65Hz), Pa 17.62 (J_{Pa-Pt} 3252Hz, J_{Pa-Pb} 57Hz), Pb 6.01 (J_{Pb-Pt} 2942Hz, J_{Pa-Pb} 57Hz) and Pb' 7.21ppm ($J_{Pb'-Pt}$ 2947Hz, $J_{Pa'-Pb'}$ 59Hz).

6.3.6 Preparation of Bis(propionitrile)dichloropalladium(II)

Palladium(II)dichloride (2.21g, 12.5mmol) was dissolved in propionitrile (10cm^3, 140mmol) under nitrogen and the solution heated at reflux (97°C) for 3 hours. After cooling the solvent was removed under reduced pressure and the residue washed free of excess propionitrile by repeated addition of ethanol (5cm^3) and removal under reduced pressure leaving a brown solid (2.3g, 70%); δ_P (C_6D_6, 101MHz) 15.2ppm.

6.3.7 Preparation of 2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butanedichloropalladium(II)

Bis(propionitrile)dichloropalladium(II) (239mg, 0.83mmol) was dissolved in dried dichloromethane (7cm^3). A solution containing (-)DIOP (415mg, 0.83mmol) in dried dichloromethane (4cm^3) was slowly injected into the solution of the palladium complex. The mixture was stirred for 30 minutes and then the volume of solvent was reduced and the product was precipitated as a yellow solid by the addition of methanol (1cm^3), (500mg, 86%); δ_P (CD_2Cl_2, 101MHz) 16.1ppm.

6.3.8 Preparation of 2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butanepalladium(0)-ethene (59)

DIOP-palladium(II)-dichloride (321mg, 0.47mmol) was dissolved in dried dichloromethane (5cm^3) and dried ethanol (3cm^3) under a stream of ethene. The stirring solution was cooled to -78°C. Sodium borohydride (36mg, 0.96mmol, 2.3 equivalents) was dissolved in dried ethanol (3cm^3) and also cooled to -78°C before being slowly injected into the solution of the palladium complex under a vigourous stream of ethene. After stirring at -78°C for 30 minutes the mixture was allowed to slowly warm up to room temperature still under ethene, the

product then precipitated out as grey microcrystals. These were allowed to settle out before the supernatent liquid was removed. The solid was then washed with cold ethanol (2*0.5cm^3) and dried under reduced pressure (203mg, 68%); δ_P (C_6D_6, 101MHz) 6.8ppm; crystal data for $C_{33}H_{36}PdO_2P_2$: M=633, monoclinic, space group $P2_1$, a=10.664(3), b=11.023(4), c=13.926(2)A, β=109.41(2)°, U=1543.9A^3, Z=2, D_c=1.36gcm^{-3}, F(000)=652, T=296K. λ=0.71073A, μ(Mo-Kα)=7.2cm^{-1}. Data were collected with an Enraf-Nonius CAD-4 diffractometer, and at convergence R was 0.034(R_w=0.037) for the 2220 unique observed reflections.

6.3.9 Derivatisation Experiments with DIOP-Pd-Ethene (59)

(A) (-)(DIOP)-Pd-tetracyanoethene [Substrate: Aldrich T880-9] δ_P (CD_2Cl_2, 101MHz) 9.2ppm.

(B) (-)(DIOP)-Pd-norbornene [Substrate: Aldrich N3,240-7] δ_P (CD_2Cl_2, 101MHz) 6.2ppm.

(C) (-)(DIOP)-Pd-allyl acetate (60) [Substrate: Aldrich 18,524-8] δ_P (CD_2Cl_2, 101MHz) 8.1ppm.

(D) (-)(DIOP)-Pd-allyl chloride [Substrate: Aldrich A3,070-2] δ_P (CD_2Cl_2, 101MHz) Pa 20.8 and Pb 2.0ppm (J_{Pa-Pb} 40Hz).

(E) (-)(DIOP)-Pd-cis-phenyliodide [Substrate: Aldrich I-763-2] δ_P (CD_2Cl_2, 101MHz) Pa 13.2 and Pb -3.2ppm (J_{Pa-Pb} 41Hz).

(F) (-)(DIOP)-Pd-(±)-Carvone [Substrate: Fluka Chemika A.G. 22070-(+), 22060-(-)] δ_P (C_6D_6, 101MHz) Pa 8.5, Pb 3.5 (J_{Pa-Pb} 47Hz) and Pa 7.3, Pb 4.3 (J_{Pa-Pb} 47Hz).

