Chiral analysis by NMR spectroscopy

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Chiral Analysis by NMR Spectroscopy

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Declaration

The work contained herein was carried out between the dates of October 1989 to November 1992, in the Department of Chemistry, Science Laboratories, at the University of Durham. Unless otherwise stated the research described here is original, and has not been duplicated in any other establishment.

Abstract

The analysis of the enantiomeric purity of chiral carboxylic acids requires a reagent to give acceptable NMR chemical shift non-equivalence with a wide range of substrate acids. Extensive studies of the behaviour of N-mono-methyl, N,N-dimethyl and cyclic amines as chiral solvating agents led to the finding that 1,2 diphenyl-1,2-diaminoethane can induce substantial non-equivalence in the diastereomeric salts of chiral α-phenyl and α-halo carboxylic acids. The diastereoisomeric complexes of the diamine with primary carboxylic acids (RCH_2CO_2H) presents an unusual case in which the internally enantiotopic methylene protons are rendered internally diasteretopic by an external non-covalently bonded reagent. Investigations of the physical parameters determining non-equivalence (stoichiometry, concentration, temperature and substrate enantiomeric purity), combined with NOE observations of the diastereomeric pairs and the crystal structure of the mono-hydrobromide salt were used to suggest the structure for the conformation responsible for shift non-equivalence.

The zero valent platinum complex, 3-0-isopropylidene-2,3-dihydroxy-1,4-bis(diphenyl-phosphino)butane-platinum(0)-ethene (DIOP-Pt-ethene) was shown to be a versatile chiral derivatising agent for electron poor and strained η^2-donors. This was demonstrated by the enantiomeric purity determinations for alkynes, enones and norbornene derivatives. The crystal structure of DIOP-Pt-ethene was determined and found to be similar to the palladium analogue.

If the achiral rhodium complex rhodium(I)-acetylacetone-diethene undergoes a reaction with 2 equivalents of a suitable chiral η^2-donor, it will result in the formation of 4 stereoisomers, two meso forms and a pair of enantiomers. The diasteroisomers should display chemical shift non-equivalence in the NMR spectrum of the product, reflecting the enantiomeric purity of the η^2-donor (self recognition). The derivatisation of rhodium(I)-acetylacetone-diethene with chiral η^2-donors was attempted.

Abbreviations

CDA	-	Chiral Derivatising Agent
CLSR	-	Chiral Lanthanide Shift Reagent
CMPA	-	Chiral Mobile Phase Additive
CSA	-	Chiral Solvating Agent
CSP	-	Chiral Stationary Phase
DPDAE	-	1,2-DiPhenyl-1,2-DiAminoEthane
GC	-	Gas Chromatography
HPLC	-	High Pressure Liquid Chromatography
LSR	-	Lanthanide Shift Reagent
MA	-	Mandelic Acid
MBCA	-	2-Methoxy-1,1'-Binaphthyl-2-Carboxylic Acid
MTPA	-	α-Methoxy-α-Trifluoromethyl-2-Phenylethanoic Acid
NMR	-	Nuclear Magnetic Resonance
OAM	-	O-Acetyl Mandelic acid
THF	-	TetraHydroFuran
ee	-	enantiomeric excess
$\Delta\delta$	-	Chemical shift non-equivalence

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First and foremost I would like to express my thanks to Professor David Parker for all the help and encouragement over the past three years, and to express my gratitude to Dr Dave O'Hagan for the gift of reagents and helpful suggestions. I would also like to acknowledge the dedication of the technical staff, particularly Dr Ray Mathews, Dr Alan Kenwrght and especially Julia Say for NMR analysis, I also thank Professor George Ferguson for X-ray crystallography, Dr Euan Ross,Tom Caygill and Jim Lincoln (who gives a whole new meaning to the word 'service').

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To my sisters, my parents and that undervalued and misunderstood group of people scientists.

Contents

CHAPTER 1

Introduction

1.1 Chirality: A Brief Review of Enantiomeric Discrimination

The increasing interest in asymmetric synthesis has sustained interest in techniques for the production of chiral reagents. Such reagents require accurate and reliable methods of enantiomeric analysis. The pharmaceutical industry under regulations imposed by the E.C. in Europe and by the F.D.A. in the USA will be required to market chiral drugs as a single enantiomer. This is reasonable when it is considered that potential drugs with chiral centres can give enantiomers with different pharmacological responses. One enantiomer may possess the desirable properties whilst the other may be at best ballast or at worst may exhibiting potentially harmful side effects. S-Warfarin 1 is an anticoagulant with six times the activity of its R-enantiomer, whilst S-propanolol 2 is used as an antihypertensive and antiarythmic but the R-enantiomer acts as a contraceptive!

There is a clear requirement for enantiomeric discrimination and enantiomeric excess determination in clinical pharmacology and pharmacokinetics where assignment of activity due to particular enantiomeric composition is often absent [1].

The methods of chiral analysis are varied [2, 3] but most require the intervention of a chiral auxiliary to convert the enantiomeric mixture into a mixture of diastereoisomers with different physical properties. The wide range of techniques available permit a degree of choice in the measurement of enantiomeric purity. It is desirable that at least two of these methods are used to avoid any discrepancy between actual and observed enantiomeric composition arising from the systematic error of the procedure.

The rest of this section will summarise the chromatographic and spectroscopic techniques routinely used to determine enantiomeric excess. Further emphasis will be placed on NMR methods of analysis in the following sections.

1.1.1 Chiroptical Methods

Polarimetry, optical rotatory dispersion and circular dichroism methods are often used in the assignment of absolute configuration and the determination of enantiomeric purity. The measurement of enantiomeric purity involves recording the optical rotation (α) of a sample of known concentration, solvent temperature and wavelength of the incident plane-polarised light. The specific optical rotation defined in (1) is used to determine optical purity, (2).

$$[\alpha]_D^t = \frac{[\alpha]_D^{obs}}{l\rho} \quad -(1).$$

$$\text{Optical purity} = \frac{[\alpha]_D^t}{[\alpha]_{DMax}^t} \times 100 \quad -(2).$$

$[\alpha]_D^t$ - Specific rotation of Sodium D line at temperature t

l - Path lengh (dm)

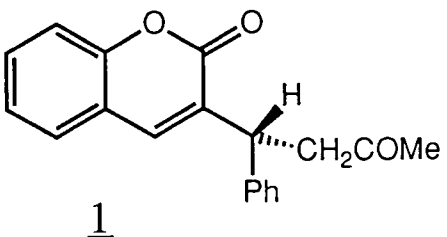
ρ - Density of solution $g.dm^{-3}$

$[\alpha]_{DMax}^t$ - Absolute optical rotation for pure enantiomer.

This is an essentially simple and straightforward technique, but it suffers from several problems. Enantiomeric purity and optical purity are not always consistent. For example optical purity may not vary linearly with enantiomeric purity with 2-methyl-2-ethyl-butanoic acid [4] in non-polar solvents. Reports of inconsistencies of optical purity with enantiomeric purity in polar solvents have also been noted [5].

To determine optical purities the maximum rotation of the pure enantiomer must be known. There are, however, numerous examples of incorrect optical rotations quoted in the literature. Consider (+)-3-methyl cyclopentene 3 before 1974 $[\alpha]_D^{20} = +78°$. After having used a chiral gas chromatographic method [6] the rotation was revised upwards $[\alpha]_D^{20} = +174.5°$. The enone 4 has an optical rotation $[\alpha]_D^{20} = +34°$ (C. 1.0, $CHCl_3$) [7] but it has also been reported to have a negative rotation $[\alpha]_D^{20} = -115.4°$ (C. 0.2, $CHCl_3$) [8].

Large samples must often be used to give measurable optical rotations (particularly with compounds chiral by virtue of isotopic substitution) and it is not always possible to correlate absolute configuration with the sense of optical rotation.



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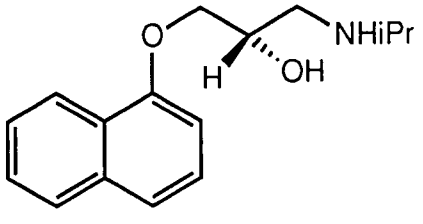

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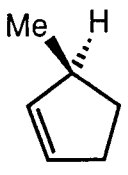

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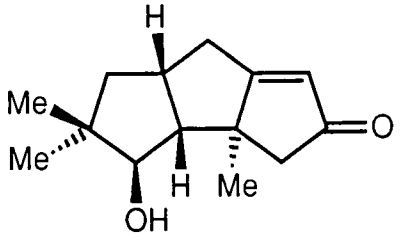

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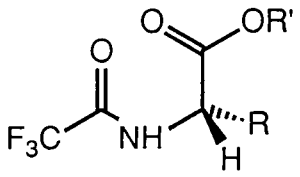
1.1.2 Gas Chromatography (GC)

Gas chromatography offers a sensitive and accurate method of chiral analysis [9]. A chiral auxiliary is required to separate the enantiomers. The method may involve the formation of diastereomers [10, 11] which are separated on a stationary phase. Alternatively a chiral auxiliary can be bound to the stationary phase and resolution is brought about by diastereomeric interactions between the chiral analyte and a chiral stationary phase (CSP). *Gil-Av* performed the first resolution with the CSP N-tri-fluoroacetyl-i-isoleucine lauryl ester 5 (coated on a glass capillary column) on esters of N-trifluroacetyl-amino acids [12]. Care must to taken to avoid racemisation or kinetic resolution during diastereomer formation. The resolving agent must be enantiomerically pure or an error between actual and calculated purities will arise. The detector must of course respond equally to both diastereoisomers. The diastereoisomers formed must be sufficiently volatile and possess sufficient thermal stability to allow GC analysis.

GC utilising a CSP is preferred because it suffers from fewer sources of error. The detector responds equally to both enantiomers, and the entiomeric purity of the chiral stationery phase will only perturb the size of the separation factor α (defined by equation (3)).

$$\alpha = \frac{K_2}{K_1} \qquad \text{- (3)}$$

K = additional volume above the void volume of the column required to elute the sample divided by the void volume of the column.



R = sec-Butyl
R' = dodecyl

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Absolute configuration can be correlated with enantiomer elution order for closely related series on specific CSP [12-15]. The major disadvantage with this method is that the substrate must have sufficient volatility and thermal stability. This requires pre-derivatisation in many cases which at worst leads to racemisation, and at best is tedious.

1.1.3 High Pressure Liquid Chromatography (HPLC)

Liquid chromatography is now a popular technique for chiral analysis [16,17,18] and is amenable to most chiral substrates. The separation of enantiomers requires the intervention of a chiral auxiliary and can be carried out in one of three ways. The first indirect method involves derivatisation with a chiral agent followed by chromatographic separation of the diastereoisomers. The second involves direct analysis with a chiral auxiliary bound to the stationary phase (CSP). Finally a chiral auxiliary may be added to the achiral solvent creating a chiral mobile phase additive (CMPA). Diastereomeric complexes are formed in situ which elute at different rates.

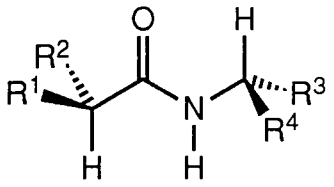
Helmchen carried out the early work on indirect resolution [19-21] with diastereomeric amide derivatives such as 6 on silica and alumina columns with separation factor $\alpha = 2.5$. *Pirkle* [22-25] analysed diastereomeric carbamates of general structure 7 derived from chiral alcohols and

isocyanates or chloroformates and amines. The separation factor was on average $\alpha = 1.5$. After resolution the chiral substrate may be recovered. Analogously to GC derivatisation, the chiral auxiliary must not undergo kinetic resolution or racemisation during the derivatisation reaction. A reduction in the enantiomeric purity of the chiral derivatising agent will reduce the observed enantiomeric purity.

Direct resolution on a CSP is usually achieved by binding a chiral auxiliary on to an achiral polymeric support, but there are now a large number of reported cases of direct resolution with chiral polymeric supports [26] or with polymeric supports which possess chiral cavities [27, 28]. There is a wealth of data relating to synthetic chiral stationary phases [18]. Most of this data supports the "three point mechanism" wherein the CSP must possess a minimum of three binding interactions, one of which is stereochemical, to bring about chiral recognition.

This model has been questioned by *Topiol* [29], who suggested that one or two point mechanisms may also be operating in competition.

Gil-AV [30] and *Linder* [31] had early success in resolving amino acids with chiral mobile phase additives comprising amino acids, amino acid derivatives or chiral amines. The separation mechanism is complex and the technique is rarely used since it required a constant supply of the CMPA to be in the mobile phase.



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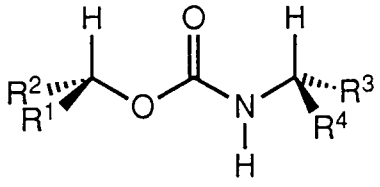

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1.1.4 Analysis by NMR Spectroscopy

Introduction and Historical Perspective

The NMR analysis of chiral substrates can be accomplished by one of three techniques [32] involving either chiral lanthanide shift reagents (CLSR), chiral solvating agents (CSA) [33], or chiral derivatising agents (CDA). Each method requires a chiral auxiliary to induce magnetic non-equivalence in the enantiomeric substrate.

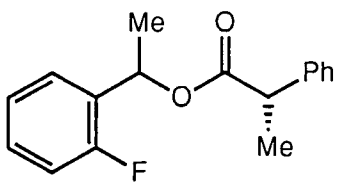
Chiral derivatising agents react with substrate enantiomers to form discrete diastereoisomers. *Mislow* and *Raban* first reported chemical shift non-equivalence ($\Delta\delta$) in esters of 1-(2-fluorophenyl)-ethanol with the CDA 1-methylphenylethanoic acid [34]. The proton NMR spectrum showed $\Delta\delta = 0.09$ ppm (CCl_4) for the methyl group of the substrate in diastereoisomer 8.

Chemical shift non-equivalence with CDA's can be large, usually 5 times greater than with the corresponding chiral solvating agent. Kinetic resolution and racemisation of the CDA must be avoided during derivatisation. The chance of kinetic resolution can be minimised by using an excess of the chiral derivatising agent. Racemisation during the use of a CDA is usually avoided by careful design of the CDA and of the methods used in derivatisation. The CDA must be enantiopure for accurate enantiomeric excess determinations. A reduction in the enantiomeric purity of the CDA will reduce the derived enantiomeric excess value.

Chiral lanthanide shift reagents and chiral solvating agents form association complexes in solution with the chiral substrate. These chiral complexes are in rapid equilibrium with the uncomplexed reagents. *Mislow* and *Raban* first suggested that enantiomers could be distinguished if a chiral solvent was used [34]. The first examples were reported by Pirkle [35, 36] with the CSA α-methylbenzylamine acting as the solvent for 1-phenyl-2,2,2-trifluoroethanol, 9, ($\Delta\delta$ =0.04 ppm for the -CF_3 group in ^{19}F NMR).

Normally only 2-3 equivalents of CSA to substrate are used. The components are dissolved in a polar, non-protic NMR solvent (eg CCl_4, $CDCl_3$ or C_6D_6). The method is quick, convenient and the enantiomeric purity of the CSA has no effect on the observed enantiomeric purity. Peak intensities remain the same but the effect of decreasing CSA enantiomeric purity is to decrease the size of the chemical shift non-equivalence, $\Delta\delta$. The size of this non-equivalence is small compared to those obtained with a CLSR or a CDA.

Whitesides and *Lewis* [37] first applied chiral lanthanide shift reagents to enantiomeric purity determination using the CLSR Eu(pvc)$_3$ 10. Large $\Delta\delta_H$ was observed with α-phenylethylamine for the methyl, methine and ortho aromatic protons. Chiral lanthanide shift reagents may suffer from solubility problems and are prone to decomposition, Hydrolysis for example leads to formation of Eu_2O_3 which causes excessive line-broadening. These reagents are best used at low or medium NMR field strengths. At higher fields exchange line-broadening (proportional to B_0^2) may be excessive.



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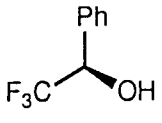

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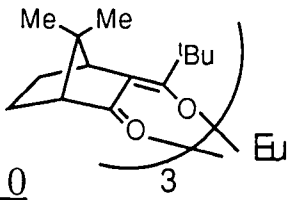

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1.2 NMR Methods of Analysis

The popularity of the NMR assay of Enantiomeric composition is reflected in the literature by the wide range and rich diversity of chiral reagents and substrates tested.

There are several comprehensive reviews detailing the progress and the use of CDA, CLSR and CSA [32, 33, 40]. The following sections will discuss recent developments in each of these areas.

1.2.1 Chiral Derivatising Agents

Derivatisation of an enantiopure compound with a mixture of enantiomers yields distinct diastereoisomers. To maximise chemical shift non-equivalence, a minimum of two interactions, one of which is stereospecific must be present (**Figure 1**).

a b

a) Ph - R^1 Stereospecific interactions
b) Ph - R^2

Figure 1 Esters derived from mandelic acid [38].

As mentioned before, derivatisation must exclude the possibility of racemisation or kinetic resolution i.e. the rates of diastereomer formation must be similar.

This effect may be minimised by the addition of an excess of the derivatising agent. Purification must proceed without the selective enrichment of one diastereomer. Purification by means of chromatography is generally used instead of crystallisation.

1.2.1.1 CDA's for ^{1}H and ^{19}F NMR Analysis

Acids

Mosher's reagent, α-methoxy-α-trifluoromethyl-2-phenyl-ethanoic acid (MTPA) 11, first published in 1969 [39] is the most utilised CDA in ^{1}H and ^{19}F NMR. Unable to undergo racemisation due to the lack of a α-hydrogen, it is used principally in the analysis of chiral amines and 1°, 2° alcohols by derivatisation with the chiral acid or acid chloride [40-47]. Chemical shift non-equivalence $\Delta\delta_H$ is usually in the order of 0.1 - 0.2 ppm and $\Delta\delta_F$ = 0.3 - 0.7 ppm ($CDCl_3$, 298K). MTPA has undergone kinetic resolution in only isolated occasions (e.g. with timolol 12 [43] or the enone 13 [44]) and is usually reliable. It has recently been applied to the analysis of absolute configuration. *Kakisawa* has examined various synthetic and natural substrates [48-52] by the application of "Mosher's model" (**Figure 2a**). In this model the carbinyl hydrogen, C-O carbonyl bond and the trifluoro methyl group lie in the same plane. The R_1 group in the S-MTPA derivative will be subject to diamagnetic shielding of the benzene ring and hence will appear to lower frequency relative to the R-MTPA derivative.

The enantiopure substrate is reacted with both MTPA enantiomers then resonances from the R-MTPA derivative are subtracted from the S-MTPA derivative to give $\Delta\delta$ ($\Delta\delta = \delta_S - \delta_R$). The $\Delta\delta$ values will be positive on the right hand side of the MTPA plane and negative on the left hand side (**Figure 2b**). This is due solely to the shielding effect of the phenyl moiety.

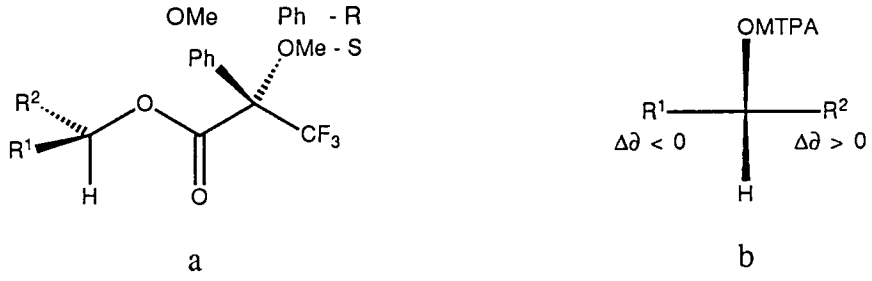
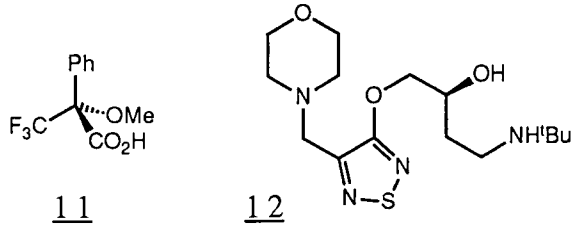
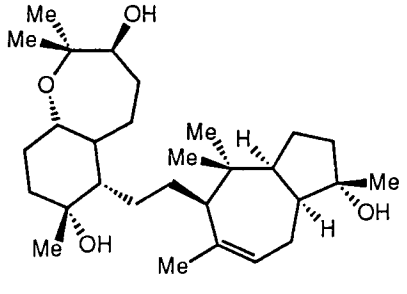
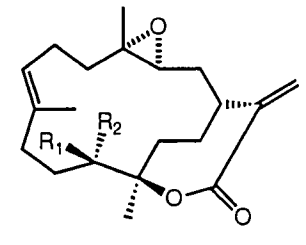


Figure 2

Substrates such as Sipholenol-A 14, Sinulariolide 15a and 11-episinulariolide 15b which contain a sterically hindered secondary hydroxyl group are not amenable to MTPA analysis of configuration [48, 49, 50]. Steric crowding of the MTPA groups forces it into a non-ideal conformation, producing irregular results. A suggested solution to this problem is to invert the hydroxy group into a less hindered position, although this might not be possible in all cases.