6.4 Experimental for Chapter Four

6.4.1 Preparation of 9-Methoxycarbonylsulphenylanthracene (66)

Anthracene (9.00g, 50.56mmol) was dissolved in dichloromethane (180cm^3) and carbon disulphide (40cm^3). Boron trifluoride-diethyletherate was added (6.5cm^3, 51.73mmol) and the mixture stirred whilst methoxycarbonylsulphenylchloride (5cm^3, 55.27mmol) was injected. The solution was stirred for 42 hours and then poured into a mixture of hydrochloric acid (0.1M; 100cm^3) and ice (150cm^3). The organic layer was separated, washed with water (2*25cm^3) and dried over anhydrous magnesium sulphate; the solvent was removed under reduced pressure to leave the crude product as a brown solid. TLC on silica (40-60°C petroleum ether/ethyl acetate,1:1,v/v) R_f=0.73, 0.69. The product sublimed (130°C, 0.001mm Hg) as yellow flakes (10.05g, 75%), m.p. 145-147°C (Found: C, 71.1; H, 4.2. Calc. for $C_{16}H_{12}SO_2$: C, 71.6; H, 4.5%); δ_H ($CDCl_3$, 60MHz) 8.7-8.5 (3H,m,ArH), 8.1-7.8 (2H,m,ArH), 7.6-7.4 (4H,m,ArH) and 3.8ppm (3H,s,CH_3); $\nu_{max.}$ (KBr) 3090(w), 1655(s), 1190(m), 1155(m) and 1135cm^{-1} (s).

6.4.2 Preparation of 9-Anthrylmethylsulphide (64) {from (66)}

9-Methoxycarbonylsulphenylanthracene (2.00g, 7.46mmol) was dissolved in warm methanol (30cm^3, 45°C) under nitrogen. Potassium hydroxide (0.56g, 10mmol) and tetrahexylammonium bromide (5mg) were added, the mixture was heated at reflux for 30 minutes. After allowing to cool, methyl iodide (0.5cm^3, 8.00mmol) was added dropwise and the solution heated at reflux for a further 30 minutes. The cooled solution was then poured into an ether/water mixture (30cm^3:30cm^3), the aqueous

layer was extracted with ether (3*10cm^3) and the combined organic layers dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure to leave an orange oil which sublimed (100°C, 0.001mm Hg) as an orange-yellow solid (1.05g, 63%), m.p. 96-97°C (Found: C, 80.1; H, 5.2; S, 14.4. Calc. for $C_{15}H_{12}S$: C,80.3; H, 5.4; S, 14.3%); δ_H ($CDCl_3$, 60MHz) 9.05-8.90 (2H,m,ArH), 8.45 (1H,s,ArH), 8.10-7.80 (2H,m,ArH), 7.65-7.45 (4H,m,ArH) and 2.38ppm (3H,s,CH_3); $\nu_{max.}$ (hexachlorobutadiene): 3090 (w), 2920 (w) and 740cm^{-1} (s); m/e (E.I.) 224, 209, 165 and 104.

6.4.3 Preparation of 9-Anthrylthiol (63) {from (66)}

9-Methoxycarbonylsulphenylanthracene (2.00g, 7.46mmol) was dissolved in methanol (30cm^3) under nitrogen. Potassium hydroxide (0.56g, 10mmol) was added and the mixture heated at reflux for 30 minutes. The cooled solution was acidified with dilute hydrochloric acid to pH 6.5 and the inorganic precipitate filtered off and washed with methanol (2*10cm^3). The filtrate was poured into an ether/water mixture (30cm^3:30cm^3), the aqueous layer was washed with ether (2*20cm^3) and the combined organic layers were dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure leaving an orange-yellow solid (0.94g, 60%), m.p. 90-91°C (Found: C, 79.8; H, 4.6. Calc. for $C_{14}H_{10}S$: C, 80.0; H, 4.8%); δ_H ($CDCl_3$, 60MHz) 8.70-8.55 (2H,m,ArH), 8.3 (1H,s,ArH), 8.05-7.90 (2H,m,ArH) and 3.6ppm (1H,s,SH); m/e (E.I.) 210, 209, 177 and 165.

6.4.4 Preparation of Arylmethylsulphides from Arylthiols

[For example the preparation of 2-naphthylmethylsulphide from 2-naphthylthiol]

2-Naphthylthiol (4.17g, 26.06mmol) was dissolved in dried diethylether (50cm^3) and a freshly prepared solution of diazomethane in diethylether (45cm^3, 30.00mmol) was added. After evolution of nitrogen had ceased the solvent was removed under reduced pressure leaving a colourless solid (4.34g, 96%), m.p. 62-64°C (Found: C, 76.1; H, 5.5; S, 18.1. Calc. for $C_{11}H_{10}S$: C, 75.9; H, 5.8; S, 18.4%); δ_H ($CDCl_3$, 60MHz) 7.80-7.20 (7H,m,ArH) and 2.55ppm (3H,s,CH_3); $\nu_{max.}$ (nujol) 3090 (w), 820 (m), and 735cm^{-1} (m).

6.4.5 Preparation of 9-Anthryldithiochloride (62)

Disulphurdichloride (8cm3, 96.06mmol) was added to anthracene (10.00g, 56.18mmol) and the mixture shaken vigourously. Once evolution of hydrogen chloride has ceased the excess disulphurdichloride was extracted into 40-60°C petroleum ether and the product recrystallised twice from carbon disulphide (5.59g, 36%), m.p.115-117°C (Found: C, 60.2; H, 2.9. Calc. for $C_{14}H_9S_2Cl$: C, 60.8; H, 3.3%).

6.4.6 Preparation of 9-Anthrylthiol (63) {from (62)}

9-Anthryldithiochloride (3.50g, 12.66mmol) was dissolved in methanol (30cm^3) with sodium sulphide (1.30g, 16.67mmol) and the mixture heated at reflux for one hour. The cooled solution was acidified with dilute hydrochloric acid, and the product was extracted into dichloromethane (2*30cm3). The organic layer was dried over anhydrous magnesium sulphate and the

solvent removed under reduced pressure to give 9-anthrylthiol (0.77g, 29%) (as before).

6.4.7 Preparation of 9-Anthrylmethylsulphide (64) {from (63)}

9-Anthrylthiol (220mg, 10.5mmol) was dissolved in methanol (30cm^3) under nitrogen. Potassium hydroxide (2.0g, 35.7mmol) was added and the mixture heated at reflux for 15 minutes. Methyl iodide (1.0cm^3, 15.9mmol) was added dropwise to the cooled solution and the mixture heated at reflux for a further 15 minutes then poured into an ether/water mixture (30cm^3:30cm^3). The organic layer was separated, dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure to give 9-Anthrylmethylsulphide (136mg, 58%) (as before).

6.4.8 Preparation of Dry Tert-butylhydroperoxide

Tert-butylhydroperoxide (125cm^3, 70% solution in water: Aldrich 18471-3) was swirled with dichloromethane (215cm^3) for two minutes [shaking gave an emulsion]. The organic layer (310cm^3) was separated from the aqueous layer (30cm^3) and cautiously distilled. After 100cm^3 of cloudy distillate had been collected, a further 60cm^3 was distilled leaving 150cm^3 of a dry solution of tert-butylhydroperoxide in dichloromethane. Concentration is 6.58M (60MHz ^{1}H N.M.R. integration).

6.4.9 Asymmetric Oxidation of Arylmethylsulphides to Arylmethylsulphoxides

(A) The oxidation of 2-naphthylmethyl sulphide to 2-naphthylmethyl sulphoxide.

Titanium isopropoxide (6.0cm^3, 20mmol) was dissolved in dried dichloromethane (70cm^3) at 25°C under nitrogen. (R,R)-

Diethyltartrate (6.8cm^3, 40mmol) was added followed by water (360μL, 20mmol) and the mixture was stirred until it was homogeneous (15 minutes). 2-Naphthylmethyl sulphide (3.48g, 20mmol) was dissolved in dried dichloromethane (20cm^3) and this solution was added to that of the titanium-diethyltartrate complex. The mixture was cooled to -20°C and freshly dried solution of tert-butylhydroperoxide in dichloromethane (3.7cm^3, [6.58M], 24mmol) was injected. The solution was stirred at -20°C for 3 hours then water (50cm^3) was added and the mixture stirred for a further hour (-20°C to +25°C). The precipitated titanium dioxide was filtered off {alumina was used to assist filtration}. The organic layer was separated from the filtrate and washed with sodium hydroxide (0.1M; 3*50cm^3), saturated brine (3*50cm^3) and water (2*30cm^3) and dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure leaving a colourless solid which was purified by chromatography on silica gel (hexane/ethylacetate, 1:1,v/v) or by sublimation (96°C, 0.001mmHg), (2.85g, 75%), m.p. 123-125°C; $[\alpha]^{20}$ +121.4° (c=2, $CHCl_3$) {lit[218] $[\alpha]^{20}$ +141° (c=2, $CHCl_3$)}; (Found: C, 69.9; H, 5.4; S, 17.0. Calc. for $C_{11}H_{10}SO$: C, 69.5; H, 5.3; S, 16.8%); δ_H ($CDCl_3$, 60MHz) 8.30 (1H,m,ArH), 8.00 (1H,m,ArH), 7.75-7.55 (3H,m,ArH) and 2.80ppm (3H,s,CH_3); $\nu_{max.}$ (nujol) 3090 (w), 1065 (w), 1030 (m) and 820cm^{-1}.

(B) The oxidation of 9-Anthrylmethyl sulphide to 9-Anthrylmethyl sulphoxide.

Reaction as for 2-naphthylmethyl sulphoxide using 9-Anthrylmethyl sulphide (1.72g, 8.0mmol), (i.e. 1/5 scale).

The reaction was worked up after 5 hours and the product purified by preparative T.L.C. on silica (40-60°C petroleum ether/ethylacetate, 1:1, v/v) to give a yellow solid (576mg, 30%); $[\alpha]_{20}$ 90.2° (c=2, $CHCl_3$) {lit[219] $[\alpha]_{20}$ 112.8° (c=2, $(CH_3)_2CO$)}; (Found: C, 74.4; H, 4.7. Calc. for $C_{15}H_{12}SO$: C, 75.0; H, 5.0%); δ_H ($CDCl_3$, 60MHz) 9.30-9.10 (2H,m,ArH), 8.65 (1H,s,ArH), 8.25-7.80 (2H,m,ArH), 7.75-7.55 (4H,m,ArH) and 3.10ppm (3H,s,CH_3); $\nu_{max.}$ (nujol) 3090 (w), 1030 (m) and 730cm^{-1}.

(C) The oxidation of Phenylmethyl sulphide to Phenylmethyl sulphoxide.