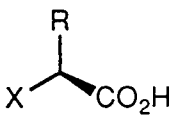




15 a) $R_1 = H$, $R_2 = OH$
b) $R_1 = OH$, $R_2 = H$

Many analogues of MTPA have been prepared 16a-j [53-55], 17 [56] with the intention of improving $\Delta\delta$ and enhancing reactivity. This has only been partially successful. Most analogues studied undergo racemisation under the reaction conditions required for sterically hindered alcohols and many α-fluorometic acid derivatives, e.g. 16f-j, are highly toxic requiring special handling [54,55].

The continuing popularity of MTPA overshadows alternative carboxylic CDA, for instance O-methyl mandelic acid [57-59] 18 and O-acetyl mandelic acid [60] 19. These CDA's often give bigger $\Delta\delta_H$ than the equivalent MTPA derivatives. The chiral derivatising agent Camphanic acid [61-63] 20 and more recently 2'-methoxy-1,1'-binaphthyl-2-carboxylic acid [64] 21 (MBCA), also both give consistent results for a range of enantiomeric alchohols and amines. They sometimes require the addition



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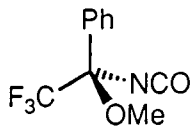
a) R = Ph , X = OMe
b) R = Ph , X = ^{t}Bu
c) R = Ph , X = CF_3
d) R = Ph , X = OH
e) R = Ph , X = Cl
f) R = SPh , X = F
g) R = Ph , X = F
h) R = OPh , X = F
i) R = CH_2Ph , X = F
j) R =Ph , X = CN



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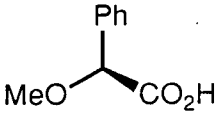

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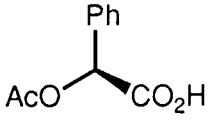

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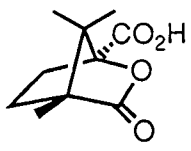

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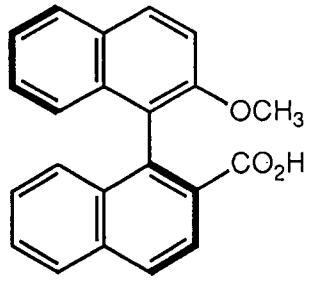

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of an achiral lanthanide shift reagent to enhance $\Delta\delta$ ($Eu(fod)_3$, fod = 6,6, 7,7, 8,8,8 -heptafluro-2,2-dimethyl-3,5-octanedione). The MBCA derivative of menthol 22 has a value of $\Delta\delta_H$ = 0.05 ppm (C_6D_6) for MeO- proton. This increases when 1 equivalent of $Eu(fod)_3$ is added, to $\Delta\delta_H$ = 0.70 ppm.

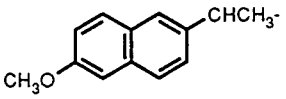
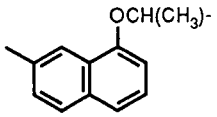
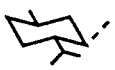
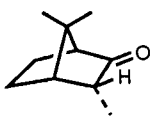
1.2.1.2 Amines and alcohols

Chiral amines are mainly used in the analysis of enantiomeric carboxylic acids, via the formation of the corresponding diastereomeric amides. An early example is α-Phenylethylamine [65, 66] 23 which was used for ^1H NMR enantiomeric analysis. Later the CDA 2-Fluoro-2-phenyl-ethylamine [67] 24 was examined and an MTPA analogue 2,2,2-Trifluoro-1-phenethylamine [68] 25 was studied by Mosher. Both used ^{19}F NMR and $\Delta\delta_F$ values for 24 ranged from 0.1 - 0.6 ppm ($CDCl_3$, 298K) while 25 had smaller values 0.05 - 0.092 ppm ($CDCl_3$, 298K), **Table 1**. Methyl mandelate 26 has been used as a CDA for carboxylic acids [60, 70, 71]. Typical values of $\Delta\delta_H$ = 0.2 ppm for diastereomeric esters were observed.

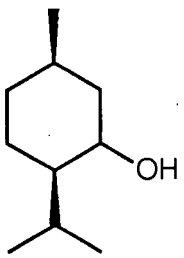
Chiral 1,2-diaryldiamines 27 have been used in the analysis of carbonyl compounds by the formation of diastereoisomeric imidazolidines [72,73]. This diamine fails to react with ketones restricting its use to chiral aldehydes. Chemical shift non-equivalence ranges from 0.04 - 0.17 ppm (C_6D_6) for ^{19}F NMR, and ^1H NMR analysis gave an average value in the range 0.08 - 0.16 ppm (C_6D_6). Chiral diols e.g. butan-2,3-diol and pentan-2,4-diol [74-77] have similarly been used in the analysis of carbonyl compounds operating via formation of diastereomeric 1,3-dioxolanes.

Table 1

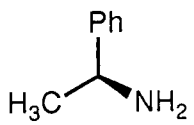
^{19}F Chemical shift non-equivalence data for derivatives of 24 and 25.

Entry	$R^1-C(=O)-NHCH(CF_3)Ph$[a] R^1	$\Delta\partial_F$[b] ppm	$R^2CHR^3-C(=O)-NHCH_2CHFPh$[c] R^2	R^3	$\Delta\partial_F$[d] ppm
1.	$PhCH(OCH_3)$-	0.050	Ph	F	0.62
2.	PhCH(OAc)-	0.070	Ph	$OCOCH_3$	0.56
3.	$PhCH(CH_3)$-	0.089	Ph	OH	0.48
4.		0.088	iPr	$NHCOCF_3$	0.28
5.		0.066	Ph	$NHCOCH_3$	0.23
6.	$PhC(OCH_3)(CF_3)$-	0.087	CH_3	$NHCOCF_3$	0.30
7.		0.092	Ph	CH_3	0.17
8.		0.084	C_2H_5	CH_3	0.10

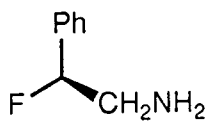
a) Observed at 400 MHz in $CDCl_3$. The diatereoisomers resonate in the range 4.015 to 3.538 ppm (relative to CF_3CO_2H external standared).
b) $\Delta\partial_F$ is defined as the differance between R-acid; S-amine and R-acid; R-amine diastereoisomers.
c) Observed at 94.18 MHz in $CDCl_3$. The diatereoisomers resonate in the range -22.45 to -21.48 ppm (relative to C_6F_6).
d) $\Delta\partial_F$ is defined as the differance between enantiopure amine and R/S acid.



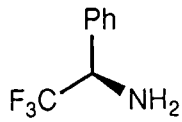
22



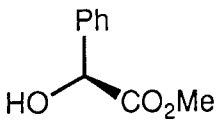
23



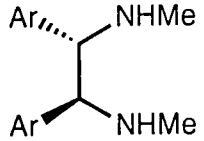
24



25



26



27

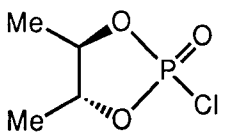
a) Ar = C_6H_5
b) Ar = o-$CF_3C_6H_4$
c) Ar = m-$CF_3C_6H_4$
d) Ar = p-$CF_3C_6H_4$

1.2.1.3 CDA for ^{31}P NMR Analysis

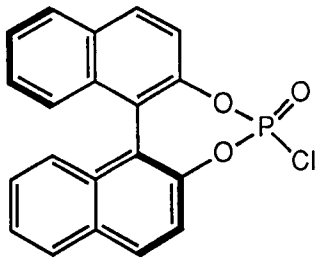
There are several distinguishing features that make phosphorus-31 NMR desirable in the NMR determination of enantiomeric purity. The sensitivity of the nucleus is quite high with a large chemical shift dispersion. The availability of broad-band proton decoupling reduces the complexity of the spectrum. Usually only signals for the diastereoisomers are observed with no interference from other peaks. A number of reagents with similar structures have been examined. Chlorodioxaphospholane 28 [78] for instance is a CDA for enantiomeric 1° and 2° alcohols and gives $\Delta\delta_P$ 0 - 0.13 ppm ($CDCl_3$). The binaphthyl 29 [79] forms diasteroisomeric phosphates with larger $\Delta\delta_P$ in the presence of 1-methylimidazole. For both these reagents derivatisation with an enantiopure alcohol produces only one diastereoisomer due to the enantiotopic nature of the phosphorus atom which results from the C_2 symmetry of the molecule.

The chiral derivatising agent 30 [80] derived from (1R,2S)-ephedrine reacts with chiral amines and alcohols usually with retention of configuration [81] although some stereochemical scrambling is possible [82]. Values of $\Delta\delta_H$ for the thio analogue are larger than for the equivalent phosphate and typically range from 0.11-0.84 ppm.

Investigations by *Alexakis* [83, 84] have led to the evaluation of several phosphorus(V) 31a-e and phosphorus(III) 32a-c based CDA's. The reactivity of reagents 31a-e with many simple enantiomeric alcohols was very low. The lithium or sodium alkoxide was formed therefore (nBuLi or NaH) before adding the phosphorus(V) CDA, followed by reflux in THF for 2-6 hours. Although this solved the problem of reactivity, no reaction was seen with hindered secondary or tertiary alcohols. The strongly basic conditions made it impracticable to analyse C-silylated propargylic alcohols e.g. 33 due to partial



28



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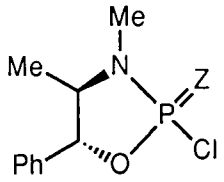
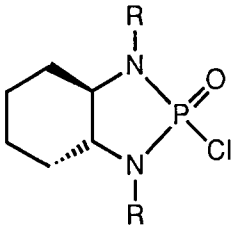
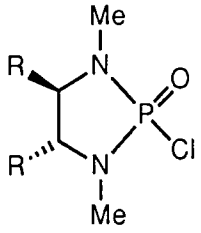


30

Z = O or S



a) R = iPr
b) R = Me



c) R = Ph
d) R = Ph
e) R = p-$CF_3C_6H_4$

31

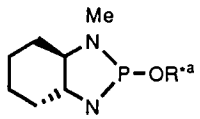
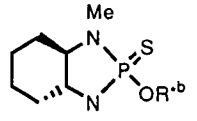
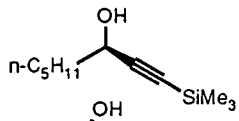
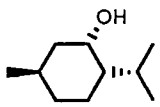
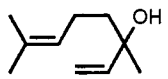
desilylation. The reagent 31e gave the largest $\Delta\delta_P$ with 2-Butanol $\Delta\delta$ = 0.54 ppm (C_6D_6) although its applicability to other chiral alcohols was not stated. The reagent 31b gave consistent results with both 1° and 2° alcohols ($\Delta\delta_P$ = 0.34-1.3 ppm).

The high reactivity of chiral phosphorus(III) CDAs 32a-c under mild reaction conditions (Toluene, RT., 2-15 hours) makes these reagents of more general use in analysis. The largest chemical shift non-equivalence was observed with 32c (**Table 2** gives selected data for 1°, 2° and 3° alcohols). Reactions of the air sensitive derivatives 32c with sulphur yield diastereomeric thiophosphorimidates, which are air stable and suitable for GC analysis, but have reduced $\Delta\delta_P$ values. Problems were encountered with diols and some alkyne and allene functionalised alcohols which underwent rearrangement or further reactions.

Analysis of chiral ketones with a chiral hydrazine CDA 34 [85], has met with limited success and only some chiral monosubstituted cyclohexanones have been studied.

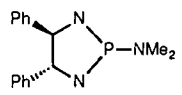
Table 2

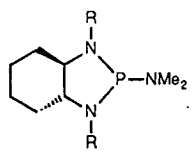
^{31}P Chemical shift non-equivalence data for derivative of 32 with 1°, 2° and 3° alcohols.

Entry	 R=	$\Delta\partial_P$ ppm	 ppm
1.	$PhCH(CH_3)CH_2OH$	0.673	0.065
2.	$nBuCH(CH_3)CH_2OH$	0.539	0.016
3.	$(CH_3)_2CCHCH_2CH_2CH(CH_3)OH$	0.538	0.032
4.		1.750	0.024
5.	$PhCH(OH)CHCl_2$	12.182	1.010
6.	$PhCH(OH)C(CH_3)N(CH_3)_2$	11.442	1.386
7.		16.221	0
8.		6.192	0.606
9.	$CH_3CH_2CCH_3(OH)Ph$	1.728	0.118
10.		0.606	0

a) ^{31}P NMR spectra were recorded at 36.22 MHz in C_6D_6. The diastereomeric resonances were in the range of 147.061 to 130.840 ppm.

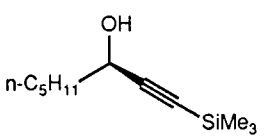
b) ^{31}P NMR spectra of the Thio derivative were recorded at 36.22 MHz in C_6D_6. The diastereomeric resonances were in the range of 88.427 to 85.600 ppm.

a) 

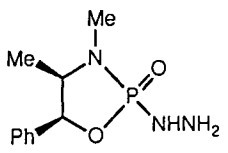


b) R = iPr
c) R = Me

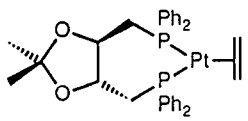
32



33



34



35

The achiral reagent PCl_3 introduced by *Feringa*[86] will react with 2 equivalents of a chiral alcohol or thiol to produce *two meso*-forms and a *pair of enantiomers*, **Figure 3**. Recognition derives only from the combination of interactions of the enantiomeric substrates. For instance 1-phenyl-1-propanol will react with PCl_3 in pyridine to yield four isomers $(R^*O)_2PHO$, which give three singlets in the ^{31}P NMR spectrum: Two for the *meso* form and one for the *2 enantiomers*. It has been suggested recently that formation of the equivalent tri ester will impart greater accuracy in enantiopurity measurements[87]. Feringa has continued this work with the introduction of several phosphorus analogues[88-90] with increased $\Delta\delta_P$. The reagents $MePOCl_2$ and $MePSCl_2$ give rise to typical values of $\Delta\delta_P$ = 0.5 ppm ($CDCl_3$)[88].

The organometallic CDA 35 has been devised for the ^{31}P NMR analysis of chiral 2-electron donors such as alkenes, alkynes and allenes. The zero valent DIOP-platinum and palladium ethene complexes were studied[91-93]. Displacement of ethene with electron-poor or strained alkenes, alkynes or allenes in situ (THF or C_6D_6) followed by subsequent ^{31}P NMR analysis gives good $\Delta\delta$ for the diastereomeric complexes.

The enantiomeric purity of α-amino-phosphonic acids has been analysed by the formation of their palladium(II) complexes with $PdCl_4^{2-}$ in D_2O[44]. This yielded a single *meso* diastereoisomer and an *enantiomeric pair* 36 for which $\Delta\delta_P$ = 0.1 ppm (pD 8.5, 298K).

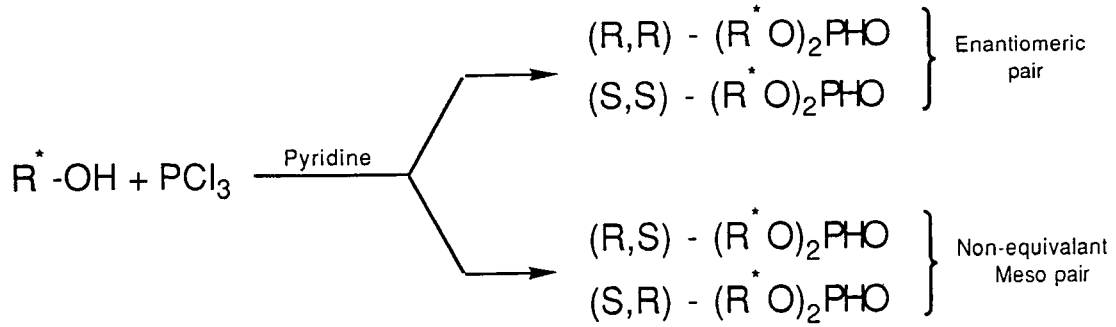
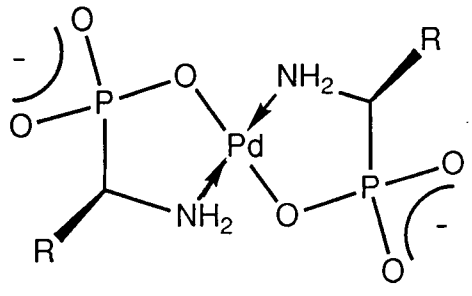


Figure 3

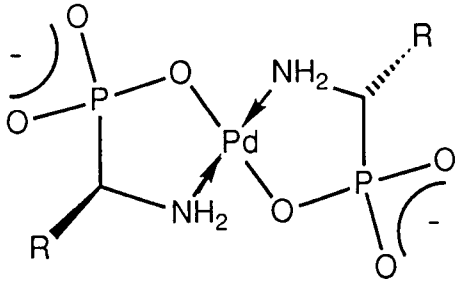
1.2.1.4 CDA's for NMR Analysis of Other Nuclei.

Diphenyldichlorosilane has been used as a CDA in the determination of the enantiomeric purity of chiral alcohols using both ^{29}Si NMR [95] and ^{13}C NMR [96]. Initially, derivatisation was carried out in two stages, first with an enantiomerically pure alcohol, menthol, quinine or methyl mandelate, followed by reaction with the enantiomeric alcohol to be analysed, e.g. the silyl metal diastereoisomers 37 had $\Delta\delta_{Si}$ = 0.053 ppm ($CDCl_3$, 298K). ^{13}C NMR investigations involved derivatisation using two equivalents of the chiral alcohol with the achiral coupling reagent Ph_2SiCl_2, to produce two equivalent meso forms and a pair of enantiomers in an analogous manner to the ^{31}P NMR achiral reagents [86-90] discussed earlier. Non-equivalence was typically $\Delta\delta_C$ = 0.07 ppm ($CDCl_3$, 298K) with a value of $\Delta\delta_C$ = 0.10 ppm reported for the menthol derivation 38. No data for ^{29}Si non-equivalence was given [96].

The chiral Pt amine complex 39 has been used in the determination of the enantiomeric purity of chiral allylic ethers, alcohols [97] and chiral trisubstituted allenes [98]. The chiral substrate displaces the bound ethene in the complex to form four diastereomeric complexes (**Figure 4**). Non-equivalence is of the order of $\Delta\delta_{Pt}$ = 22 ppm (d_6-Me_2CO, 298K).



(R,R)

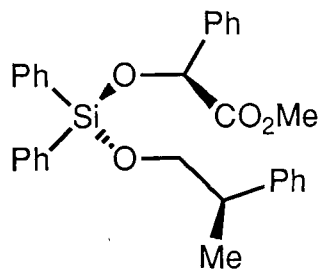


(R,S) meso

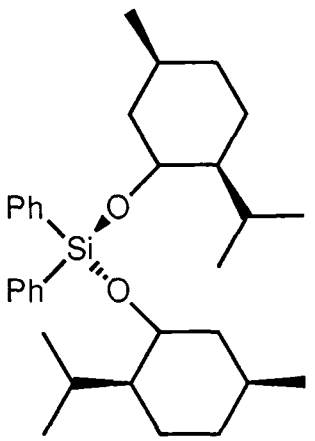
36

The insensitivity of ^{195}Pt and the line broadening associated with chemical shift anisotropy at high field of ^{195}Pt NMR means that a considerable amount of complex is required (>100 mg) for adequate signal/noise to be attained. This problem renders this technique unsuitable for routine analysis.

The selenium based reagent (45,5R)-(-)-4-methyl-5-phenyl-oxazolidine-2-selone 40 was recently reported as a CDA for chiral acids [99,100]. The relative sensitivity of ^{77}Se nucleus (2.98 compared to carbon, 6.93 x 10^{-3} with respect to hydrogen) coupled with a large chemical shift range (~3400 ppm) and a particular sensitivity to electronic environment makes such a reagent worth considering as a CDA. The selenocarbonyl group itself has a relatively short relaxation times (1-8 seconds) with a large chemical shift range (2,600 ppm). The CDA 40 has subsequently been used to assay acids with remote chiral centres. The reaction of RS-5-methyl-heptanoic acid and lipoic acid with the enantiopure selone yielded the N-acylated selones 41 with $\Delta\delta_{Se}$ = 0.09 ppm and $\Delta\delta_{Se}$ = 0.119 ppm respectively.