Reaction as for 2-naphthylmethyl sulphoxide using phenylmethylsulphide (2.4cm^3, 20mmol) [Aldrich]. The reaction was worked up after 8 hours and the product purified by chromatography on silica gel (40-60°C petroleum ether/ethylacetate, 1:1, v/v) to give a colourless solid (1.5g, 61%); $[\alpha]_{20}$ 69.5° (c=2, $CHCl_3$) {lit[217] $[\alpha]_{20}$ 146.1° (c=1.7 $(CH_3)_2CO$)}; (Found: C, 59.6; H, 5.3. Calc. for C_7H_8SO: C, 60.0; H, 5.7%); δ_H ($CDCl_3$, 60MHz) 7.7-7.2 (5H,m,ArH) and 2.55ppm (3H,m,CH_3); $\nu_{max.}$ (nujol) 3090 (w), 2900 (w), 1090 (m), 920 (s) and 730cm^{-1} (s).

6.4.10 Preparation of N-(3,5-dinitrobenzoyl)phenylethylamine (67)

(R)-(+)-Phenylethylamine (2.90g, 23.9mmol) was added to a solution of 3,5-dinitrobenzoylchloride (5.83g, 25.3mmol) and triethylamine (4cm^3, 28.7mmol) in chloroform (50cm^3) at 0°C. The mixture was stirred for 3 hours and then the precipitated triethylamine hydrochloride was filtered off. The filtrate was washed with sodium hydroxide (0.1M; 2*30cm^3), hydrochloric acid (0.1M; 2*30cm^3) and with water (3*20cm^3) then dried over

anhydrous magnesium sulphate. The solvent was removed under reduced pressure leaving a colourless oil which slowly crystallised. The product was recrystallised from diethylether (4.73g, 63%), m.p. 161-163°C {lit[167] 158-160°C}; $[\alpha]_D^{20}$ -16.4° (c=0.8, $CHCl_3$) {lit[167] $[\alpha]_D^{20}$ -17.5 (c=0.9, $(CH_3)_2CO$)}; (Found: C, 56.8; H, 4.0; N, 12.9. Calc. for $C_{15}H_{13}N_3O_5$: C, 57.1; H, 4.1; N, 12.9%); δ_H ($CDCl_3$, 60MHz) 9.06 (1H,m,Bz), 8.94 (2H,m,Bz), 7.38-7.20 (5H,m,ArH), 5.24 (1H,qt,CH) and 1.62ppm (3H,d,CH_3); $\nu_{max.}$ (nujol) 3090 (w), 1635 (s) and 1540cm^{-1} (s).

6.4.11 Preparation of 2-Naphthyltrifluoromethylsulphide

(A) 2-Naphthylthiol (0.93g, 5.8mmol) was dissolved in HPLC Grade DMF (10cm^3) and the solution was cooled to -50°C. Sodium hydride (0.15g, 6.3mmol) was dissolved in HPLC Grade DMF (4cm^3) and also cooled to -50°C before being slowly added to the solution of the thiol. After stirring for 5 minutes at -50°C dibromodifluoromethane (1.8cm^3, 20mmol) was added and the mixture stirred for 1 hour (-50°C to +20°C). The solution was poured into a mixture of water and dichloromethane (30cm^3:30cm^3) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2*20cm^3) and the combined organic layers were washed with water (2*20cm^3) and dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure and the product (9-anthryl-difluorobromomethyl sulphide) was recrystallised from 80-100°C petroleum ether (0.36g, 40%); δ_F ($CDCl_3$, 56MHz) -22ppm.

(B) 9-Anthryldifluorobromomethyl sulphide (0.36g, 1.3mmol) was dissolved in dichloromethane (10cm^3) under nitrogen. Silver tetrafluoroborate (0.27g, 1.4mmol) was added and the

stirring solution was heated at reflux in the dark for 2 hours. The solution was then poured into a mixture of water and dichloromethane ($20cm^3 : 20cm^3$), the organic layer was separated and the aqueous layer was extracted with dichloromethane ($2*10cm^3$). The combined organic layers were washed with water ($2*20cm^3$), dried over anhydrous magnesium sulphate and the solvent was removed under reduced pressure leaving a colourless solid which was recrystallised from 80-100°C petroleum ether (0.51g, 39%) (Found: C, 64.5; H, 3.1; S, 11.2. Calc. for $C_{15}H_9SF_3$: C, 64.8; H, 3.2; S, 11.5%); δ_F ($CDCl_3$, 56MHz) -43ppm.

6.4.12 The C.S.A. Experiment

The solute (0.05mmol) and the chiral solvating agent (0.05-0.50mmol) {i.e. 1:1-1:10} were dissolved in a suitable deuterated solvent (d_6-benzene or d-chloroform) and the N.M.R. spectrum recorded.

6.5 Experimental for Chapter Five

6.5.1 The C.S.A. Experiment

The solute (0.05mmol) and the chiral solvating agent (0.05mmol) were dissolved in d_6-benzene and/or d_5-pyridine or d-chloroform and the ^1H N.M.R. spectrum recorded.