37



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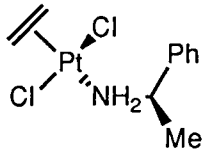
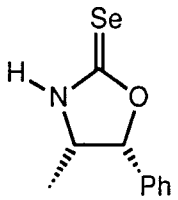


39



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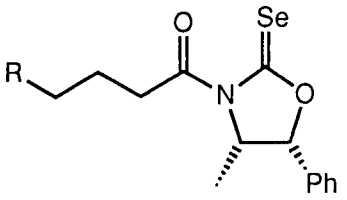
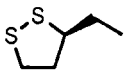


41

a) R = $CH_3CH_2CH(CH_3)$ -

b) R = 

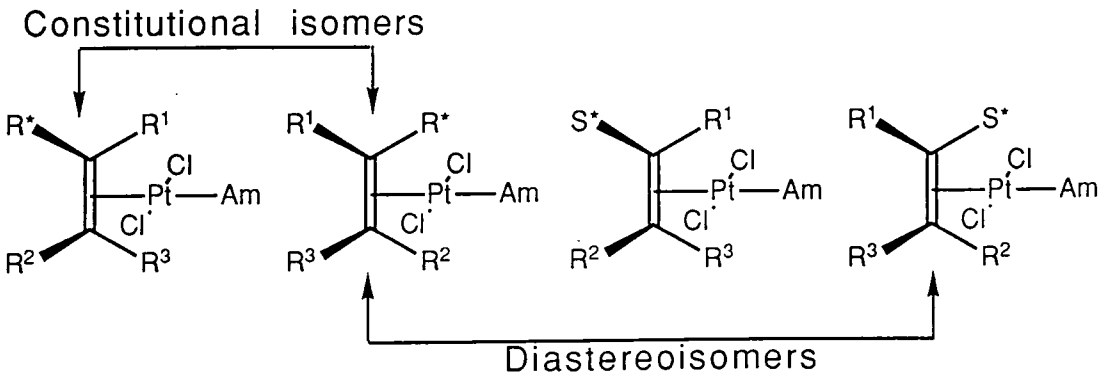


Figure 4

1.2.2 Chiral Lanthanide Shift Reagents

The hexacoordinate lanthanide shift reagents form weak addition complexes with enantiomeric substrates, which are in rapid equilibrium with their unbound entities. Chemical shift non-equivalence results from the proximity of a given nucleus from the chiral lanthanide donor in the diastereomeric

complex. The induced shift arising from the through space magnetic effects of unpaired electron magnetic moments (pseudo contact shift) in the seven co-ordinate complex is described by the McConnell equation (4).

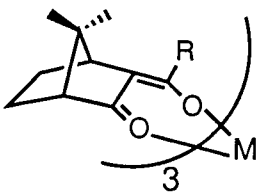
$$\Delta\delta = k(1-3\cos^2\phi)r^{-3} \qquad - (4)$$

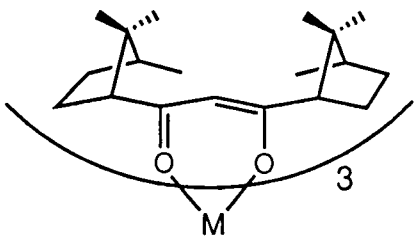
r - distance from metal centre.

ø - number of degrees the nucleus deviates from the principle axis of symmetry.

As can be seen in (4), small changes in distance may lead to large non-equivalence. Line broadening for LSR is proportional to B_0^2 (The applied field). This increases their usefulness at low field (≤ 100 MHz) where overlap of broad resonances is greatly reduced or eliminated.

Many commonly used CLSR are camphor based ligands and are structurally similar to the CLSR first introduced by *Whitesides*[37] 10 (**Figure 5**) [101, 102, 103].





10 R = ^{t}Bu , M = Eu - Eu[pvc]$_3$

42 a) R = CF_3 , M = Eu - Eu[tfc]$_3$
b) R = CF_3 , M = Pr - Pr[tfc]$_3$
c) R = CF_3 , M = Yb - Yb[tfc]$_3$
d) R = C_3F_7 , M = Eu - Eu[hfc]$_3$
e) R = C_3F_7 , M = Pr - Pr[hfc]$_3$
f) R = C_3F_7 , M = Yb - Yb[hfc]$_3$

43 M = Eu - Eu[dcm]$_3$

tfc = trifluorohydroxymethylene-d-camphorato
hfc = heptafuorohydroxymethylene-d-camphorato
dcm = dicamphoyl-d-methanato

Figure 5

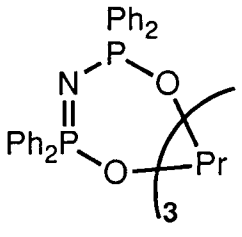
The reagent $Eu(dcm)_3$ 43 displays considerable differential shift dispersion, $Eu(hfc)_3$ 42d gives large $\Delta\delta$ for diastereomeric complex in ^{13}C NMR but is out performed by $Pr(Hfc)_3$ 42e in ^1H NMR displaying large $\Delta\delta$ for low concentrations of shift reagent, while $Yb(hfc)_3$ 42f is better for analysing chiral sulphoxides [104, 105, 106].

The achiral shift reagent $Pr(tpip)_3$ 44 [tpip = tris (tetraphenyl-limidodiphosphinateo)] has been used as a CLSR for the determination of enantiomeric purity of carboxylic acids [107, 108, 109]. The chiral potassium carboxylate salts form dinuclear complexes with the reagent which are in slow exchange on the NMR time scale. The diasteromeric complexes (SS/RR, RS) are observed in the ^1H NMR spectrum.

$Eu(tfc)_3$ and $Eu(hfc)_3$ are routinely used in the analysis of enantiomeric donors [110-114] and have become an unofficial defacto standard for such analysis, regardless of the performance or better alternatives. These reagents need to be dried before use or the hydrolysis product Eu_2O_3 may cause severe line-broadening.

Chiral carboxylic acids are analysed as 3° amides [115] or directly in aqueous solution [116, 117]. There are also reported cases of the analysis of chiral α-amino acids in aqueous solution with Eu(EDDS) [118] 45 [EDDS = (S,S)-ethylene diamine-N, N'-disuccinic acid] and Eu(pdta) [119] 46 [pdta = 1,2-propane diaminetetra-acetate]. Chiral alkenes, arenes and allenes have been analysed with a mixture of $Yb(hfc)_3$ 42f and achiral shift reagent Ag(fod) 47 [120-127]. Chemical shift non-equivalence is typically 1 ppm for chiral alkenes and 0.3 ppm for arenes and allenes.

By optimising data acquisition parameters and manipulation of the free-induction decay, accurate values for enantiomeric excess can be obtained [128]. At low e.e. values (40-60%) accuracy is of the order ±2% [129], but this increases to ±10% with e.e. ≥ 90% [130]. High enantiomeric purities are prone to error because it is difficult to identify the exact position of the minor diastereomeric resonance. It is possible to determine the S-minor diastereomeric position with calibration plots [131] of the induced shift of the S-enantiomer against induced shift for the R-enantiomer, following successive addition of the shift reagent to the racemic substrate.



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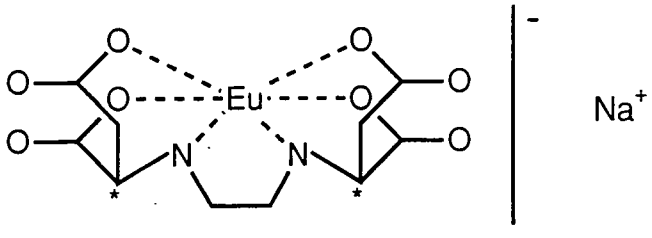

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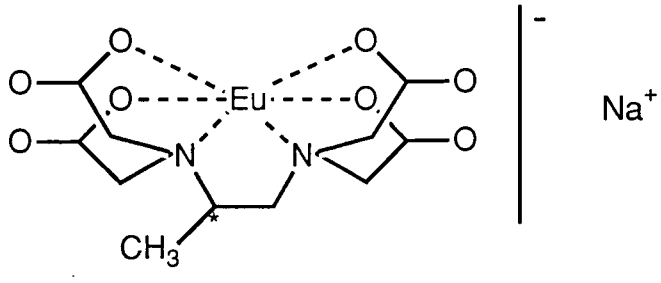

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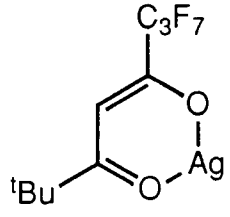

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1.2.3 Chiral Solvating Agents

Unlike CDA's and CLSR's chiral solvating agents form diastereoisomeric solvation complexes with solute enantiomers which are in rapid equilibrium with the solvent.

$$R_{CSA} + \underset{\delta_{ach}}{R^*} \underset{}{\overset{K_R}{\rightleftharpoons}} \underset{\delta_R}{R_{CSA}.R^*} \qquad \text{- (5).}$$

$$R_{CSA} + \underset{\delta_{ach}}{S^*} \underset{}{\overset{K_S}{\rightleftharpoons}} \underset{\delta_S}{R_{CSA}.S^*} \qquad \text{- (6).}$$

Chemical shift non-equivalence may be induced by several factors, including solute-solute interactions [132, 133] but such interactions are negligible in the presence of a strongly solvating CSA and only become apparent at high concentrations.

The two major factors determining chemical shift anisochrony are described by equations (5) and (6). Firstly, the two diastereomeric solvates may have slightly different spectra, possibly due to the position of a magnetically anisotropic group in the solvation complex. Secondly, if solvation causes changes in chemical shift, then the extent to which the enantiomers are solvated (K_R and K_S) will result in non-equivalence.

Exchange between 'solvent solvated' solute (R* and S*) and the 'chiral solvated' solute ($R_{CSA}R^*$ and $R_{CSA}S^*$) is rapid on the NMR time scale. The observed chemical shift for each enantiomer δ^R_{obs} and δ^S_{obs} is a function of the

weighted averages for the populations of the achiral, δ_{ach} and chiral δ_R, δ_S solvate resonances. If $\varnothing_R$ and $\varnothing_S$ are the fractional populations of achiral solute, then equations (7), (8) and (9) are derived.

$$K_R = (1-\varnothing_R)/\varnothing_R \quad ; \quad K_S = (1-\varnothing_S)/\varnothing_S \qquad - (7)$$

$$\delta^R_{obs} = \varnothing_R.\delta_{ach} + (1-\varnothing_R).\delta_R \quad ; \quad \delta^S_{obs} = \varnothing_S.\delta_{ach} + (1-\varnothing_S).\delta_S \qquad - (8)$$

$$\Delta\delta = \delta^R_{obs} - \delta^S_{obs}$$

$$\Delta\delta = \varnothing_R(\delta_{ach} + K_R.\delta_R) - \varnothing_S(\delta_{ach} + K_S.\delta_S) \qquad - (9)$$

It can be seen that $\Delta\delta$ depends on the equilibrium constant for solvation and hence the relative amounts of CSA and solute.

The most common model used to account for CSA chiral molecular recognition is the "Three Point Rule". This states that chiral recognition requires a minimum of three interactions between CSA and solvate to bring about non-equivalence, one of which must be stereochemically dependent. The types of interactions include single point i.e. hydrogen bonding, end to end dipole-dipole interactions, proton transfer or multi-point interactions including dipole stacking and charge transfer complexation (π-acid to π-base). The stereochemical interaction must distinguish between solute enantiomers and not be collinear with the others.

There is a considerable range of compounds which could be considered as CSA, for instance molecules involved in host-guest complexation e.g. cyclodextrins, chiral crown ethers, chiral synthetic receptors or any other substrate that will bring about NMR non-equivalence by chiral molecular recognition.

The essential requirements of a CSA are that it must have complementary functionality to the solute, a simple NMR spectrum which will not interfere with observed solute resonances, it should incorporate anisochronous groups such as aryl, carbonyl or lone-pairs and it must be soluble in the solvent used.

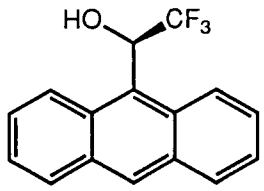
The enantiomeric purity of the CSA will not affect the diastereomeric composition observed in the NMR spectrum. Decreasing the enantiomeric purity of the CSA merely decreases the observed $\Delta\delta$ by the introduction of δ_S, and δ_R, terms into equations (5) and (6) respectively. This is due to the formation of their enantiomers by the complementary CSA.

Usually the chemical shift non-equivalence induced by a CSA is relatively small. The technique is rather limited to relatively non-polar solvents e.g. $CDCl_3$, C_6D_6, CCl_4, CD_2Cl_2. These solvents maximise anisochrony by ion-pair formation. More polar solvents lead to the break-up (solvation) of ion-pairs and give reduced or zero values of $\Delta\delta$.

Although CSA's offer distinct advantages in ease of utilisation and analysis they remain perhaps the least popular technique. This is reflected in the published literature. Chiral solvating agents can be divided into two types: Those in which primary association between CSA and solute is electrostatic (mainly hydrogen bonds) and secondly those where complexation is achieved by complete proton transfer (salt formation).

1.2.3.1 Electrostatic CSA

The most commonly used CSA of this type is 1-(9-anthryl)-2,2,2-trifluoro-ethanol 48 [138-143] introduced by *Pirkle* [134] from earlier observations of 2,2-trifluoro-1-phenylethanol with CSA R-α-phenylethylamine and R-2-naphthylethylamine [35]. The alcohol 48 has been used for lactones [141, 144],



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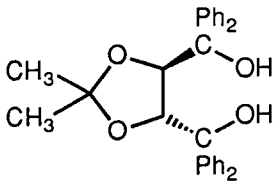

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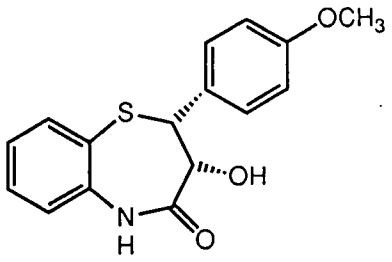
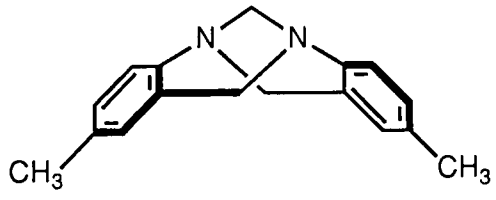


50

ethers [145], oxaziridenes [137, 138] and sulphinate esters [136]. A more recent example of a CSA the primary interaction of which is hydrogen bonding is that of 49 with selected primary and secondary alcohols [146]. Typical non-equivalence was of the order of 0.05 ppm (1:2 ratio alcohol: 49, $CDCl_3$, RT). 1,5-Benzothiazepine 50 reportedly acts as a CSA for chiral alcohols, acids and other 1,5-Benzothiazepines [147] but non-equivalence is very low, typically 0.003 ppm ($CDCl_3$, RT.).

An unusual CSA is *Tröger's base* 51, a chiral tertiary amine with nitrogen stereogenic centres, used in the analysis of secondary and tertiary alcohols [148]. It is ineffective in the analysis of chiral acids which bring about racemisation of the base, although the strongly acidic (-)-1,1-binaphthalene-2,2'-diylhydrogen phosphate 52 was used to resolve the base by crystallisation-induced asymmetric transformations of the salt. Non-equivalence is typically of the order of $\Delta\delta$ = 0.02 ppm ($CDCl_3$, 298K).



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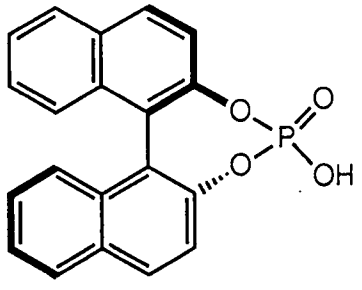

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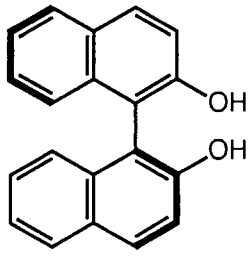
The CSA 2,2'-dihydroxy-1,1'-binaphthyl 53 introduced by *Toda* [149,150] has been used in the analysis of a wide variety of chiral compounds, recently *Michalik* [151] has suggested (based on experimental observations) that optimal non-equivalence may be observed with the cyclic amimo alcohol 54 and the CSA 53 in which both hydroxyl groups are involved in complexation. The diol 55 has been used by Toda in the enantiomeric purity determination of chiral amine oxides [150, 152]. Chemical shift non-equivalence in the N-methyl groups of 56 was approximately 0.05 ppm ($CDCl_3$, 295K). The general purpose CSA 4,4',6,6'-Tetra chloro-2,2'-bis-(hydroxydiphenylmethyl)-biphenyl 57 [153] has been reported for the determination of non-equivalence in a range of N, P, S containing compounds. It was found to be effective in the determination of the absolute configuration of sulphoxides (**Table 3**). R-sulphoxides appear to lower frequency and non-equivalence was ≥ 0.05 ppm.



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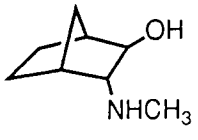

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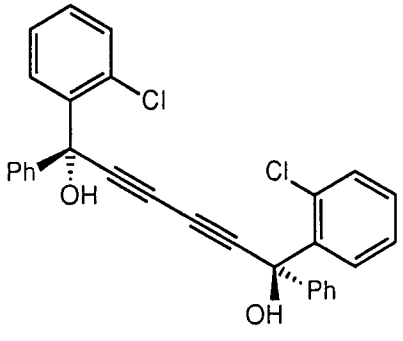

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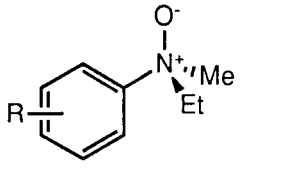

R = H , Me

56

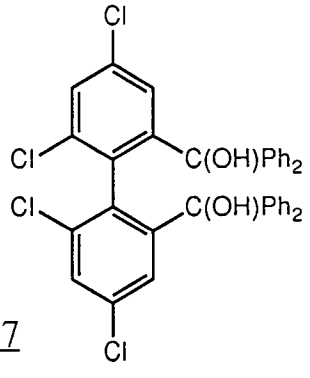

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Table 3

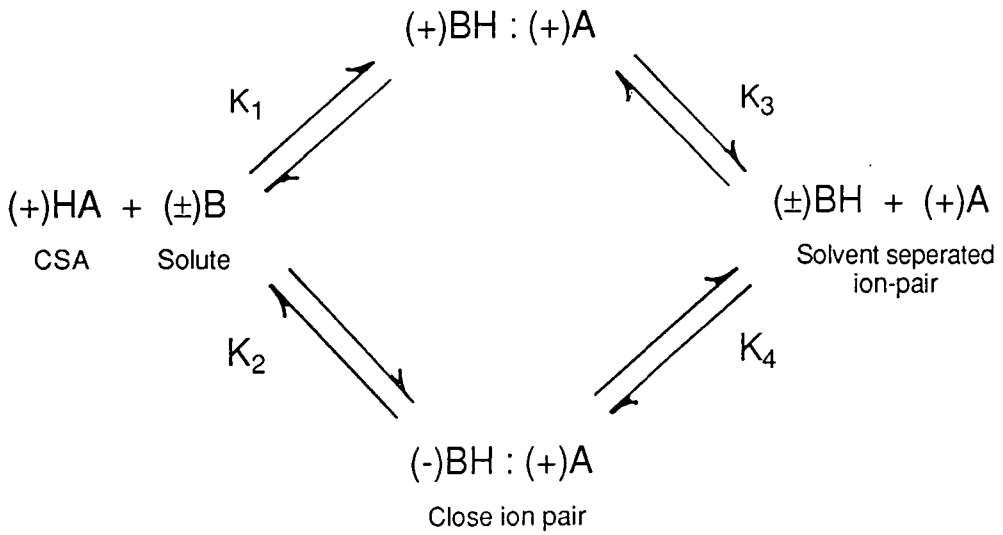
The chemical shift non-equivalence and the assignment of absolute configuration of selected sulphoxides with CSA 57.

Entry	Substrate[a] Observed resonance underlined	Diastereomeric resonance[b] ppm	$\Delta\delta_H$ ppm
1.	Ph-SO-C<u>H</u>$_3$	2.446 R-(+) 2.498 S-(+)	0.052
2.	m-Tol-SO-C<u>H</u>$_3$	2.375 R-(+) 2.480 S-(+)	0.105
3.	p-Tol-SO-C<u>H</u>$_3$	2.513 R-(+) 2.561 S-(+)	0.048
4.	n-Bu-SO-C<u>H</u>$_3$	2.217 R-(+) 2.297 S-(+)	0.080
5.	n-Am-SO-C<u>H</u>$_3$	2.300 R-(+) 2.388 S-(+)	0.088
6.	n-Hex-SO-C<u>H</u>$_3$	2.286 R-(+) 2.334 S-(+)	0.048
7.	n-Hep-SO-C<u>H</u>$_3$	2.318 R-(+) 2.358 S-(+)	0.040
8.	n-oct-SO-C<u>H</u>$_3$	2.227 R-(+) 2.280 S-(+)	0.053

a) The Spectra were recorded in $CDCl_3$
b) Absolute configuration of the solute is assigned to the observed resonances.

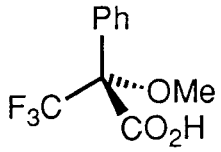
1.2.3.2 Diasteromeric salt formation

Salt formation usually leads to quite large chemical shift non-equivalence. Close ion-pair formation, due to rapid exchange between the CSA and the solute in the achiral solvent, is responsible for this non-equivalence.



The CSA's (R)-α-phenylethylamine and (R)-2-naphthylethylamine have been used for the analysis of chiral carboxylic acids via diastereomeric salt formation [154-162]. The observed chemical shift non-equivalence was small, $\Delta\delta_H$ 0.05 ppm ($CDCl_3$, 298K). There are very few other amine CSA's which have been studied in this context although in this work 1,2-diphenyl-1,2-diamino-ethane [163] 58 will be shown to be an excellent CSA with typical values of $\Delta\delta$ of 0.15 ppm ($CDCl_3$, 293K) for a range of chiral acids.

A more thorough investigation has been made using carboxylic acid CSA's in the analysis of chiral amines and amino-alcohols [158, 159, 165-167]. The CDA MTPA has been examined as a potential solvating agent, but its use is limited due to the low solubility of its salts [164].



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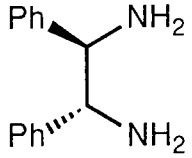

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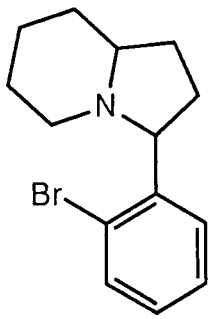

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The effect of temperature, concentration, CSA:solute ratio on $\Delta\delta_H$ has been studied for the amine 59. Decreasing the temperature increased $\Delta\delta_H$ while at high salt concentrations $\Delta\delta_H$ is reduced due to ion-pair aggregation. Non-equivalence reaches a maximum at 1:1 stoichiometry corresponding to complete salt formation. The enantiopure O-Acetyl mandelic acid 19 [167] and 1,1'-binaphthyl-2,2'-diylphosphoric acid 52 [166] gave large $\Delta\delta_H$, typically 0.08 ppm (C_6D_6, 293K) and 0.15 ppm (C_6D_6, 298K) respectively for a range of chiral substrates. These salts tend to be reasonably soluble in non polar solvents. In the case of OAM the disassociated equilibrium constants are not always equivalent for the diastereoisomers, so that the enantiomeric composition has been observed to affect $\Delta\delta_H$ [167].

CHAPTER 2

Chiral Amines as Chiral Solvating Agents

2.1 Introduction

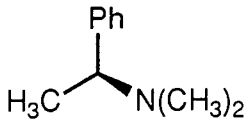
There are many examples of carboxylic acid CSA's for amines (see Section 1.2.3). The complementary experiment, where a chiral amine is used as a solvating agent for chiral carboxylic acids has received very little attention. The preferred method of chiral acid analysis requires the formation of an ester or amide derivative. With this in mind, a series of N-Mono-methyl,.N,N-dimethyl and cyclic amines were initially examined (60-67) as potential CSA's for a limited range of chiral acids. The chiral amines possessed a minimum of one anisotropic group, (aryl group, carbonyl group, or additional Nitrogen lone pair) which is required to induce magnetic non-equivalence in the diastereomeric salt complexes by stereospecific interactions between the observed functionality and the anisotropic group. The interaction usually leads to a differential anisotropic shift between the two diastereomeric salt complexes. These initial investigations and subsequent observations led on to the consideration of 1,2-diphenyl-1,2-diaminoethane as a CSA for carboxylic acids.

This chapter will discuss these chiral amines in the context of their ability as a CSA.

2.2 α-Aryl-dimethylethylamines as Chiral Solvating Agents

The chiral amines α-phenylethylamine and α-naphthylethylamine have been examined previously as CDA's for carboxylic acids. α-Phenylethylamine and the 2-naphthyl-ethylamine analogue have been examined previously as CSA's (see section 1.2.3.2), although the observed chemical shift non-equivalence was found to be small.

The tertiary amine analogues, with greater gas phase basicities then their primary and secondary amines could be considered to have increased solvating ability. The reagents 60 to 62 were examined as CSA's for the racemic acids 20, 68-70. The amine was added to the acid (1:1) in both $CDCl_3$ and C_6D_6.



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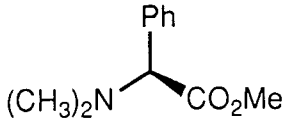

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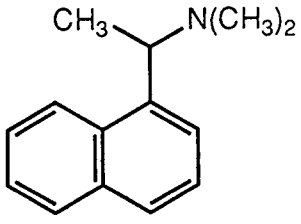

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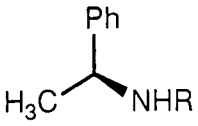
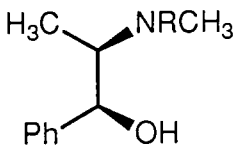


a) R = $PhCH_2$-
b) R = CH_3-

63



a) R = H
b) R = CH_3

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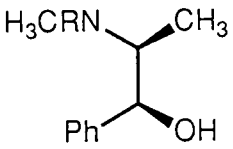
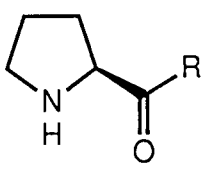


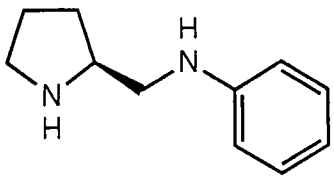
a) R = H
b) R = CH_3

65



a) R = -O^{t}Bu
b) R = $-NH_2$
c) R = -NH-p-$NO_2C_6H_4$
d) R = -NHMe

66



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2.2.1 N,N-Dimethyl-1-Phenylethylamine (60)

This commercially available reagent showed no chemical shift non-equivalence with the racemic acids studied.

2.2.2 N,N-Dimethyl-2-Phenylglycine Methyl Ester (61)

The CSA was easily derived from 2-phenylglycine but showed chemical shift non-equivalence with only camphanic acid which is itself a CSA for chiral amines. The observed chemical shift non-equivalence $\Delta\delta$ for the diastereotopic Me groups was sufficient to provide enantiomeric purity determination, **Spectrum 1**.

2.2.3 N,N-Dimethyl-1-(1-naphthyl)-ethylamine (62)

Derived from 1-(1-naphthyl)-ethylamine, this CSA also showed non-equivalence with camphanic acid only, **Spectrum 2**. The methyl doublets were only partially resolved hindering the ease of enantiomeric purity determination.

Spectrum 1

R-N,N-Dimethyl-2-phenylglycine methyl ester

(±)-Camphanic acid

61 20

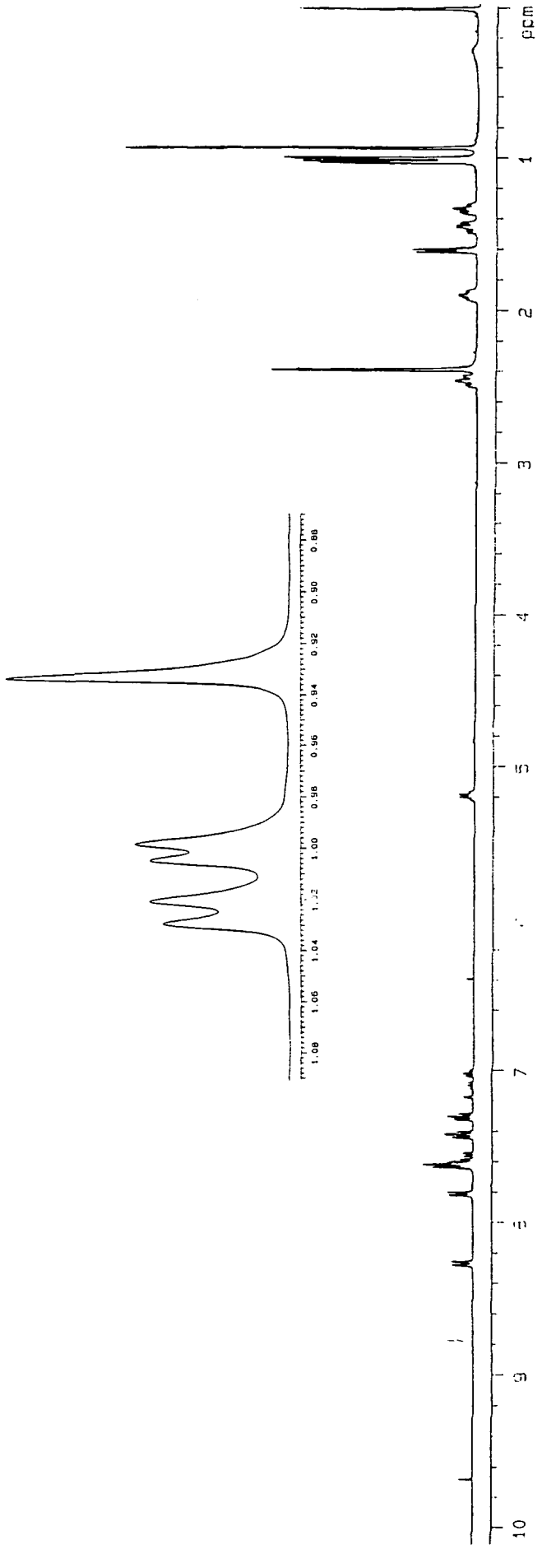
Spectrum 2

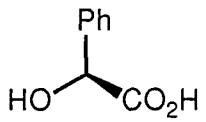
R-N,N-1-(1-Naphthyl)ethylamine

(±)-Camphanic acid

62

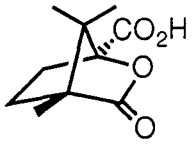
20





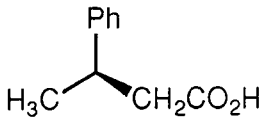
Mandelic acid

68



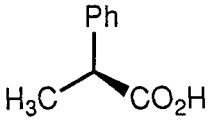
Camphanic acid

20



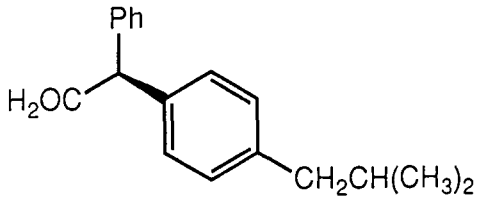
3-Phenylbutyric acid

69



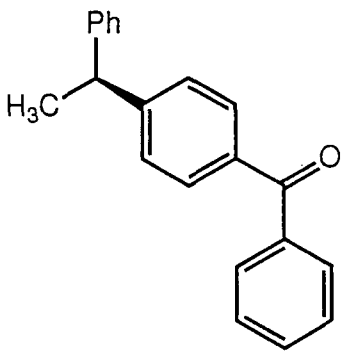
2-Phenylpropionic acid

70



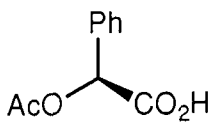
Ibuprofen

71



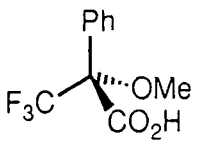
Ketoprofen

72



O-Acetylmandelic acid

19



MTPA

11

2.3 α-Aryl-N-methyl Amines as Chiral Solvating Agents

The observation that in the enantiomeric analysis of equivalent 1°, 2°, 3° amines with a carboxylic acid CSA such as mandelic acid [165], secondary amines usually gave the larger chemical shift non-equivalence compared to the 1° and 3° amine diastereoisomeric complexes led to the study of the reciprocal experiment. Two secondary chiral amines were tested against a range of racemic carboxylic acids to assess their effectiveness as CSA. The results are summarised in **Table 4**.

2.3.1 N-Benzyl-Phenylethylamine (63a)

The benzyl substituted amine was prepared from enantiopure phenylethylamine and displayed non-equivalence with only mandelic acid and to a lesser extent, with O-Acetyl mandelic acid (**Table 4**). The results suggest that non-equivalence was facilitated by the presence of an α-ether oxygen. The very limited use of this compound makes it unsuitable as a CSA.

2.3.2 N-Methyl-1-Phenethylamine (63b)

The N-methyl amine 63b gave consistent results with the chiral acids tested (**Table 4**), except in the case of 2-phenyl-propanoic acid where non-equivalence was not observed.

The poor solubility of the mandelic acid salt necessitated the addition of a small amount of d_6-pyridine. Values of $\Delta\delta$ were small, but offered some improvement over the corresponding tertiary amine analogues. The observed non-equivalence between 63b and racemic mandelic acid (1:1 in $CDCl_3$) is displayed in **Spectrum 3** for the methine portion of mandelic acid (5.0 ppm).

TABLE4

The measurement of $\Delta\delta$ for a range of chiral acids against 63a and 63b.

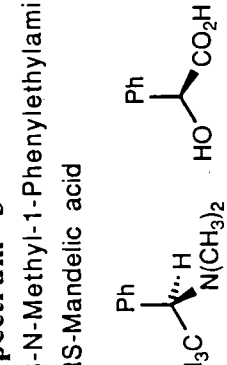
Entry	substate	63a			63b		
		Observed resonance	Solvent	$\Delta\delta_H$ ppm	Observed resonance	Solvent	$\Delta\delta_H$ ppm
1	68	2-H	$CDCl_3$	0.080	2-H	$CDCl_3$	0.022
		------	C_6D_6	0.080		C_6D_6/C_5D_5N (100:1)	0.025
2	20	------	$CDCl_3$	------	CH_3	$CDCl_3$	0.024
		------	C_6D_6	------	CH_3	C_6D_6/C_5D_5N (50:1)	0.014
3	69	------	$CDCl_3$	------	------	$CDCl_3$	------
		------	C_6D_6	------	2-CH_2-	C_6D_6/C_5D_5N (50:1)	0.005
4	70	------	$CDCl_3$	------	------	$CDCl_3$	------
		------	C_6D_6	------	------	C_6D_6	------
5	71		$CDCl_3$	------	2-CH_3	$CDCl_3$	0.010
		------	C_6D_6	------	2-H	C_6D_6/C_5D_5N (50:1)	0.018
6	72	------	$CDCl_3$	------	2-CH_3	$CDCl_3$	0.016
		------	C_6D_6	------	2-H	C_6D_6/C_5D_5N (50:1)	0.012
7	11	------	$CDCl_3$	------	2-OCH_3	$CDCl_3$	0.023
		------	C_6D_6	------	------	C_6D_6/C_5D_5N (50:1)	------
8	19	2-H	$CDCl_3$	0.038	2-OAc	$CDCl_3$	0.014
		------	C_6D_6	------	2-OAc	C_6D_6	0.012

Spectrum 3

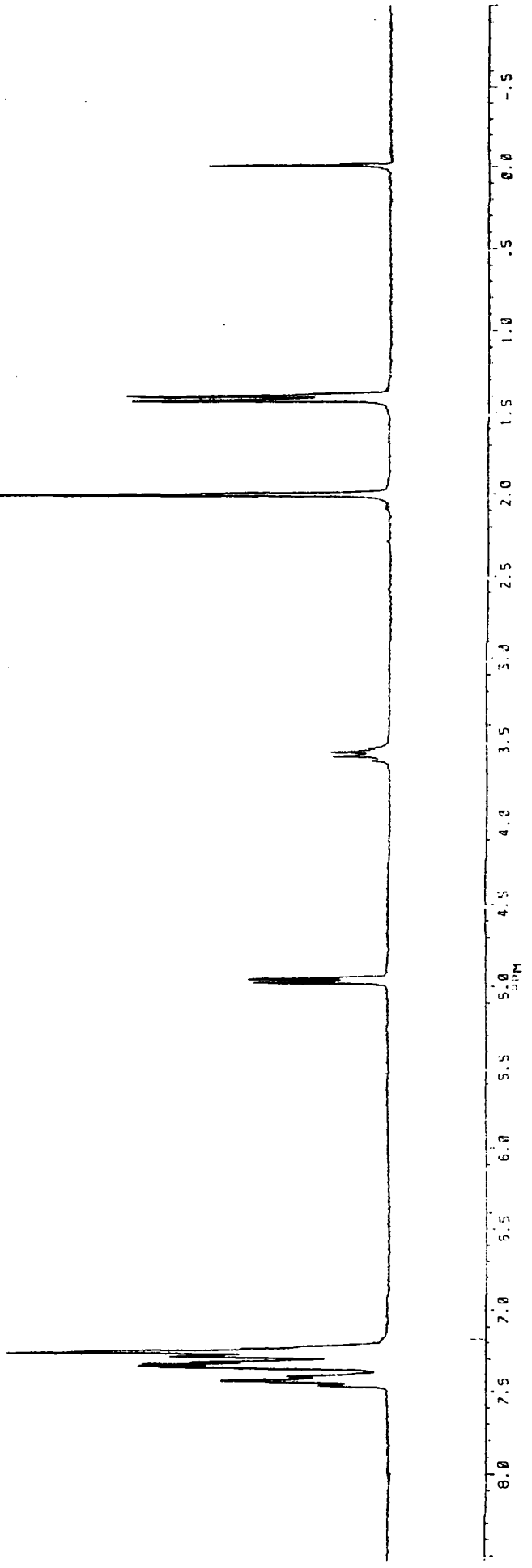
S-N-Methyl-1-Phenylethylamine

RS-Mandelic acid

63b



68



2.4 Ephedrine and N-methyl Ephedrine as CSA's

Extensively studied as reagents in chiral HPLC methods of analysis, ephedrine and its derivatives have features which were considered as desirable in a CSA.

Ephedrine (64a) is an N-substituted amine, which has been shown previously with α-Aryl-N-methylamine CSA to bring about larger chemical shift non-equivalence than their equivalent 1°, or 3° analogues (see section 2.3). The anisotropic phenyl group is two bonds away from the site of hydrogen bonding interaction. The proximate hydroxyl group was also considered to be a potential second point of interaction. These features may have allowed a degree of flexibility in the formation of the solvated complex which could lead to increased $\Delta\delta$ and greater applicability to chiral carboxylic acids. Ephedrine, its N-methyl analogue and the related diastereomer pseudo-ephedrine were tested against a limited range of chiral carboxylic acids at 1:1 stoicheiometry in either $CDCl_3$ or C_6D_6. The results are summarised in **Table 5**.