6.5.2 Chiral Solvating Agents

(R)-(-)-O-Acetylmandelic acid (69) (99%) Aldrich 25303-0
(S)-(+)-O-Acetylmandelic acid (69) (99%) Aldrich 25302-2

6.5.3 Chiral Solutes

(R)-(+)-Phenylethylamine (70) (98%) Aldrich 11554-1
(S)-(-)-Phenylethylamine (70) (98%) Aldrich 11556-8

(R)-(+)-N,N-Dimethylphenylethylamine (71)
(S)-(-)-N,N-Dimethylphenylethylamine (71)

(R)-(-)-Cyclohexylethylamine (72) Fluka A.G. 29285
(S)-(+)-Cyclohexylethylamine (72) Fluka A.G. 29287

(±)-Propranalol (73) (Glaxo Group Research)

(±)-Salbutamol (74) (Glaxo Group Research)

(±)-Adrenaline (75) (Glaxo Group Research)

(±)-Labetalol (76) (Glaxo Group Research)

(1S,2R)-(+)-Ephedrine (77) (99%) Aldrich 18742-9
(1R,2S)-(-)-Ephedrine (77) (99%) Aldrich 13491-0

(1S,2R)-(+)-N-Methylephedrine (78) (99%) Aldrich 28777-6
(1R,2S)-(-)-N-Methylephedrine (78) (99%) Aldrich 23521-0

(R)-(-)-1-Amino-2-propanol (79) Fluka A.G. 09281
(S)-(+)-1-Amino-2-propanol (79) Fluka A.G. 09283

(R)-2-Amino-3-methyl-1-butanol (80) Fluka A.G. 94674
(S)-2-Amino-3-methyl-1-butanol (80) Fluka A.G. 94672

Preparation of (71):

Phenylethylamine (29mg, 0.24mmol) was dissolved in methanol/water (2cm^3, 2:3, v/v) and methanoic acid (3.5cm^3, 93mmol) was added. The reaction mixture was heated at reflux for 18 hours. Hydrochloric acid (1M; 10cm^3) was then added and the solvent removed under reduced pressure, the hydrochloride salt was dissolved in water and the aqueous solution extracted with dichloromethane (2*20cm^3). The pH of the aqueous solution was adjusted to 10 by the addition of potassium hydroxide solution and then extracted with chloroform (2*50cm^3). The combined organic layers were washed with water (2*20cm^3), dried over magnesium sulphate and the solvent removed under reduced pressure to give a pale yellow oil (25mg, 69%).

Preparation of (73) [and (76)] from their hydrochlorides:

(±)-Propranolol hydrochloride (190mg, 0.64mmol) was dissolved in water ($4cm^3$) and potassium hydroxide solution (2M; $3cm^3$) was added. The mixture was extracted with chloroform ($2*3cm^3$) and the combined organic layers washed with water ($2*2cm^3$), dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure to give a colourless oil (134mg, 80%).

Preparation of (74) from the sulphate:

Salbutamol sulphate (113mg, 0.2mmol) was dissolved in water ($2cm^3$) and passed down an ion exchange column (BDH Amberlyst A26 Macroreticular, Strong Base {Type 1} Anion Exchange Resin). The solvent was removed as a methanol azeotrope to give a colourless oil (38mg, 80%).

APPENDICES

APPENDIX ONE

Spectrum Index

APPENDIX TWO

Research Colloquia, Seminars, Lectures and Conferences

The Board of Studies in Chemistry requires that each postgraduate research thesis contains an appendix, listing:

(1) all research colloquia, research seminars and lectures arranged by the Department of Chemistry during the period of the author's residence as a postgraduate student;

(2) lectures organised by Durham University Chemical Society;

(3) all research conferences attended and papers presented by the author during the period when research for the thesis was carried out;

(4) details of the postgraduate induction course.

(1) Lectures Organised by Durham University - 1984-1987

19.10.84 Dr. A. Germain (Languedoc, Montpellier)
"Aniodic Oxidation of Perfluoro Organic Compounds in Perfluoroalkane Sulphonic Acids"

* 24.10.84 Prof. R.K. Harris (Durham)
"N.M.R. of Solid Polymers"

28.10.84 Dr. R. Snaith (Strathclyde)
"Exploring Lithium Chemistry: Novel Structures, Bonding and Reagents"

* 7.11.84 Prof. W.W. Porterfield (Hampden-Sydney College)
"There is no Borane Chemistry (only Geometry)"

* 7.11.84 Dr. H.S. Munro (Durham)
"New Information from ESCA Data"

21.11.84 Mr. N. Everall (Durham)
"Picosecond Pulsed Laser Raman Spectroscopy"

* 27.11.84 Prof. W.J. Feast (Durham)
"A Plain Man's Guide to Polymeric Organic Metals"

* 28.11.84 Dr. T.A. Stephenson (Edinburgh)
"Some Recent Studies in Platinum Metal Chemistry"

* 12.12.84 Dr. K.B. Dillon (Durham)
"^{31}P N.M.R. Studies of some Anionic Phosphorus Complexes"

11.01.85 Emeritus Prof. H. Suschitzky (Salford)
"Fruitful Fissions of Benzofuroxanes and Isobenzimidazoles (Umpolung of o-Phenylenediamine)