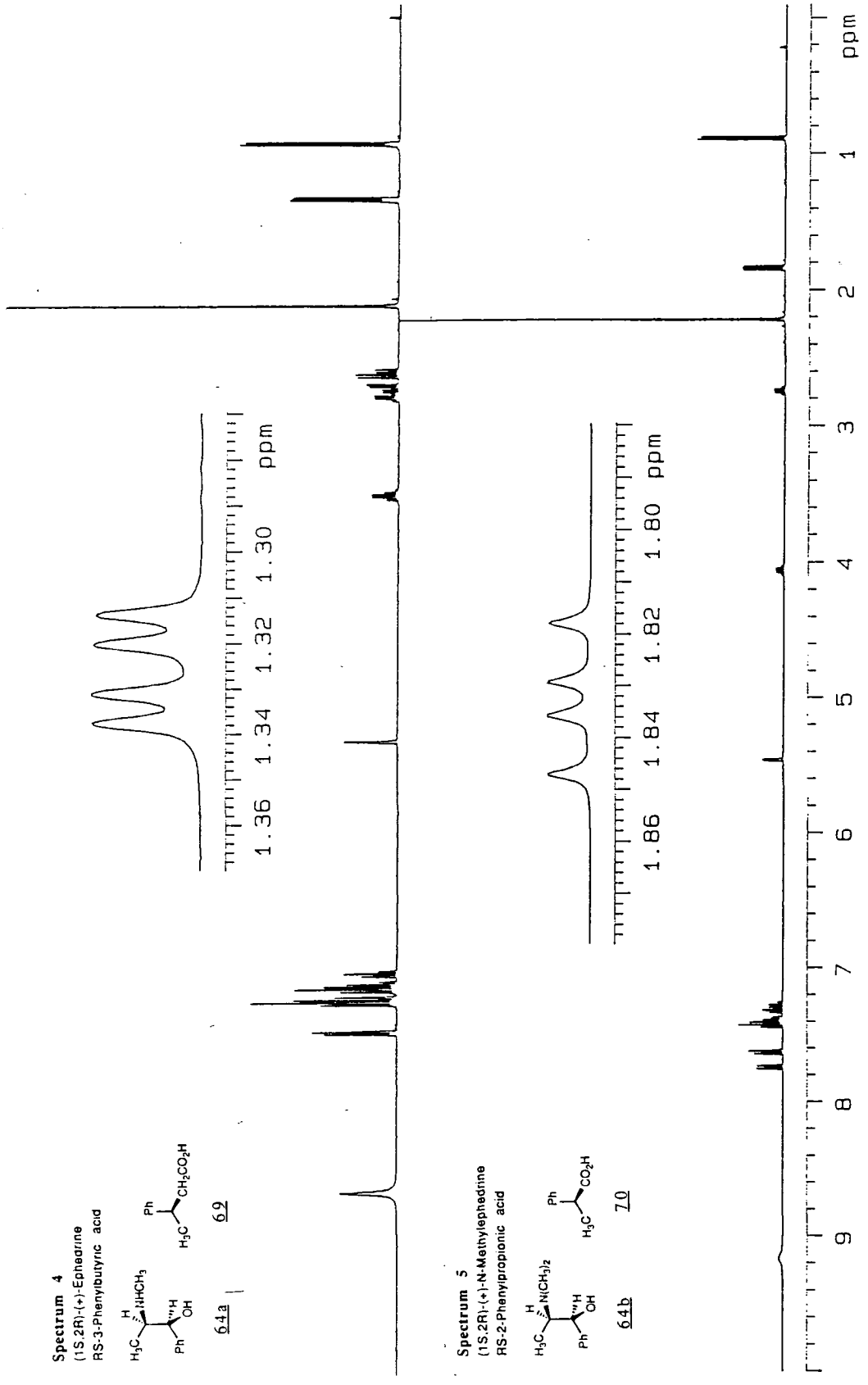
2.4.1 (1S,2R)-(+)-Ephedrine (64a)

The complexes displayed rather poor solubility in $CDCl_3$ and C_6D_6. Indeed in the case of $CDCl_3$, complexes dissolved only in the presence of a small amount of deutero methanol. Chemical shift non-equivalence was small and could be observed with complexes dissolved in C_6D_6. Only one case of shift non-equivalence was noted in $CDCl_3$ solution. An example of ^1H NMR shift non-equivalence with the methyl protons of 3-phenylbutyric acid is shown in **Spectrum 4**.

TABLE5

The measurement of Δδ for with 64 and 65 against selected chiral acids

Entry		1		2		3		4	
Substrate		68		20		69		70	
64a	Observed resonance	2-H		------	CH_3	------	2-CH_3	------	2-CH_3
	Solvent	$CDCl_3/CD_3OH$ (18:1)	C_6D_6/C_5D_5N (2:1)	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6
	Δδ ppm	0.006	------	------	0.025	------	0.017	------	0.006
64b	Observed resonance	2-H		CH_3		2-CH_3	------	2-CH_3	
	Solvent	$CDCl_3$	C_6D_6/C_5D_5N (2:1)	$CDCl_3$	C_6D_6/C_5D_5N (2:1)	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6
	Δδ ppm	0.006	0.007	0.032	0.023	0.005	------	0.002	0.018
65a	Observed resonance	------	2-H	CH_3		2-CH_2-	2-CH_3	2-CH_3	
	Solvent	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6
	Δδ ppm	------	0.021	0.017	0.046	0.019	0.005	0.007	0.002
65b	Observed resonance	2-H	------	------	CH_3	------	2-CH_3	------	2-H
	Solvent	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6/C_5D_5N (8:1)	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6
	Δδ ppm	0.015	------	------	0.008	------	0.005	------	0.004


Spectrum 4
(1S,2R)-(+)-Ephedrine
RS-3-Phenylbutyric acid
64a
69
1.36 1.34 1.32 1.30 ppm
Spectrum 5
(1S,2R)-(+)-N-Methylephedrine
RS-2-Phenylpropionic acid
64b
70
1.86 1.84 1.82 1.80 ppm
ppm

2.4.2 (1S,2R)-N-Methylephedrine (64b)

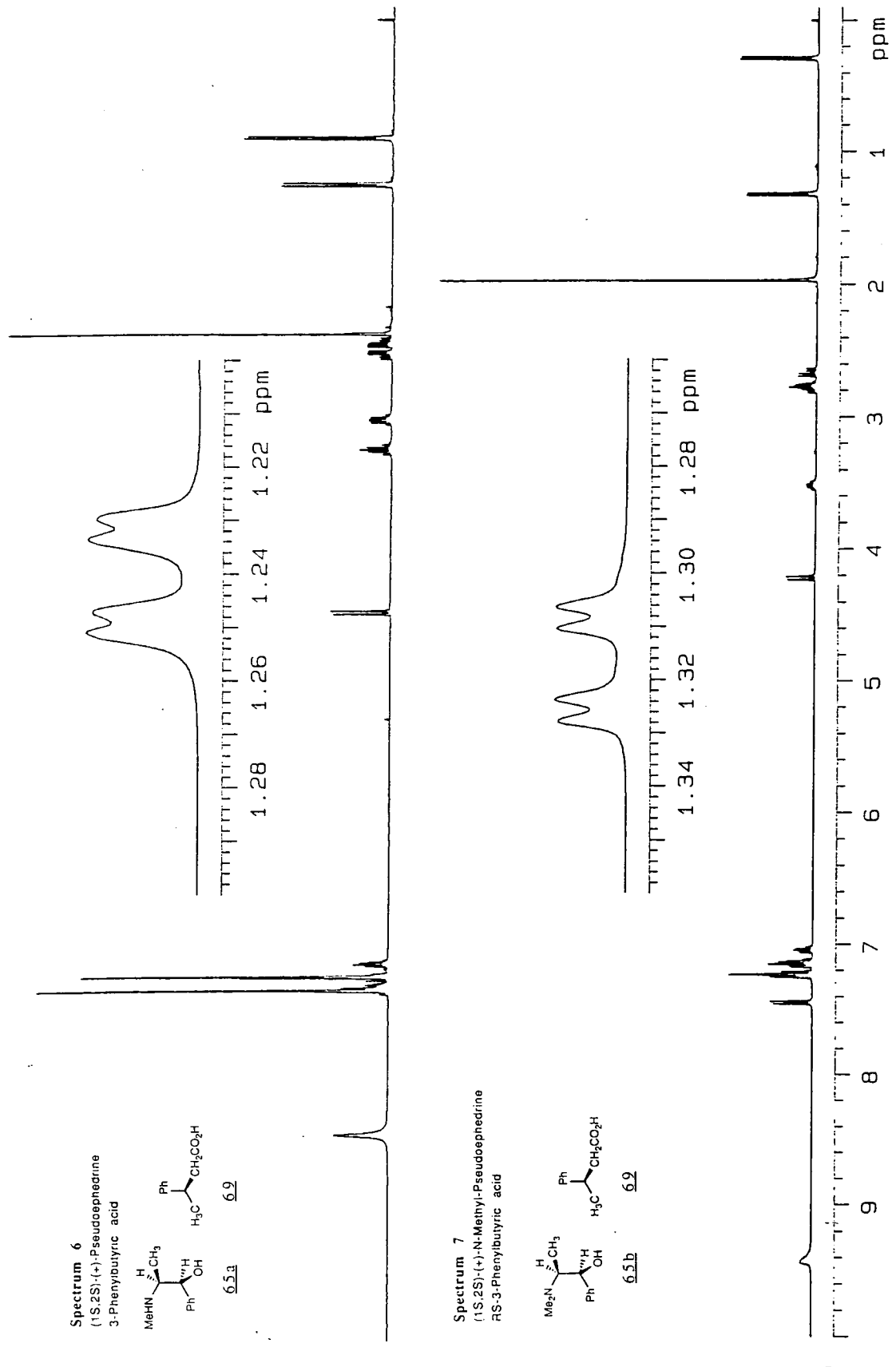
This reagent gave non-equivalence with almost all of the chiral acids studied unlike reagent 64a. However, the magnitude of $\Delta\delta$ tended to be very small. The largest chemical shift non-equivalence was given with the 2-phenylpropanoic acid methyl doublet in C_6D_6. **Spectrum 5** shows this doublet split into a pair of doublets at around 1.6 ppm. There is also a small amount of splitting in the acid methine proton at 3.8 ppm.

2.4.3 (IS,2S)-(+)-Pseudoephedrine (65a)

Unlike the situation with its diastereoisomer 64a, the mandelic acid salt of 65a was soluble in both $CDCl_3$ and C_6D_6. In most cases the observed shift non-equivalence was very small. An example of chemical shift non-equivalence was given by 3-phenylbutyric acid in $CDCl_3$, **Spectrum 6** for the methyl doublet at 1.2 ppm. The non-equivalence of the acid 2-methylene group is small at 0.019 ppm (δ = 2.50 ppm) but easily distinguished in both methylene protons.

2.4.4 (1S,2S)-(+)-N-Methyl Pseudo Ephedrine (65b)

Observation of chemical shift non-equivalence was limited to salts which were dissolved in C_6D_6 and the non-equivalence tended to be very small. **Spectrum 7** provides an example of this, the non-equivalence of the methyl doublet at 1.3 ppm is only just observed. The diastereotopic methylene group at 2.7 ppm also shows non-equivalence but with only one of the methylene protons.


Spectrum 6
(1S,2S)-(+)-Pseudoephedrine
3-Phenylbutyric acid
MeHN
Ph
OH
Ph
H3C
CH2CO2H
6.5a
6.9
1.28
1.26
1.24
1.22
ppm
Spectrum 7
(1S,2S)-(+)-N-Methyl-Pseudoephedrine
RS-3-Phenylbutyric acid
Me2N
Ph
OH
Ph
H3C
CH2CO2H
6.5b
6.9
1.34
1.32
1.30
1.28
ppm
9
8
7
6
5
4
3
2
1
ppm

It is interesting to note that the introduction of an N-methyl group enhances CSA ability with ephedrine but diminishes this ability with pseudo ephedrine. This is possibly due to the differential population of conformations giving rise to non-equivalence in the diastereoisomeric sets of solvation complexes.

In all cases $\Delta\delta_H$ was insufficient for base line resolutions hence enantiomeric purity determinations are prone to error.

2.5 L-Proline derivatives as CSA

L-Proline derivatives are known to be good chiral additives in HPLC analysis [168-171]. Their relatively simple ^1H NMR spectra and good solubility in non-polar solvents makes them worth considering as a CSA. The L-proline derivatives 66a-d and 67 were tested against a range of chiral acids, and the results are summarised in **Table 6**. The primary site of hydrogen bonding interaction with the proline derivatives tested was considered to be to the more basic proline nitrogen. The side group nitrogens 66a-d, 67, are less basic due to distribution of electron density between their carbonyl and phenyl groups respectively. Secondary and additional interactions may to be induced by those side groups containing a polar or anisotopic group.

2.5.1 L-Proline t-Butyl Ester (66a)
L-Proline Amide (66b)

The readily available L-proline derivatives 66a and 66b showed no chemical shift non-equivalence with the chiral acids studied except with 66a and camphanic acid ($\Delta\delta$ = 0.015 ppm, $CDCl_3$). In the majority of X-ray structures of L-proline and its derivatives, the carbonyl bond is essentially co-planar with the proline nitrogen [172-177], **figure 6a**, the carbonyl adopts a conformation in which it points towards the nitrogen. There are instances where the

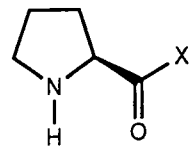
TABLE6

The measurement of Δδ for a range of chiral acids against 66c, 66d and 67.

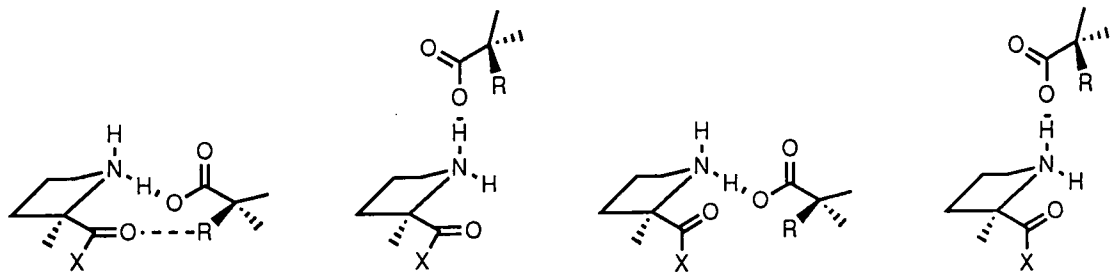
Entry	substate	66c			66d			67		
		Observed resonance	Solvent	$\Delta\delta_H$ ppm	Observed resonance	Solvent	$\Delta\delta_H$ ppm	Observed resonance	Solvent	$\Delta\delta_H$ ppm
1	68	2-H	$CDCl_3$	0.020	2-H	$CDCl_3$	0.023	2-H	$CDCl_3$	0.033
		———	C_6D_6/C_5D_5N (2:1)	———	———	C_6D_6	———		C_6D_6/C_5D_5N (70:1)	0.012
2	20	CH_3	$CDCl_3$	0.014	———	$CDCl_3$	———	CH_3	$CDCl_3$	0.008
			C_6D_6	0.009	———	C_6D_6	———		C_6D_6	0.040
3	69	2-CH_3	$CDCl_3$	0.006	———	$CDCl_3$	———	2-CH_2-	$CDCl_3$	0.009
			C_6D_6	0.006	2-CH_3	C_6D_6	0.006		C_6D_6	0.010
4	70	2-CH_3	$CDCl_3$	0.006	———	$CDCl_3$	———	2-CH_3	$CDCl_3$	0.011
		———	C_6D_6	———	———	C_6D_6	———	2-H	C_6D_6	0.004
5	71	2-CH_3	$CDCl_3$	0.005	———	$CDCl_3$	———	2-CH_3	$CDCl_3$	0.016
		———	C_6D_6	———	———	C_6D_6	———		C_6D_6	0.017
6	72	2-CH_3	$CDCl_3$	0.013	———	$CDCl_3$	———	2-CH_3	$CDCl_3$	0.048
		———	C_6D_6	———	———	C_6D_6	———		C_6D_6	0.021
7	11	2-OCH_3	$CDCl_3$	0.038	———	$CDCl_3$	———	2-OCH_3	$CDCl_3$	0.035
			C_6D_6	0.102	2-OCH_3	C_6D_6	0.013		C_6D_6	0.025
8	19	2-OAc	$CDCl_3$	0.011	2-H	$CDCl_3$	0.011	2-H	$CDCl_3$	0.014
			C_6D_6	0.045	2-OAc	C_6D_6	0.026	———	C_6D_6	———

introduction of a bulky group on the proline nitrogen or an extra polar group α to the proline nitrogen will result in an 'out of plane' carbonyl group [178,179].

It could be considered that a combination of hydrogen bonding between the L-proline nitrogen and the polar nitrogen, or oxygen moieties of the side groups in 66a,b orientate the anisotropic carbonyl groups away from the substrate acid, hence rendering it useless in inducing non-equivalence by stereospecific interaction within one of the diastereoisomeric complexes. Alternatively, the L-proline derivative could form 4 possible complexes with the acid **Figure 6b**, 3 of which have no ability to induce non-equivalence. If all these complexes were equally populated only minimal non-equivalence would be observed. The complexes of L-prolinamide also showed poor solubility in the solvents used (C_6D_6, $CDCl_3$).



a



b

Figure 6

2.5.2 L-proline N-methylamide (66d)

The N-methylamide (prepared from L-proline methyl ester) also showed only very limited CSA ability. The introduction of the N-methyl group on the amide will not significantly alter the preferred conformation of the diastereoisomeric complexes but offers some improvement in solubility.

2.5.3 (S)-2-(Anilino Methyl)-Pyrrolidine (67)
L-Proline p-Nitroanilide (66c)

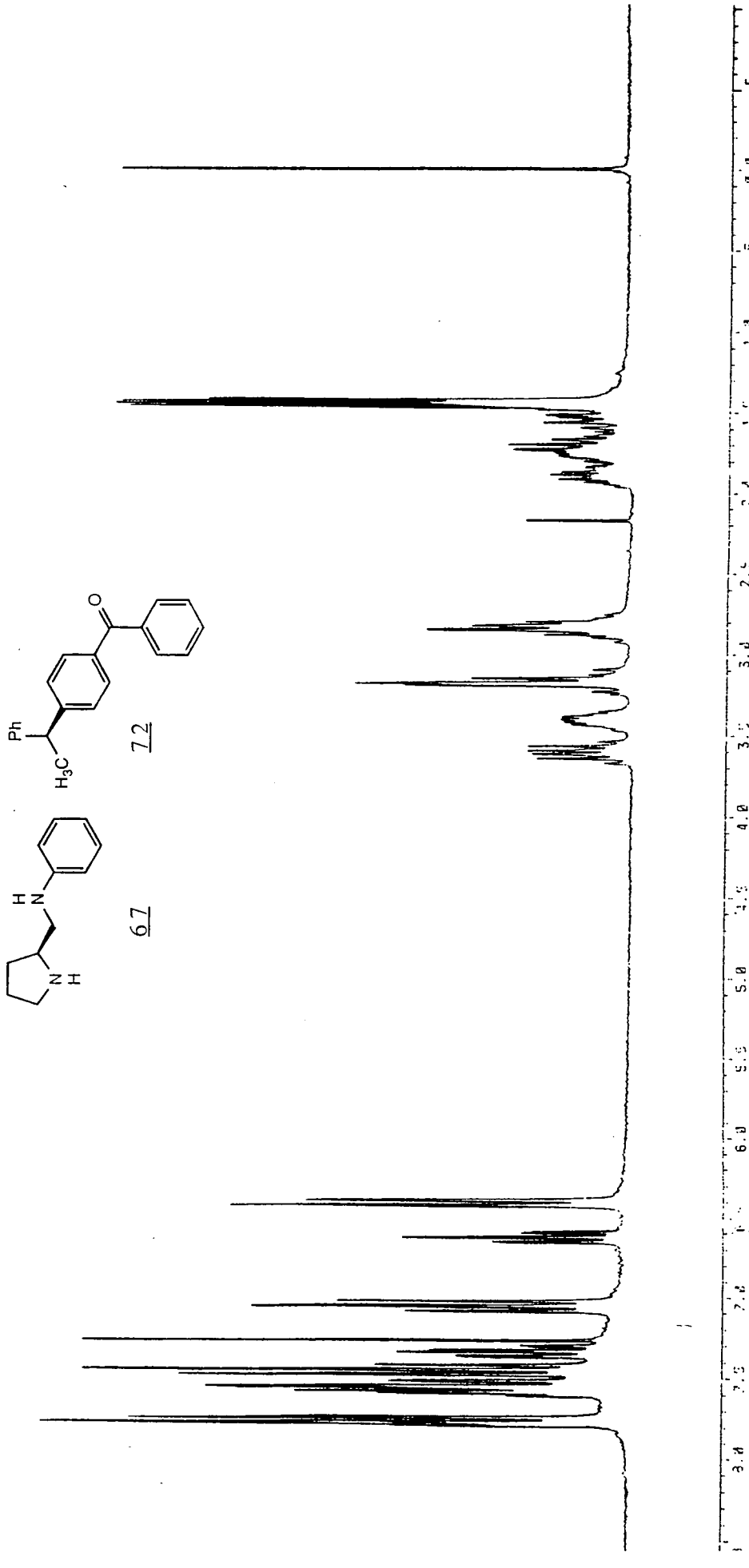
Both reagents gave measurable values of $\Delta\delta_H$ with a wide range of compounds. In the case of 67 non-equivalence was modest across the whole range of chiral acids and was usually bigger than with 66c. An example of the non-equivalence is given by **Spectrum 8** in which non-equivalence is observed at 1.5 ppm in the Me doublets of ketoprofen. An unusual case arose with 66c. The measured shift non-equivalence $\Delta\delta_H$ with MTPA as a substrate was large ($\Delta\delta_H$ = 0.102 ppm for OMe group at 3.7 ppm in C_6D_6, **Spectrum 9**). This could possibly be due to the preferential orientation of the nitroanilide group placing it proximate to the methoxy group of the MTPA in one of the diastereoisomeric complexes leading to an increase in $\Delta\delta_H$. A slight increase for 66c salt complexes in benzene-d_6 was also observed, this could also be due to the preferential orientation of the nitroanilide group in benzene.

Finally the 1,2-diamine 67 with a N-substituted phenyl group gave the best results of all of the amines tested so far. The observation that a potentially chelating chiral diamine gave the highest observed shift non-equivalence was very significant. It suggested that the primary hydrogen bonding interaction involved both N-H groups (**figure 7**) restricting the number of possible conformers available to each of the diastereoisomeric complexes, so enhancing the differentiating influence of the proximate phenyl ring.

Spectrum 8

S-2-(Anilinomethyl)-pyrrolidine

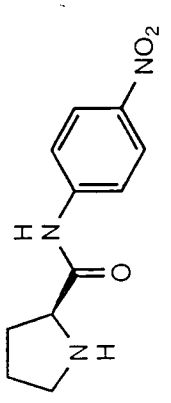
Ketoprofen



Spectrum 9

L-Proline p-Nitroanilide

MTPA



66c

11

It was considered desirable to investigate other chiral 1,2-diamines as potential CSA. After careful deliberation 1,2-diphenyl-1,2-diamimoethane 58 was chosen. Chapter 3 details the effectiveness of this reagent.

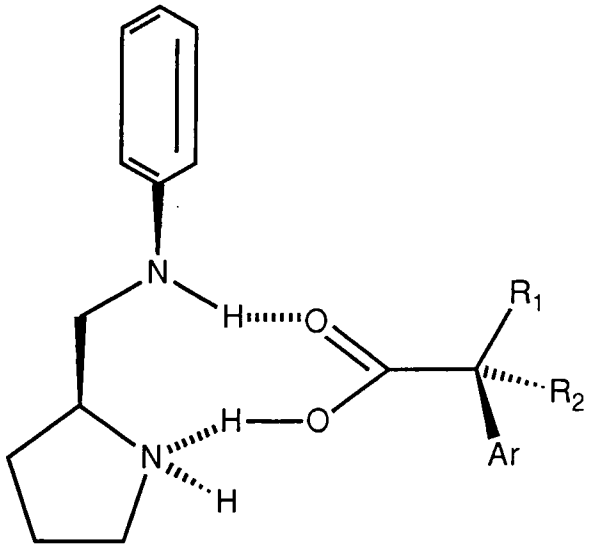


Figure 7

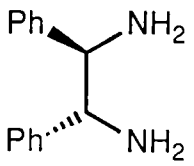
CHAPTER 3

1,2-Diphenyl-1,2-diaminoethane, a Chiral Solvating Agent for Carboxylic Acids

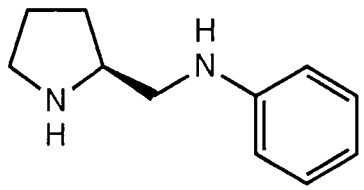
3.1 Introduction

1,2-Diphenyl-1,2-diaminoethane 58 is an easily synthesized chiral reagent, which has been used previously as the precursor for several chiral derivatising agents, such as 27[72,73] and 31c-e, 32a[83] (see sections 1.2.1.2-3). It was considered as a CSA following the observations discussed in Chapter 2 that the potentially chelating chiral diamine 2-(Anilino methyl)-pyrrolidine 67 gave the highest observed shift non-equivalence for a range of acids. It has a very simple ^1H NMR spectrum (**Spectrum 10**), and its high solubility in non-polar solvents ($CDCl_3$ and C_6D_6) and C_2 related anisotropic phenyl groups (capable of inducing non-equivalence in one diasterisomeric pair) render it highly suitable as a potential CSA.

The synthesis of the racemic diamine involved the reaction of benzil with cyclohexanone, ammonium acetate and acetic acid to form the isoimidazole (**Scheme 1**). The isoimidazole was then reduced with lithium and ammonia and the free amine obtained in excellent yield by acid catalysed hydrolysis. Resolution of the racemic mixture was achieved in high yield by differential crystallisation of the diastereoisomeric salts formed with enantiopure mandelic acid.



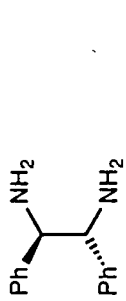
58



67

Spectrum 10

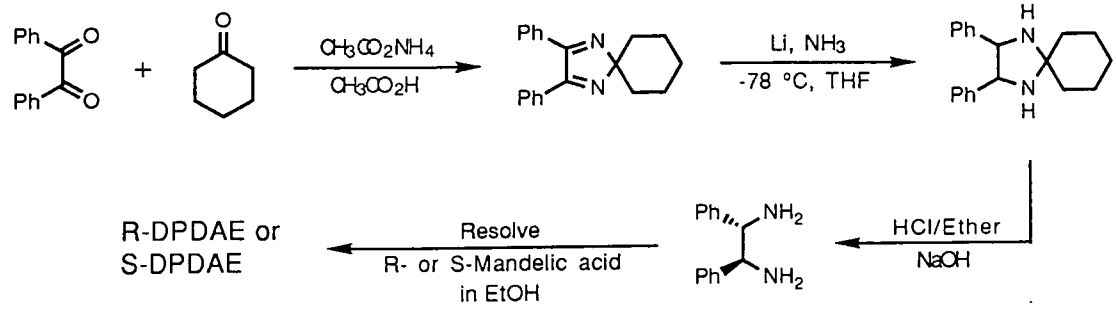
1,2-Diphenyl-1,2-diaminoethane



58

Initially the chiral diphenyldiamine was tested against a selected range of racemic acids at both 1:1 and 2:1 stoichiometry. High ^1H shift non-equivalence was observed in almost all cases in both $CDCl_3$ and C_6D_6 solvents. The unexpected result that 2:1 stoichiometry produced larger $\Delta\delta_H$ than the equivalent 1:1 stoichiometric salt complexes stimulated further investigation. The range of racemic acid substrates was increased to substantiate this observation and also to see if maximum non-equivalence was indeed observed at 2:1 stoichiometry, using both bulky mono-carboxylic or di-carboxylic acids. A thorough investigation of the parameters determining non-equivalence was carried out with selected racemic carboxylic acids including acid: amine stoichiometry, concentration, temperature and substrate enantiomeric purity.

The origins of non-equivalence were also sought, NOE difference NMR spectroscopy was used to in an attempt to determine the relative positions of neighbouring protons in both intermolecular associations within the diamine and intramolecular association in the diastereoisomer salts. The X-ray structure of the protonated salt as its mono-hydrobromide was determined and may be used as a basis for a discussion of the favoured conformation of the diamine in its solution complexes.



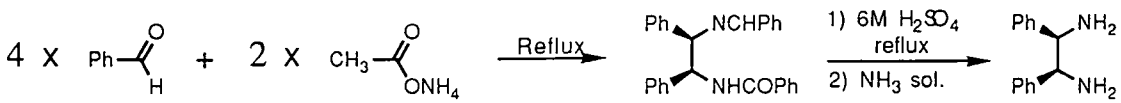
Scheme 1

Related 1,2-diamines

Non-equivalence could in theory be attributed in part or totally to a self recognition process involving the chiral carboxylic acids in the 2:1 solvation complex. Meso-1,2-Diphenyl-1,2-diaminoethane, the achiral diastereoisomer of DPDAE was synthesized therefore in an attempt to define the extent to which non-equivalence may be due to a self recognition process.

The synthesis of the meso-diamine involved the reaction of benzaldehyde with ammonium acetate to form the N-benzoyl-N^1-benzylidene-meso-1,2-diphenyl-1,2-diaminoethane followed by acid hydrolysis (**Scheme 2**). The meso-diamine was mixed with selected racemic carboxylic acids, and the results are listed in Section 3.3.5. Enantiopure 1,2-diaminocyclohexane, a diamine which is structurally similar to DPDAE, was studied in parallel as a CSA in order to assess the extent of the anisotropic effect of the phenyl groups on shift non-equivalence.

N-substituted derivatives of the chiral diamine 58 were synthesised in order to determine the effect of N-substitution on shift non-equivalence. This idea arose from the observation that secondary amines generally gave a larger $\Delta\delta_H$ than their 1° or 3° counterparts in such CSA experiments (Section 2.3).



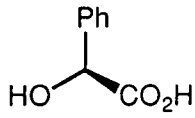
Scheme 2

The chiral diamine was found to render the methylene protons of primary carboxylic acids diastereotopic and induced considerable chemical shift non-equivalence. A range of such compounds were tested to discover the extent of this effect. Finally DPDAE 58 was used to accurately determine the enantiomeric purity of several commercially available chiral acids and to determine the absolute configuration of a sample of 2-methylbutyric acid.

3.2 The Measurement of Chemical Shift Non-equivalence with Chiral Carboxylic Acids.

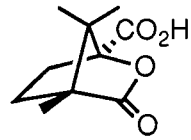
The sample preparation required for the NMR experiment is relatively straightforward. Typically 0.05 mmol of the diamine was mixed with 0.1 mmol of the chiral acid substrate (for 2:1 stoichiometry) and 0.1 mmol of both acid and diamine were used for 1:1 stoichiometry. The mixture was dissolved in the readily available halogenated solvent $CDCl_3$ or aromatic solvent C_6D_6 and the proton NMR spectrum was recorded immediately. A range of aromatic mono- and di-carboxylic acids with cyclic alkane and branched alkyl substituents were used as substrates in the analysis of $\Delta\delta_H$ in the salt complexes formed with the (IR,2R)-(-)-diamine (see **Figure 8**). The results are summarised in **Table 7**. Values for $\Delta\delta_H$ at both 1:1 and 2:1 stoichiometry are given.

Camphanic acid 20 and 2-methylbutyric acid 74 display the lowest chemical shift non-equivalence of the carboxylic acids tested. This could be attributed to the lack of a sufficiently strong secondary interaction to maintain the diastereomeric salt in a conformation where $\Delta\delta_H$ is observed. For 2-methyl butyric acid, the small difference in steric demand between a Me and Et group probably leads to little preference for a given conformer in the two diastereoisomeric salt complexes.



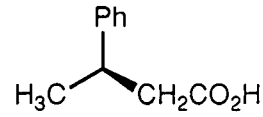
Mandelic acid

68



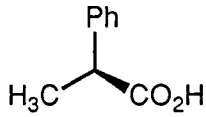
Camphanic acid

20



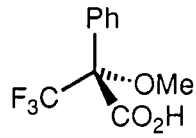
3-Phenylbutyric acid

69



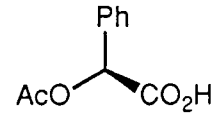
2-Phenylpropionic acid

70



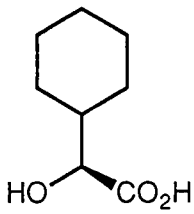
MTPA

11



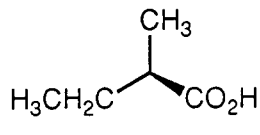
O-Acetylmandelic acid

19



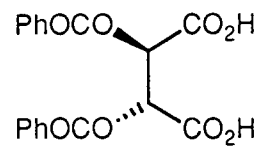
Hexahydromandelic acid

73



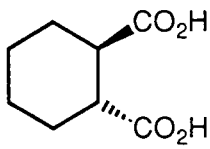
2-methylbutyric acid

74



O,O-Dibenzyl-L-tartaric acid

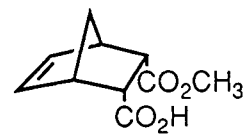
75



Trans-cyclohexane-

1,2-Dicarboxylic acid

76

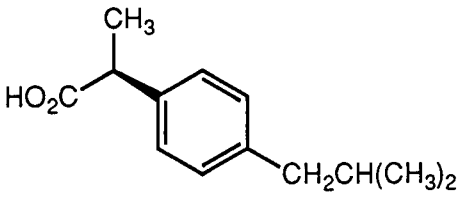


cis-endo-bicycl0[2.2.1]-6-methoxy-

carbonyl-hepta-2-ene-5-oic acid

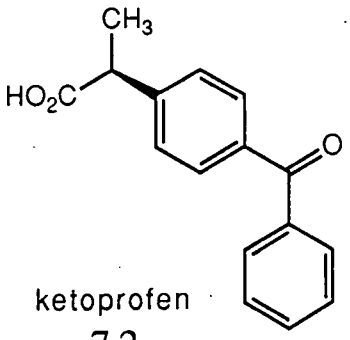
77

Figure 8



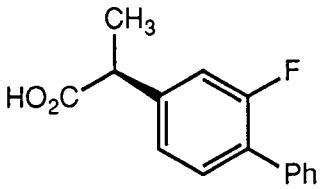
Ibuprofen

71



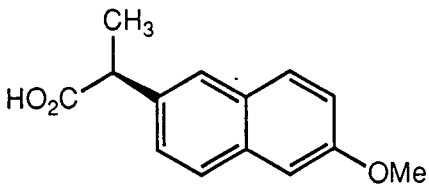
ketoprofen

72



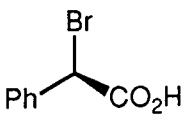
Flurbiprofen

78



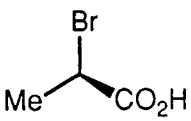
Naproxen

79



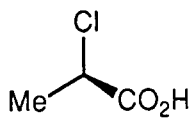
2-Bromophenylacetic acid

81



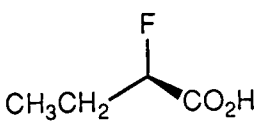
2-Bromopropionic acid

80



2-Chloropropionic acid

82



2-Fluorobutyric acid

83

Figure 9

TABLE 7

The measurement of $\Delta\delta$ for a range of mono- and di-carboxylic acids

Entry	substrate	observed resonance	solvent	$\Delta\delta_H$ Stoichiometry	
				1:1	2:1
1	68	2-H	$CDCl_3$	------	0.193
			C_6D_6/C_5D_5N (10:1)	0.049	0.059
2	20	------	$CDCl_3$	------	------
		CH_3	C_6D_6	------	0.013
3	69	2-CH_2-	$CDCl_3$	0.007	------
			C_6D_6	0.009	------
		2-H	$CDCl_3$	------	0.028
		2-CH_3	C_6D_6	0.009	0.019
4	70	2-H	$CDCl_3$	------	0.076
			C_6D_6	0.011	0.089
		2-CH_3	$CDCl_3$	------	0.027
			C_6D_6	------	0.012
5	11	2-OCH_3	$CDCl_3$	------	0.057
			C_6D_6	0.064	0.065
6	19	2-H	$CDCl_3$	0.152	0.171
			C_6D_6	0.163	0.178
		2-OAc	$CDCl_3$	0.054	0.076
			C_6D_6	0.050	0.016
7	73	2-H	$CDCl_3$	0.076	0.098
8	74	2-CH_3	$CDCl_3$	------	0.006
		------	C_6D_6	------	------
9	75	2-H	$CDCl_3/C_5D_5N$ (5:1)	0.039	------
10	76	2-H	$CDCl_3$	0.027	------
			C_6D_6	0.053	------
11	77	OCH_3	$CDCl_3$	0.027	0.006
			C_6D_6	0.015	0.017

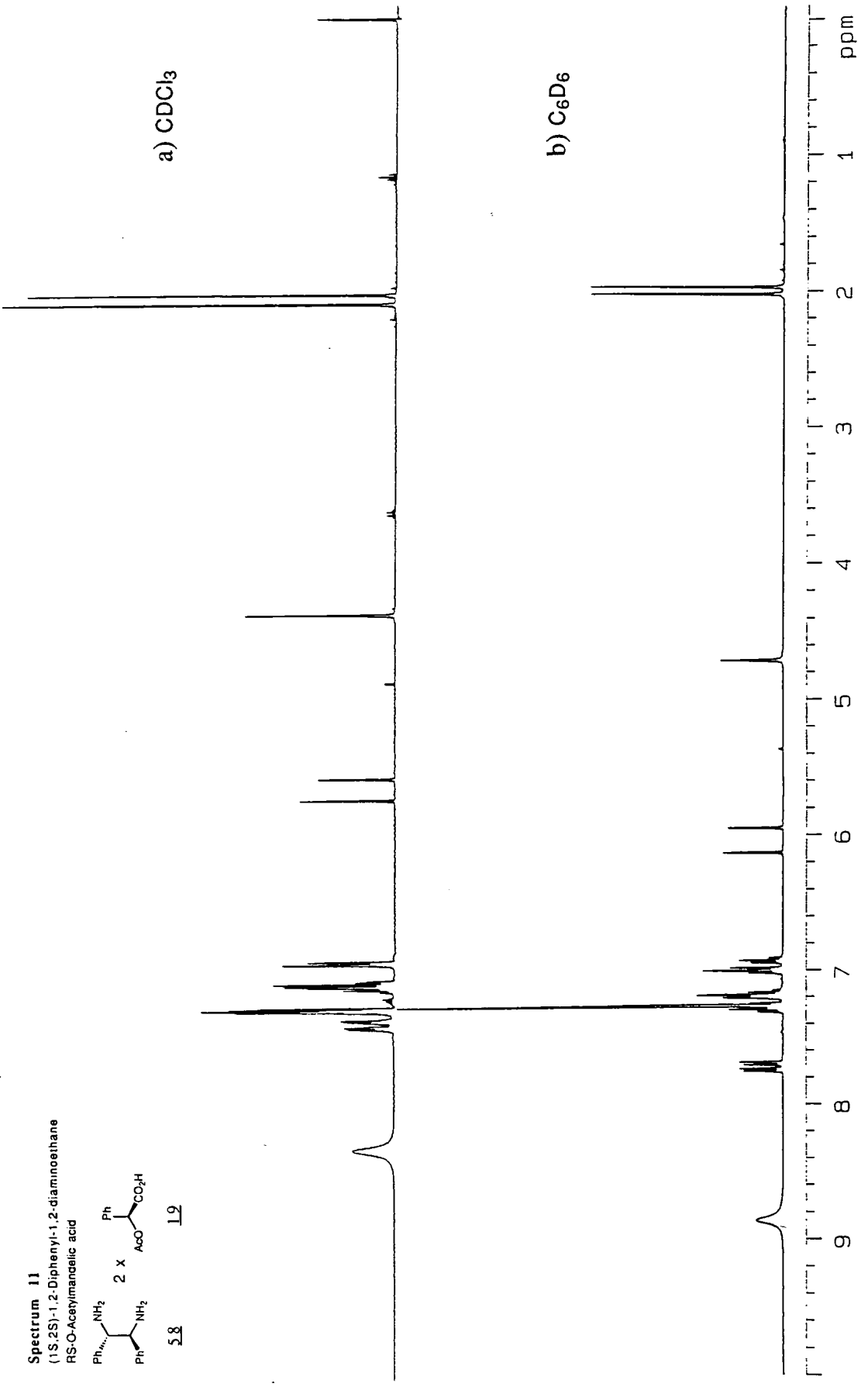
The sense of the chemical shift non-equivalence is consistent and the value is large ($\Delta\delta_H$ > 0.05 ppm) for the majority of acids tested. The largest shift difference observed between the chiral diamine and a racemic acid involved 1R,2R-(-)-1,2-diphenyl-1,2-diaminoethane and O-acetyl-mandelic acid at 2:1

stoichiometry (**Spectra 11a,b**). The marked non-equivalence between the diastereomeric resonance of the acetyl group at 2.0 ppm and the methine resonance at 5.6 ppm is evident in **spectra 11a** and **11b**. Mono-α-phenyl carboxylic acids gave the bigger $\Delta\delta_H$ compared to their di-acid or alkyl counterparts.

3-Phenylbutyric acid 69 displays a small degree of non-equivalence in the 2-methylene protons at 1:1 stoichiometry which is not present at 2:1 stoichiometry. This could be due to the different conformations adopted by each complex which in the case of 1:1 stoichiometry places the methylene protons near a stereochemically dependent group such as the phenyl ring.

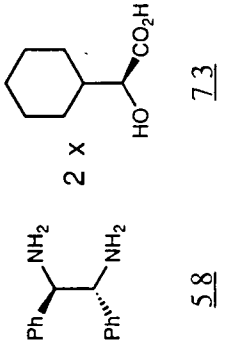
Salts of both hexahydromandelic acid 73 and O,O-dibenzyl-L-tartaric acid 75 suffered from poor solubility in the solvents examined. Compound 73 displayed good chemical shift non-equivalence ($\Delta\delta_H$ = 0.098 ppm, $CDCl_3$, 2:1 ratio). This could be related to the strong secondary hydrogen bonding interaction caused by the hydroxyl group. The chemical shift non-equivalence is observed in the methine group at 3.7 ppm, **Spectrum 12** shows the non-equivalence observed for the 2:1 complex.

The chiral di-acids O,O-dibenzoyl-L-tartaric acid 75 and Trans-cyclohexan-1,2-dicarboxylic acid 76 (**Spectrum 13**) display shift non-equivalence at 1:1 stoichiometry only. The loss of observed chemical shift non-equivalence at 2:1 stoichiometry is possible due to a combination of factors in the rapidly reversible equilibrium, one of which could be the formation of a low energy complex with low $\Delta\delta_H$.