* 13.02.85 Dr. G.W.J. Fleet (Oxford)
"Synthesis of some Alkaloids from Carbohydrates"

* 19.02.85 Dr. D.J. Mincher (Durham)
"Stereoselective Synthesis of some Novel Anthracyclinones related to the Anti-Cancer Drug Adriamycin and to the Steffimycin Antibiotics"

* 27.02.85 Dr. R. Mulvey (Durham)
"Some unusual Lithium Complexes"

6.03.85 Dr. P.J. Kocienski (Leeds)
"Some Synthetic Applications of Silicon-Mediated Annulation Reactions"

7.03.85 Dr. P.J. Rodgers (I.C.I. plc. Agricultural Division)
"Industrial Polymers from Bacteria"

* 12.03.85 Prof. K.J. Packer (B.P. Ltd./East Anglia)
"N.M.R. Investigations of the Stucture of Solid Polymers"

* 14.03.85 Prof. A. Katritzky F.R.S. (Florida)
"Some Adventures in Heterocyclic Chemistry"

20.03.85 Dr. M. Poliakoff (Nottingham)
"New Methods for Detecting Organometallic Intermediates in Solution"

* 28.03.85 Prof. H. Ringsdorf (Mainz)
"Polymeric Liposomes as Models for Biomembranes and Cells?"

* 24.04.85 Dr. M.C. Grossel (Bedford College, London)
"Hydroxypyridone Dyes - Bleachable one-dimensional Metals?"

* 25.04.85 Major S.A. Shackelford (U.S. Air Force)
"In Situ Mechanistic Studies on Condensed Phase Thermochemical Reaction Processes: Deuterium Isotope Effects in HMX Decomposition, Explosives and Combustion"

* 1.05.85 Dr. D. Parker (I.C.I. plc.)
"Applications of Radioisotopes in Industrial Research"

* 7.05.85 Prof. G.E. Coates (Formerly of University of Wyoming, USA)
"Chemical Education in England and America: Successes and Deficiencies"

8.05.85 Prof. D. Tuck (Windsor, Ontario)
"Lower Oxidation State of Indium"

8.05.85 Prof. G. Williams (U.C.W. Aberystwyth)
"Liquid Crystalline Polymers"

* 9.05.85 Prof. R.K. Harris (Durham)
"Chemistry in a Spin: Nuclear Magnetic Resonance"

* 14.05.85 Prof. J. Passmore (New Brunswick, USA)
"The Synthesis and Characterisation of some Novel Selenium-Iodine Cations, aided by ^{77}Se N.M.R. Spectroscopy"

15.05.85 Dr. J.E. Packer (Aukland, New Zealand)
"Studies of Free Radical Reactions in Aqueous Solution using Ionising Radiatioon"

17.05.85 Prof. I.D. Brown (McMaster University, Canada)
"Bond Valence as as Model for Inorganic Chemistry"

21.05.85 Dr. D.L.H. Williams (Durham)
"Chemistry in Colour"

* 22.05.85 Dr. M. Hudlicky (Blacksburg, USA)
"Preferential Elimination of Hydrogen Fluoride from Vicinial Bromofluorocompounds"

22.05.85 Dr. R. Grimmett (Otago, New Zealand)
"Some Aspects of Nucleophilic Substitution in Imidazoles"

* 4.06.85 Dr. P.S. Belton (Food Research Institute, Norwich)
"Analytical Photoacoustic Spectroscopy"

13.06.85 Dr. D. Woolins (Imperial College)
"Metal - Sulphur - Nitrogen Complexes"

* 14.06.85 Prof. Z. Rappoport (Hebrew University, Jerusalem)
"The Rich Mechanistic World of Nucleophilic Vinylic Substitution"

* 19.06.85 Dr. R.N. Mitchell (Dortmund)
"Some Synthetic and N.M.R. Spectroscopic Studies of Organotin Compounds"

* 26.06.85 Prof. G. Shaw (Bradford)
"Synthetic Studies on Imidazole Nucleosides and the Antibiotic Coformycin"

* 12.07.85 Dr. K. Laali (Hydrocarbon Research Institute, University of California)
"Recent Developments in Superacid Chemistry and Mechanistic Considerations in Electrophilic Aromatic Substitution: A Progress Report"

13.09.85 Dr. V.S. Parmar (University of Delhi)
"Enzyme Assisted ERC Synthesis"

* 30.10.85 Dr. S.N. Whittleton (Durham)
"An Investigation of a Reaction Window"

* 5.11.85 Prof. M.J. O'Donnell (Indiana-Perdue University)
"New Methodology for the Synthesis of Amino Acids"

* 20.11.85 Dr. J.A.H. MacBride (Sunderland Polytechnic)
"A Heterocyclic Tour on a Distorted Tricycle-Biphenylene"

28.11.85 Prof. D.J. Waddington (York)
"Resources for the Chemistry Teacher"

* 15.01.86 Prof. N. Sheppard (East Anglia)
"Vibrational and Spectroscopic Determinations of the Structures of Molecules Chemisorbed on Metal Surfaces"

* 29.01.86 Dr. J.H. Clark (York)
"Novel Fluoride Ion Reagents"