Spectrum 11
(1S,2S)-1,2-Diphenyl-1,2-diaminoethane
RS-O-Acetylmandelic acid
2 x
5.8
19
a) $CDCl_3$
b) C_6D_6
ppm
9
8
7
6
5
4
3
2
1

Spectrum 12

(1R,2R)-1,2-Diphenyl-1,2-diaminoethane
RS-Hexahydromandelic acid

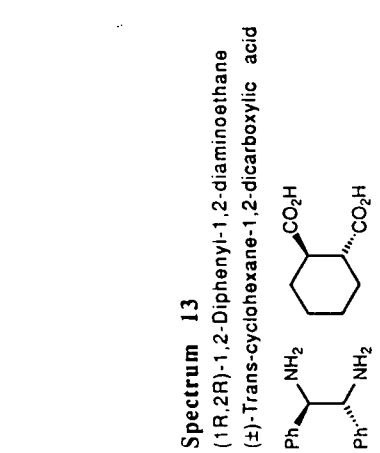


5.8 7.3

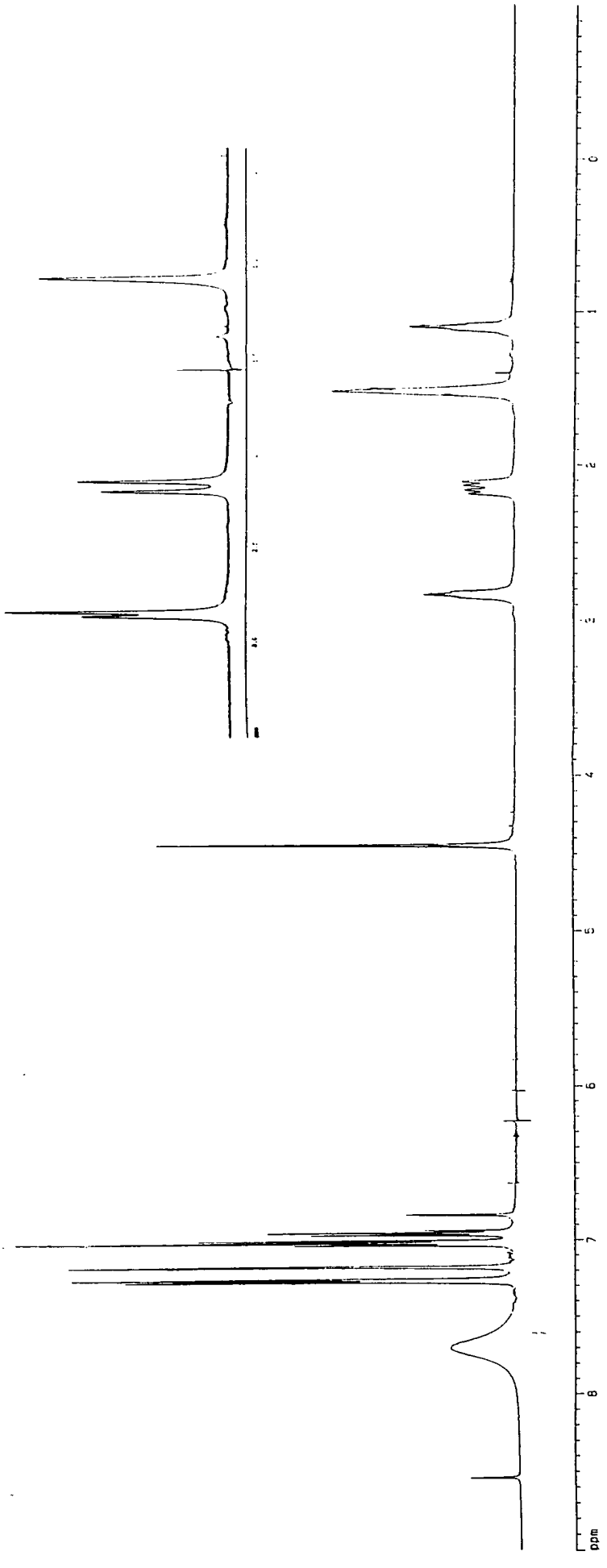
Spectrum 13

(1R,2R)-1,2-Diphenyl-1,2-diaminoethane

(±)-Trans-cyclohexane-1,2-dicarboxylic acid



5.8 7.6



The relatively bulky acid 77 shows a higher non-equivalence at 1:1 compared to 2:1 stoichiometry. This could be due to the increased steric crowding in the 2:1 complex which may force the solvate into a very different conformations with a minimal resultant $\Delta\delta_H$.

A series of antiinflammatory agents and α-halo acids (**Figure 9**) were assayed with the CSA, (**Tables 8, 9**). The summarised data shows the observed resonance in either $CDCl_3$ or C_6D_6 at 2:1 and 1:1 stoichiometry for these substrates. The antiinflammatory α-aryl propionic acid derivatives (**Table 8**) typically display large chemical shift non-equivalence for both the methyl and methine protons under the conditions used. Ibuprofen gave the largest chemical shift non-equivalence for the methine proton ($\Delta\delta_H$ = 0.168 in C_6D_6, 2:1 stoichiometry). **Spectrum 14** shows the non-equivalence of the fully resolved methine proton quartets.

Large non-equivalence was associated with α-phenyl groups in the previous chiral mono carboxylic acids (**Figure 8**). The introduction of ortho and meta substituents on the phenyl ring affects the observed non-equivalence. If these reagents are compared to 2-phenyl propionic acid 70 which has essentially the same structure, but with no phenyl substituents, both 78 and 79 show no significant change while Δδ values for 72 are reduced and 71 show significant increase in non-equivalence. The conformation which brings about non-equivalence in the diastereomeric salts is not solely influenced by steric effects; the expected values for flurbiprofen 78 and Naproxen 79 would differ more if this was so. Electronic effects could also influence $\Delta\delta_H$. The iso-butyl group of Ibuprofen will weakly enhance the π basicity of the aryl group. This may increase the solubility of the diastereoisomeric salt complex responsible for $\Delta\delta_H$. The reverse is true for Ketoprofen where the carboxyl group may be increasing the π acidity of the aryl group.

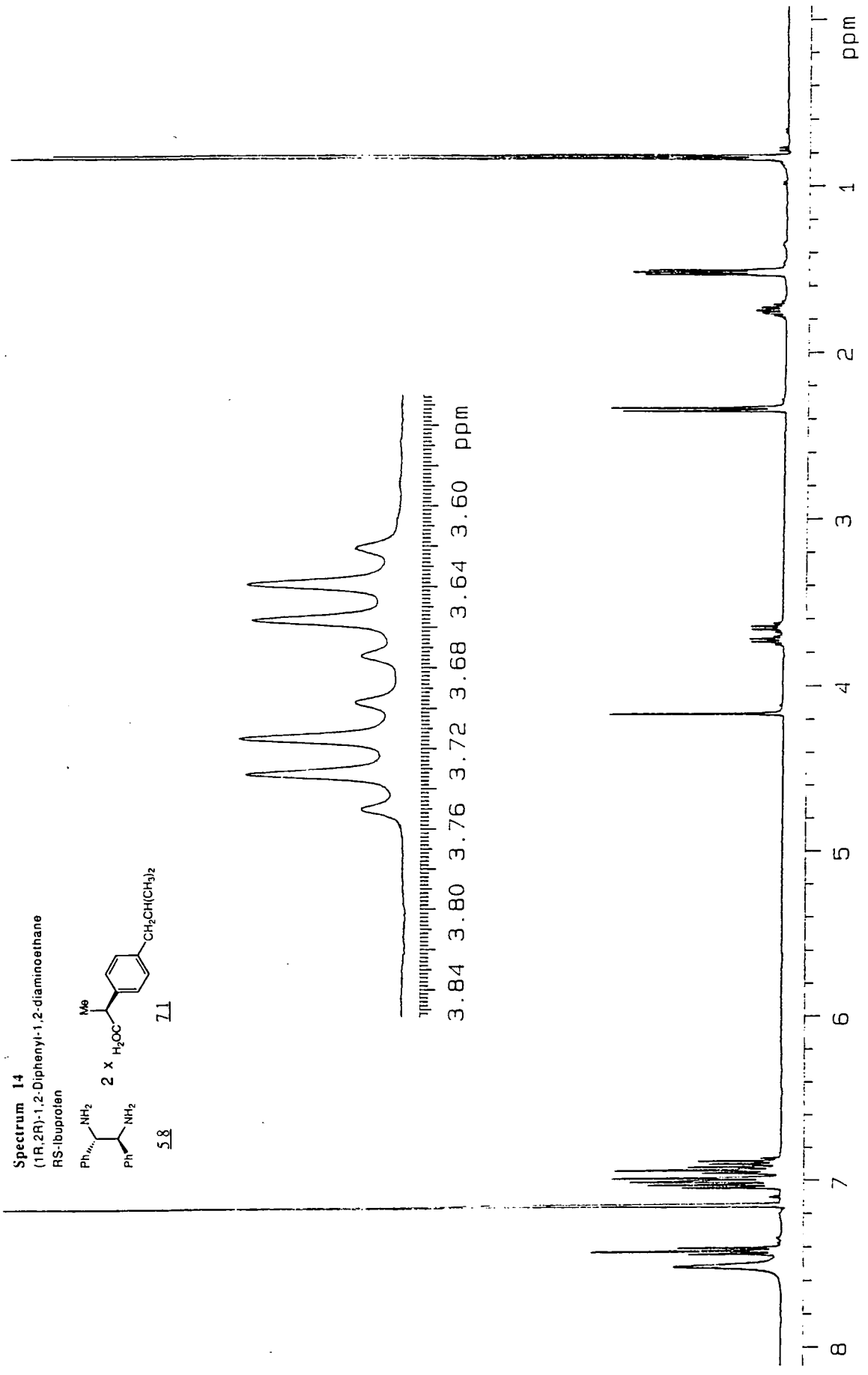

Spectrum 14
(1R,2R)-1,2-Diphenyl-1,2-diaminoethane
RS-Ibuprofen
2 x
5.8
7.1
3.84 3.80 3.76 3.72 3.68 3.64 3.60 ppm
ppm
1
2
3
4
5
6
7
8

TABLE 8

The measurement of $\Delta\delta$ for selected anti-inflaminatroy agents.

Entry	substrate	observed resonance	solvent	$\Delta\delta_H$ Stoichiometry	
				1:1	2:1
1	71	2-H	$CDCl_3$	0.049	0.099
			C_6D_6	0.014	0.168
		2-CH_3	$CDCl_3$	0.016	0.031
			C_6D_6	------	0.027
2	72	2-H	$CDCl_3$	0.014	0.032
			C_6D_6	0.019	0.056
		2-CH_3	$CDCl_3$	0.012	0.025
			C_6D_6	0.014	0.025
3	78	2-H	$CDCl_3$	0.036	0.075
			C_6D_6	0.017	0.090
		2-CH_3	$CDCl_3$	0.020	0.039
			C_6D_6	------	0.021
4	79	2-H	$CDCl_3$	0.034	0.068
			C_6D_6	0.012	0.091
		2-CH_3	$CDCl_3$	0.018	0.034
			C_6D_6	------	0.025

The nature of the solvent also affects the chemical shift non-equivalence in 1:1 and 2:1 complexes. This is particularly notable in the case of the methine non-equivalence of the anti-inflammatory agents. At 2:1 stoichiometry maximum $\Delta\delta_H$ occurs in d_6-benzene, but at 1:1 stoichiometry maximum $\Delta\delta_H$ is usually observed in deutero-chloroform, **Figure 10** shows how the methine resonances of flurbiprofen vary with solvent. The apparent change in order could be due to the preferential solvation of a given conformation in the salt complexes which leads to $\Delta\delta_H$ in the 1:1 (stoichiometry) diastereoisomeric salt complexes. This could be a result of π-stacking interactions between the aryl solvent and substrate [180].

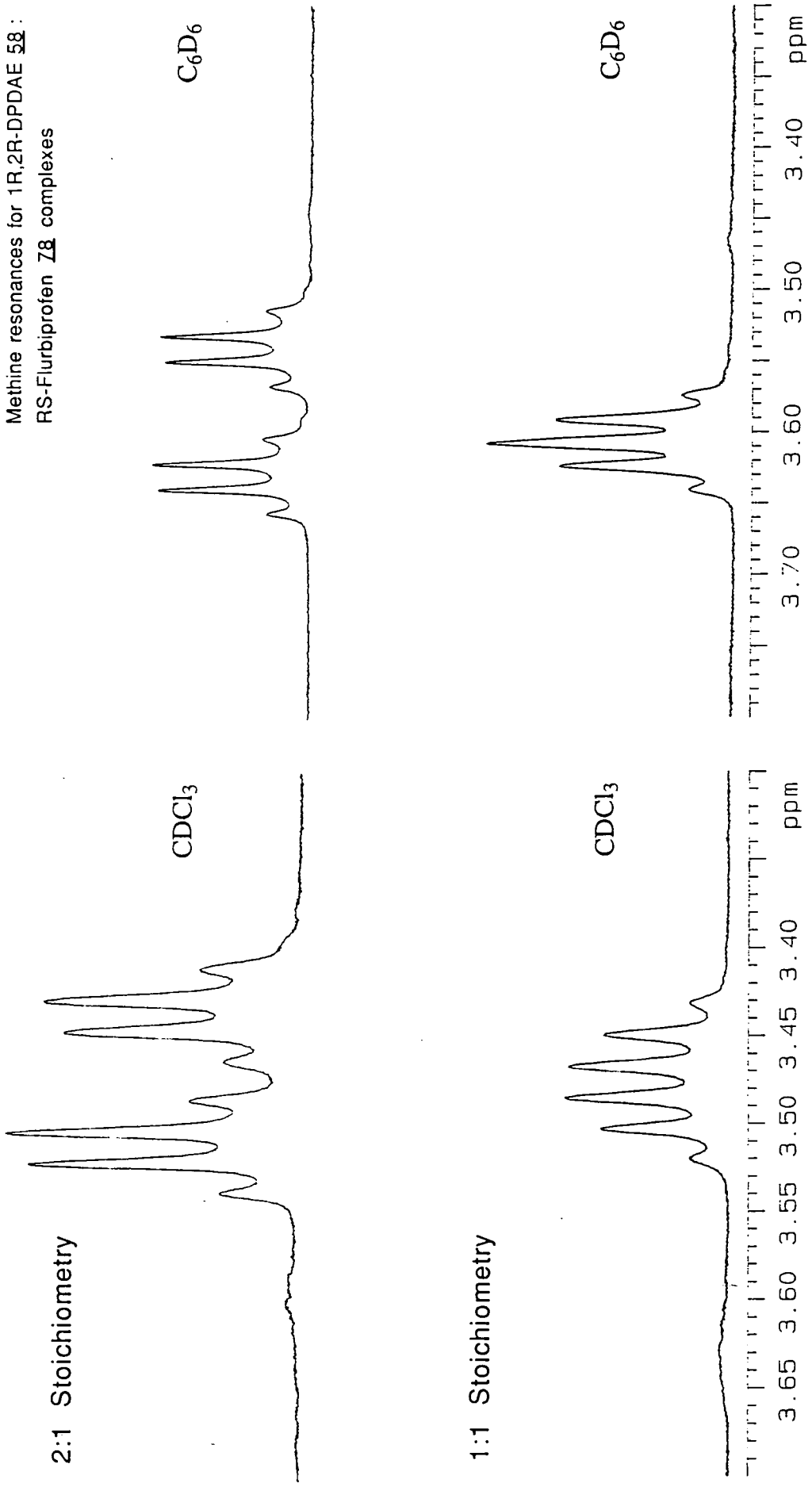


Figure 10
Methine resonances for 1R,2R-DPDAE 58 :
RS-Flurbiprofen Z8 complexes

TABLE 9

The mesurement of $\Delta\delta$ for α-halopropionic acids.

Entry	substrate	observed resonance	solvent	$\Delta\delta_H$ Stoichiometry	
				1:1	2:1
1	80	2-CH_3	$CDCl_3$	0.080	0.0230
			C_6D_6	0.118	------
		2-H	$CDCl_3$	0.086	0.037
			C_6D_6	0.046	------
2	81	2-H	$CDCl_3$	0.176	0.287
			C_6D_6	0.206	0.339
3	82	2-CH_3	$CDCl_3$	0.105	0.269
			C_6D_6	0.062	0.151
		2-H	$CDCl_3$	0.129	0.240
			C_6D_6	------	0.150
4	83	2-CH_3	$CDCl_3$	0.054	0.086
			C_6D_6	0.081	0.089
		2-F	$CDCl_3$	------	0.125
			C_6D_6	------	0.172

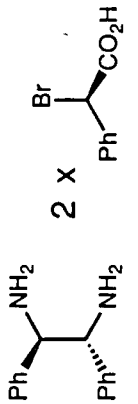
The α-halo acids displayed the highest chemical shift non-equivalence of all chiral mono-acids examined for both methyl and methine protons (**Table 9**). α-Bromophenyl-acetic acid 81 2:1 complex (**Spectrum 15**) had a chemical shift non-equivalence of 0.339 ppm in the methine protons at 5.2 ppm which was the largest observed for all the chiral carboxylic acids tested.

The introduction of the α-halogen atom substantially increases $\Delta\delta_H$ compared to the corresponding α-aryl acids. The increased acidity of the chiral acid methine proton could be involved in 2° interactions which increase non-equivalence in the conformation responsible for $\Delta\delta_H$. This could be considered similar to the effect of the acidic proton in Pirkle's reagent 1-(9-anthryl)-2,2,2-trifluoroethanol 48 [134].

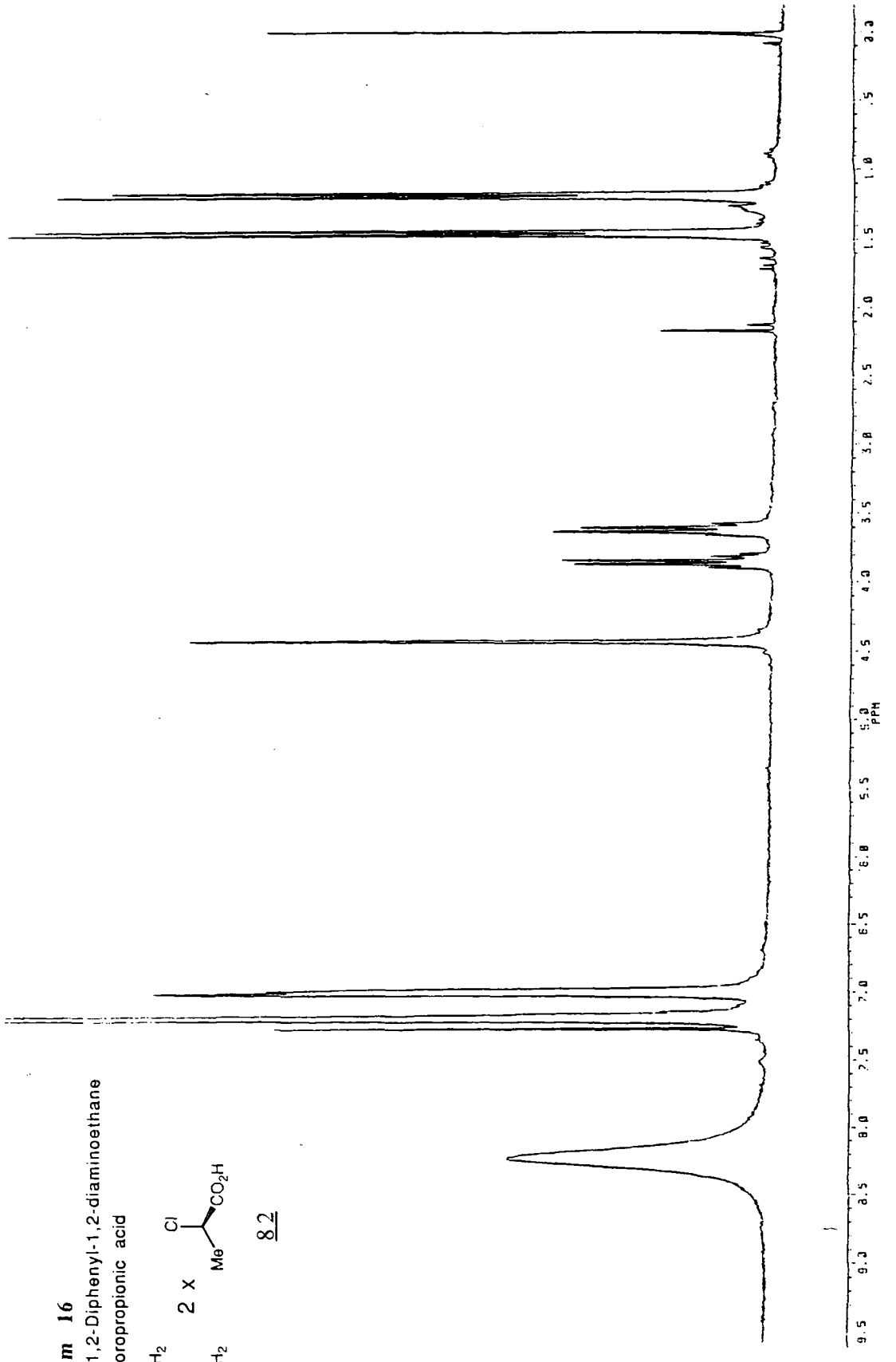
Spectrum 15

(1R,2R)-1,2-Diphenyl-1,2-diaminoethane

RS-α-Bromophenylacetic acid



58 81


Spectrum 16
(1S,2S)-1,2-Diphenyl-1,2-diaminoethane
RS-2-Chloropropionic acid
Ph
NH2
Ph
NH2
2 x
Cl
Me
CO2H
58
82
PPM

A more typical example of this class of substrate is provided by 2-chloropropionic acid with $\Delta\delta_H$ = 0.269 ppm observed between the diastereomeric methine protons at 3.8 ppm in d_6-chloroform (**Spectrum 16**).