* 12.02.86 Prof. O.S. Tee (Concordia University, Montreal)
"Bromination of Phenols"

19.02.86 Prof. G. Procter (Salford)
"Approaches to the Synthesis of Natural Products"

26.02.86 Miss. C. Till (Durham)
"ESCA and Optical Emission Studies of the Plasma Polymerisation of Perfluoroaromatics"

* 5.03.86 Dr. D. Hathaway (Durham)
"Herbicide Selectivity"

* 5.03.86 Dr. M. Schröder (Edinburgh)
"Studies on Macrocycle Complexes"

* 12.03.86 Dr. J.M. Brown (Oxford)
"Chelate Control in Homogeneous Catalysis"

* 14.05.86 Dr. P.R.R. Langridge-Smith (Edinburgh)
"Naked Metal Clusters - Synthesis, Characterisation and Chemistry"

* 9.06.86 Prof. R. Schmutzler (University of Braunschweig)
"Mixed Valence Diphosphorus Compounds"

23.06.86 Prof. R.E. Wilde (Texas Technical University)
"Molecular Dynamic Processes from Vibrational Bandshapes"

* 29.10.86 Prof. E.H. Wong (University of New Hampshire, USA)
"Coordination Chemistry of P-O-P Ligands"

* 5.11.86 Prof. D. Döpp (University of Duisburg)
"Cyclo-additions and Cyclo-reversions Involving Captodative Alkenes"

26.11.86 Dr. N.D.S. Canning (Durham)
"Surface Adsorption Studies of Relevance to Heterogeneous Ammonia Synthesis"

3.12.86 Dr. J. Miller (Dupont Central Research, USA)
"Molecular Ferromagnets; Chemistry and Physical Properties"

* 8.12.86 Prof. T. Dorfmüller (University of Bielefeld)
"Rotational Dynamics in Liquids and Polymers"

28.01.87 Dr. W. Clegg (Newcastle-upon-Tyne)
"Carboxylate Complexes of Zinc; Charting a Structural Jungle"

4.02.87 Prof. A. Thomson (East Anglia)
"Metalloproteins and Magnetooptics"

11.02.87 Dr. T. Shepherd (Durham)
"Pteridine Natural Products; Synthesis and use in Chemotherapy"

* 17.02.87 Prof. E.H. Wong (University of New Hampshire, USA)
"Symmetrical Shapes from Molecules to Art and Nature"

* 4.03.87 Dr. R. Newman (Oxford)
"Change and Decay: a Carbon-13 CP/MAS N.M.R. Study of Humification and Coalification Processes"

11.03.87 Dr. R.D. Cannon (East Anglia)
"Electron Transfer in Polynuclear Complexes"

* 17.03.87 Prof. R.F. Hudson (Kent)
"Aspects of Organophosphorus Chemistry"

18.03.87 Prof. R.F. Hudson (Kent)
"Homolytic Rearrangements of Free Radical Stability"

* 3.04.87 Prof. G. Ferguson (University of Guelph, Ontario)
"Crystallographic Studies of Macrocycles"

* 6.05.87 Dr. R. Bartsch (Sussex)
"Low Co-ordinated Phosphorus Complexes"

7.05.87 Dr. M. Harmer (I.C.I. Chemicals and Polymer Group)
"The Role of Organometallics in Advanced Materials"

11.05.87 Prof. S. Pasynkiewicz (Technical University, Warsaw)
"Thermal Decomposition of Methyl Copper and its Reactions with Trialkylaluminium"

* 27.05.87 Dr. M. Blackburn (Sheffield)
"Phosphonates as Analogues of Biological Phosphate Esters"

* 24.06.87 Prof. S.M. Roberts (Exeter)
"Synthesis of Novel Antiviral Agents"

26.06.87 Dr. C. Krespan (E.I. Dupont de Nemours)
"Nickel(O) and Iron(O) as Reagents in Organofluorine Chemistry"

(2) Lectures Organised by Durham University Chemical Society - 1984-1987

18.10.84 Dr. N. Logan (Nottingham)
"N_2O_4 and Rocket Fuels"

* 23.10.84 Prof. W.J. Feast (Durham)
Synthesis of Conjugated Polymers. How and Why?"

8.11.84 Prof. B.J. Aylett (Queen Mary College)
"Silicon - Dead Common or Refined?"

* 15.11.84 Prof. B.T. Golding (Newcastle-upon-Tyne)
"The Vitamin B_{12} Mystery"

* 22.11.84 Prof. D.T. Clarke (I.C.I. New Science Group)
"Structure, Bonding, Reactivity and Synthesis as revealed by ESCA"
(R.S.C. Tilden Lecture)

29.11.84 Prof. C.J.M. Stirling (University College of North Wales)
"Molecules Taking the Strain"

* 6.12.84 Prof. R.D. Chambers (Durham)
"The Unusual World of Fluorine"

24.01.85 Dr. A.K. Covington (Newcastle-upon-Tyne)
"Chemistry with Chips"

* 31.01.85 Dr. M.L.H. Green (Oxford)
"Naked Atoms and Negligee Ligands"

* 7.02.85 Prof. A. Ledwith (Pilkington Bros.)
"Glass as a high Technology Material"
(Joint Lecture with the Society of Chemical Industry)

* 14.02.85 Dr. J.A. Salthouse (Manchester)
"Son et Lumiere"

* 21.02.85 Prof. P.M. Maitlis, F.R.S. (Sheffield)
"What Use is Rhodium?"

* 7.03.85 Dr. P.W. Atkins (Oxford)
"Magnetic Reactions"

* 17.10.85 Dr. C.J. Ludman (Durham)
"Some Thermochemical Aspects of Explosions"

* 24.10.85 Dr. J. Dewing (U.M.I.S.T)
"Zeolites - Small Holes, Big Opportunities"

* 31.10.85 Dr. P. Timms (Bristol)
"Some Chemistry of Fireworks"

* 7.11.85 Prof. G. Ertl (University of Munich)
"Heterogeneous Catalysis"
(R.S.C. Centenary Lecture)

* 14.11.85 Dr. S.G. Davies (Oxford)
"Chirality Control and Molecular Recognition"

* 21.11.85 Prof. K.H. Jack, F.R.S. (Newcastle-upon-Tyne)
"Chemistry of Si-Al-O-N Engineering Ceramics"

* 28.11.85 Dr. B.A.J. Clark (Research Division, Kodak Ltd.)
"Chemistry and Principles of Colour Photography"

* 23.01.86 Prof. Sir Jack Lewis, F.R.S. (Cambridge)
"Some More Recent Aspects in the Cluster Chemistry of Ruthenium and Osmium Carbonyls"
(The Waddington Memorial Lecture)

* 30.01.86 Dr. N.J. Phillips (Loughborough)
"Laser Holography"

* 13.02.86 Prof. R. Grigg (Queens University, Belfast)
"Thermal Generation of 1,3-Dipoles"
(R.S.C. Tilden Lecture)

* 20.02.86 Dr. C.F.J. Barnard (Johnson Matthey Group Research)
"Platinum Anti-Cancer Drug Development - from Serendipity to Science"

* 27.02.86 Prof. R.K. Harris (Durham)
"The Magic of Solid State N.M.R.

* 6.03.86 Dr. B. Iddon (Salford)
"The Magic of Chemistry"

* 16.10.86 Prof. N.N. Greenwood (Leeds)
"Glorious Gaffes in Chemistry"

23.10.86 Prof. H.W. Kroto (Sussex)
"Chemistry in Stars, Between Stars and in the Laboratory"

* 30.10.86 Prof. D. Detteridge (B.P. Research)
"Can Molecules Talk Intelligently?"

6.11.86 Dr. R.M. Scrowston (Hull)
"From Myth and Magic to Modern Medicine"

* 13.11.86 Prof. Sir G. Allen (Unilever Research)
"Biotechnology and the Future of the Chemical Industry"
(Joint Lecture with the Society of Chemical Industry)

20.11.86 Dr. A. Milne and Mr. S. Christie (International Paints)
"Chemical Serendipity - A Real Life Case Study"

27.11.86 Prof. R.L. Williams (Metropolitan Police Forensic Science)
"Science and Crime"

* 22.01.87 Prof. R.H. Ottewill (Bristol)
"Colloid Science - a Challenging Subject"

5.02.87 Dr. P. Hubbersley (Nottingham)
"Demonstration Lecture on Various Aspects of Alkali Metal Chemistry"

12.02.87 Dr. P.J. Rodgers (I.C.I. Billingham)
"Industrial Polymers from Bacteria"

* 19.02.87 Dr. M. Jarman (Institute of Cancer Research)
"The Design of Anti-Cancer Drugs"

* 5.03.87 Prof. S.V. Ley (Imperial College)
"Fact and Fantasy in Organic Synthesis"

9.03.87 Prof. F.G. Bordwell (Northeastern University, USA)
"Carbon Anions, Radicals, Radical Anions and Radical Cations"
(R.S.C. Ingold Lecture)

* 12.03.87 Dr. E.M. Goodger (Cranfield Institute of Technology)
"Alternative Fuels For Transport"

(3) Research Conferences Attended

19.12.84 18th Sheffield Symposium on "Modern Aspects of Stereochemistry", University of Sheffield.

11.12.85 Royal Society of Chemistry, Newcastle and North East section, General Poster Meeting, University of Newcastle-upon-Tyne.

3.05.87 to 9.05.87
23rd EUCHEM Conference on Stereochemistry, Bürgenstock, Central Switzerland.

6.07.87 to 10.07.87
Royal Society of Chemistry 8th International Meeting on N.M.R. Spectroscopy, University of Kent at Canterbury.

(4) First Year Induction Course - October 1984

This course consists of a series of one hour lectures on the services available in the department.

(a) Departmental organisation.

(b) Safety matters.

(c) Electrical appliances and infrared spectroscopy.

(d) Chromatography and microanalysis.

(e) Atomic absorptiometry and inorganic analysis.

(f) Library facilities.

(g) Mass spectrometry.

(h) Nuclear magnetic resonance spectroscopy.

(i) Glassblowing technique.

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