3.2.1 Comparison of DPDAE with α-Methylbenzylamine

The conformation which the 1,2-diamine adopts with the chiral acid at 2:1 stoichiometry could be affected by the neighbouring phenyl and amine substitute. In an attempt to resolve this point the known CSA α-methylbenzylamine, with an essentially similar structure to a mono amine subunit of the diamine was tested against a limited range of chiral acids (at 1:1 stoichiometry) **Table 10**. The majority of diastereoisomeric complexes gave significantly lower chemical shift non-equivalence indicating that the β-substituents of 1,2-diphenyl-1,2-diaminoethane do indeed influence the structure and relative population of the preferred low-energy conformation.

Whether this was sterically induced or due to the interactions between the two possible complexing acids was not clear. Further investigations were thought necessary. The anomaly of entry 3 in **Table 10**, where $\Delta\delta_H$ is larger for the di-acid trans-cyclohexane-1,2-dicarboxylic acid 76 with the mono-amine when compared to the diamine is notable.

TABLE 10

The measurement of Δδ with 2-methylbenzylamine for selected chiral carboxylic acids[a].

Entry	substrate	observed resonance	solvent	$\Delta\delta_H$
1	20	CH_3	C_6D_6	0.045
2	19	2-H 2-OAc	C_6D_6	0.157 0.016
3	76	2-H	C_6D_6	0.086
4	71	2-CH_3	C_6D_6	0.041
5	82	2-CH_3	C_6D_6	0.014

a) Chemical shift non-equivalence was measured at one molar equivalent of acid to amine

3.3 Parameters Determining Chemical Shift Non-equivalence

In an attempt to discover the origins of anisochronicity and to examine how the magnitude of chemical shift non-equivalence varies with experimental conditions, several NMR experiments were carried out. These involved observing how the magnitude of the chemical shift non-equivalence varied with changes in a) amine: acid stoichiometry, b) concentrations, c) substrate enantiomeric purity and d) temperature.

In addition the nature of the 1,2-diamine structure was investigated. The X-ray structure of the mono-hydrobromide salt was used as a basis for considering the possible conformation in the related 2:1 complexes with 2 carboxylate anions. Meso-1,2-diphenyl-1,2-diamino ethane was synthesised and a series of racemic acids were tested. This allowed an assessment of the possible contribution of 'self recognition' in the observed shift non-equivalence. In the case of 2:1 complexes of chiral acids with an achiral amine substrate, two sets of enantiomeric complexes may form (which are isochronous) and one meso complex may form (RS = SR). The relative ratio of these diastereoisomeric complexes (RR/SS versus meso) allows enantiomeric purity to be determined in principle (see section 1.2.1.3).

The extent of the contribution of the phenyl group of the 1,2-diamine to induce non-equivalence was assessed by comparing shift non-equivalence values with 2:1 complexes of enantiopure trans-1,2-cyclohexyldiamine (using parallel chiral acid complexes of the diamine). The extent to which the primary amine structure in DPDAE determines non-equivalence was studied by comparing its behaviour with its NHR analogue. As discussed previously, higher $\Delta\delta_H$ values have been noted using 2° amines compared to 1° amines in such CSA experiments.

3.3.1 The Effect of Stoichiometry on Observed $\Delta\delta_H$

Standard solutions of both acid and diamine (0.1 M) were prepared in a suitable deuterated solvent. The solutions were mixed to give the required stoichiometric ratio. Care was taken to maintain the concentration of the combined acid and amine solution at 0.1 mmol ml^{-1}.

Variable stoichiometry data for 2-chloropropionic 82 acid and (1R,2R)-1,2-diphenyl-1,2-diaminoethane in $CDCl_3$ is given in **Table 11**. The shift non-equivalence values are recorded in the range of 10:1 to 2:5 ratio of acid to 1,2-diamine. A plot of the fractional ratio of diamine against the observed shift non-equivalence for the α-methyl resonance of the acid displays some interesting features of the data (**Graph 1**). Maximum shift non-equivalence was observed at 2:1 stoichiometry of the acid:amine. The rapid rate of change in non-equivalence with increasing acid ratio in the range 10:1 to 2:1 acid:amine could be attributed to several factors. The concentration of uncomplexed acid although enhancing 2:1 acid:amine complexation through time averaged exchange does not contribute to the observed non-equivalence (See section 1.2.3). Secondly acid-amine complexation competes with acid dimerisation in the non-polar solvent used. Although less effective, dimerisation will tend to increase the amount of uncomplexed acid. The increase in the CSA relative to the acid substrate between 2:1 and 1:1 stoichiometry also decreased chemical shift non-equivalence. This could be due to competitive formation of the 1:1 diastereomeric salt complexes with lower intrinsic $\Delta\delta_H$ values. The increase in 1,2-diamine stoichiometry beyond 1:1 ratio does not significantly perturb shift non-equivalence. A threshold value is reached which is probably a good measure of the intrinsic value of $\Delta\delta_H$ for the 1:1 complex. It is particularly striking that this is smaller compared to the related 2:1 complex (0.28 ppm 2:1, 0.07 ppm 1:1 for 2-chloropropionic acid).

Graph 1

The plot of non-equivalence against stoichiometry for 1,2-DPDAE and 2-chloropropionic acid 82

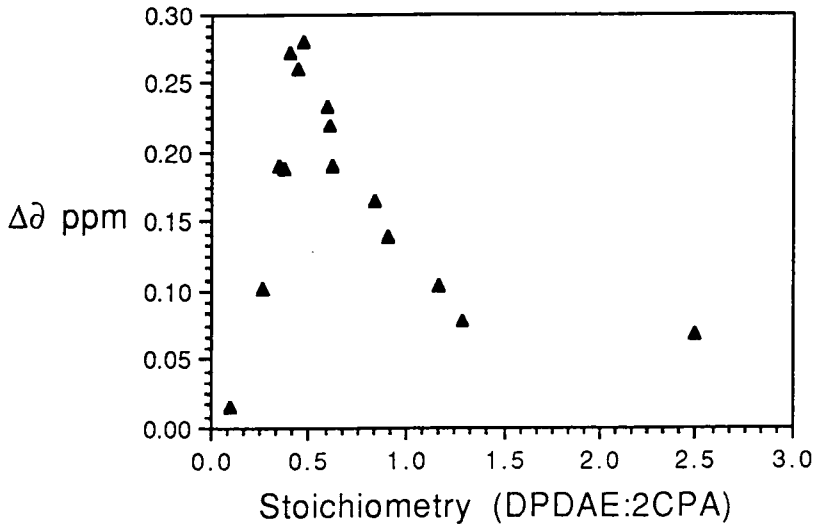


TABLE 11

The measurement of $\Delta\delta_H$ against stoichiometry for 2-chloropropionic acid 82

Fractional ratio DPEDA	observed α-methine resonance (ppm)			observed α-methyl resonance (ppm)		
	Hf	Lf	$\Delta\delta_H$	Hf	Lf	$\Delta\delta_H$
0.099	4.389	4.380	0.009	1.678	1.661	0.016
0.255	4.194	4.127	0.067	1.587	1.485	0.102
0.258	4.194	4.127	0.067	1.587	1.484	0.103
0.034	4.032	3.898	0.134	1.529	1.338	0.191
0.374	4.025	3.885	0.140	1.523	1.334	0.189
0.403	3.869	3.642	0.227	1.467	1.194	0.273
0.434	3.901	3.694	0.207	1.482	1.221	0.261
0.461	3.846	3.601	0.245	1.456	1.176	0.280
0.590	3.875	3.643	0.232	1.442	1.208	0.234
0.608	3.893	3.670	0.223	1.447	1.227	0.220
0.615	3.930	3.731	0.199	1.455	1.264	0.191
0.833	3.969	3.787	0.182	1.461	1.297	0.164
0.907	4.004	3.845	0.159	1.466	1.327	0.139
1.628	4.069	3.945	0.124	1.485	1.381	0.104
1.282	4.120	4.029	0.091	1.504	1.426	0.078
2.500	_____	_____	_____	1.530	1.462	0.068

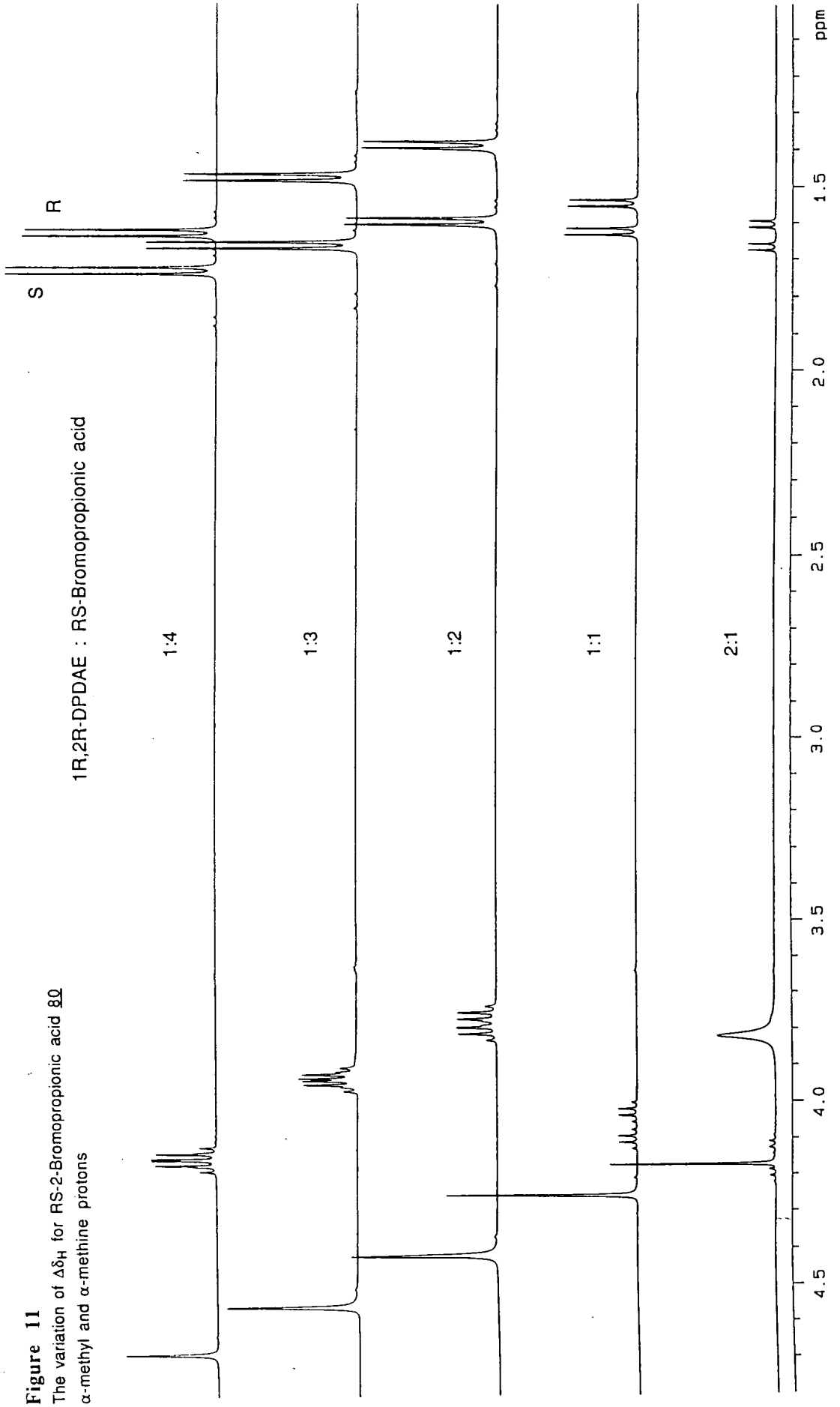


Figure 11
The variation of $\Delta\delta_H$ for RS-2-Bromopropionic acid 80
α-methyl and α-methine protons

The variation of $\Delta\delta_H$ vs stoichiometry was also studied for 2-bromopropionic acid 80 (**figure 11**). The diastereotopic α-methyl doublets in each complex are shifted to lower frequency, when approaching the optimal 2:1 stoichiometry. The R-2-bromopropionic acid (IR,2R)-1,2-DPDAE diastereomeric salt complex shows the larger change in shift difference with varying stoichiometry. This implies that the diastereotopic methyl groups in the R-RR complex are closer, on average to the neighbouring anisotropic phenyl group in the preferred conformation. A different behaviour is observed simultaneously for the diastereotopic methine quartets, in this case, maximal $\Delta\delta$ is observed at 1:1 stoichiometry.

3.3.2 The Effect of Concentration on Observed $\Delta\delta_H$

A concentrated solution of the salt complex in a suitable NMR solvent was diluted incrementally; at each stage the ^1H NMR Spectrum was recorded. The concentration dependence of the shift non-equivalence for 2-phenylpropionic acid 70 and (IR,2R)-1,2-DPDAE was measured in the range of 0.005 M to 0.5 M CSA. The results are listed in **Table 12**. The variation of concentration with $\Delta\delta_H$ (**Graph 2**) for the α-methyl protons of 2-phenylpropionic acid show a rapid increase in shift non-equivalence with concentration to approximately 0.1 M. Thereafter there is a less steep dependence. A reduction in $\Delta\delta_H$ due to ion-pair aggregation was not noted in the concentration range studied, but was apparent at ≥ 0.5 M for the equivalent complex in C_6D_6. Examination of the spin coupled methine peaks yielded analogous results. Both diastereomeric methine protons of 2-phenyl-propionic acid are shifted to lower frequency with increasing concentration. The diastereomeric complex of S-2-phenyl-propionic acid (1R,2R)-1,2-DPDAE (lower frequency doublet) displayed the larger sensitivity of shift difference with change in concentration. Increasing the concentration of salt favours the formation of the diastereomeric complexes. This would be expected due to the nature of the rapid equilibrium

between the free and complexed acids and the differential sensitivity of the observed chemical shift for the methyl doublet in the diastereoisomeric complexes must relate to the fact that their association constants are non-equivalent.

Graph 2

A plot of chemical shift non-equivalence against 1,2-DPDAE, and 2-phenylpropionic acid 70 concentration

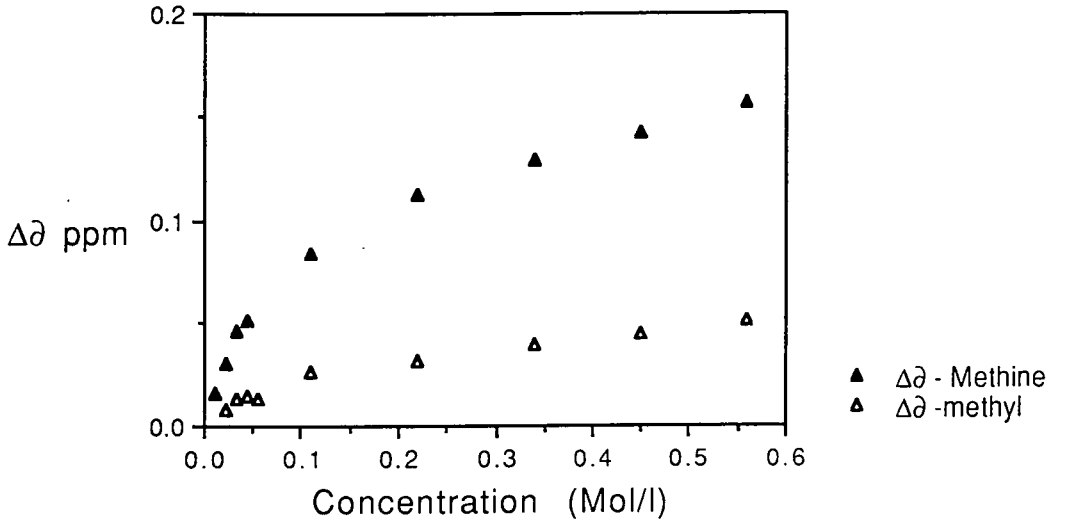


TABLE 12

The concentration dependance of $\Delta\delta_H$ for 2-phenylpropionic acid 70

concentration w.r.t. DPEDA	observed α-methine resonance (ppm)			observed α-methyl resonance (ppm)		
	Hf	Lf	$\Delta\delta_H$	Hf	Lf	$\Delta\delta_H$
0.560	3.384	3.227	0.157	1.297	1.246	0.051
0.450	3.404	3.262	0.142	1.305	1.260	0.045
0.340	3.423	3.293	0.130	1.314	1.274	0.040
0.220	3.449	3.336	0.113	1.324	1.292	0.031
0.110	3.501	3.418	0.083	1.356	1.330	0.026
0.056	_____	_____	_____	1.400	1.387	0.013
0.045	3.565	3.514	0.051	1.395	1.380	0.015
0.034	3.577	3.532	0.045	1.404	1.390	0.014
0.022	3.603	3.573	0.030	1.408	1.400	0.008
0.011	3.653	3.637	0.015	_____	_____	_____

3.3.3 The Effect of Enantiomeric Composition on $\Delta\delta_H$

Standard solutions of O-acetylmandelic acids, [OAM], (0.1 mmol ml^{-1}) at various enantiomeric compositions were prepared. The solutions were mixed with 0.5 molar equivalents of 1S,2S-(+)-1,2-diphenyl-1,2-diaminoethane. The data is collated in **Table 13** and displayed graphically (**Graph 3**) for the variation of the OAM α-methine proton against increasing enantiomeric composition of R-OAM. An approximately linear or a weakly sigmoidal relationship between these two parameters may be considered. This has previously been observed with other systems[154,160,163,167,181] and is a consequence of the non-equivalence of the associated constants for diastereoisomeric salt formation K_R and K_S.

Graph 3

A plot of enantiomeric purity versus chemical shift non-equivalence for the 1,2-DPDAE salt complexes of O-acetylmandelic acid.

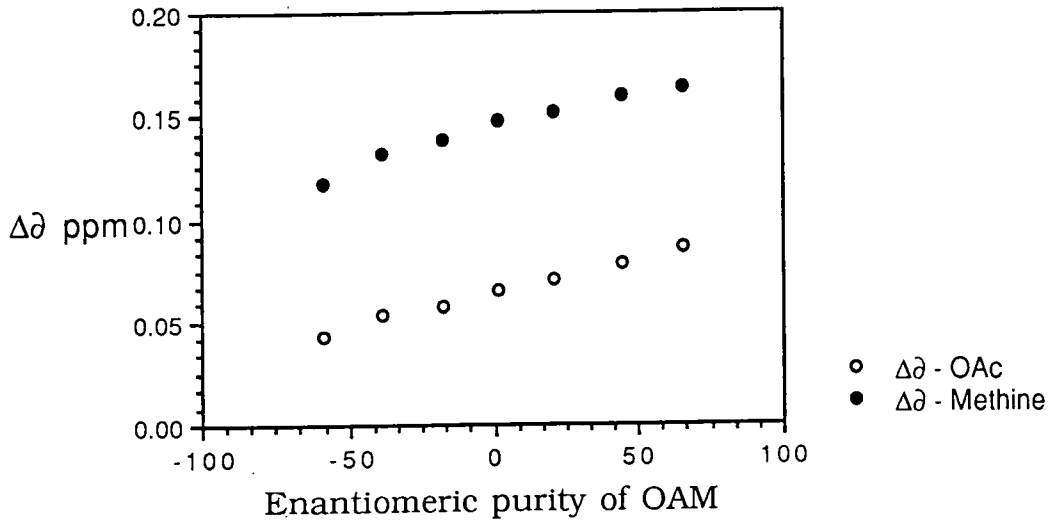


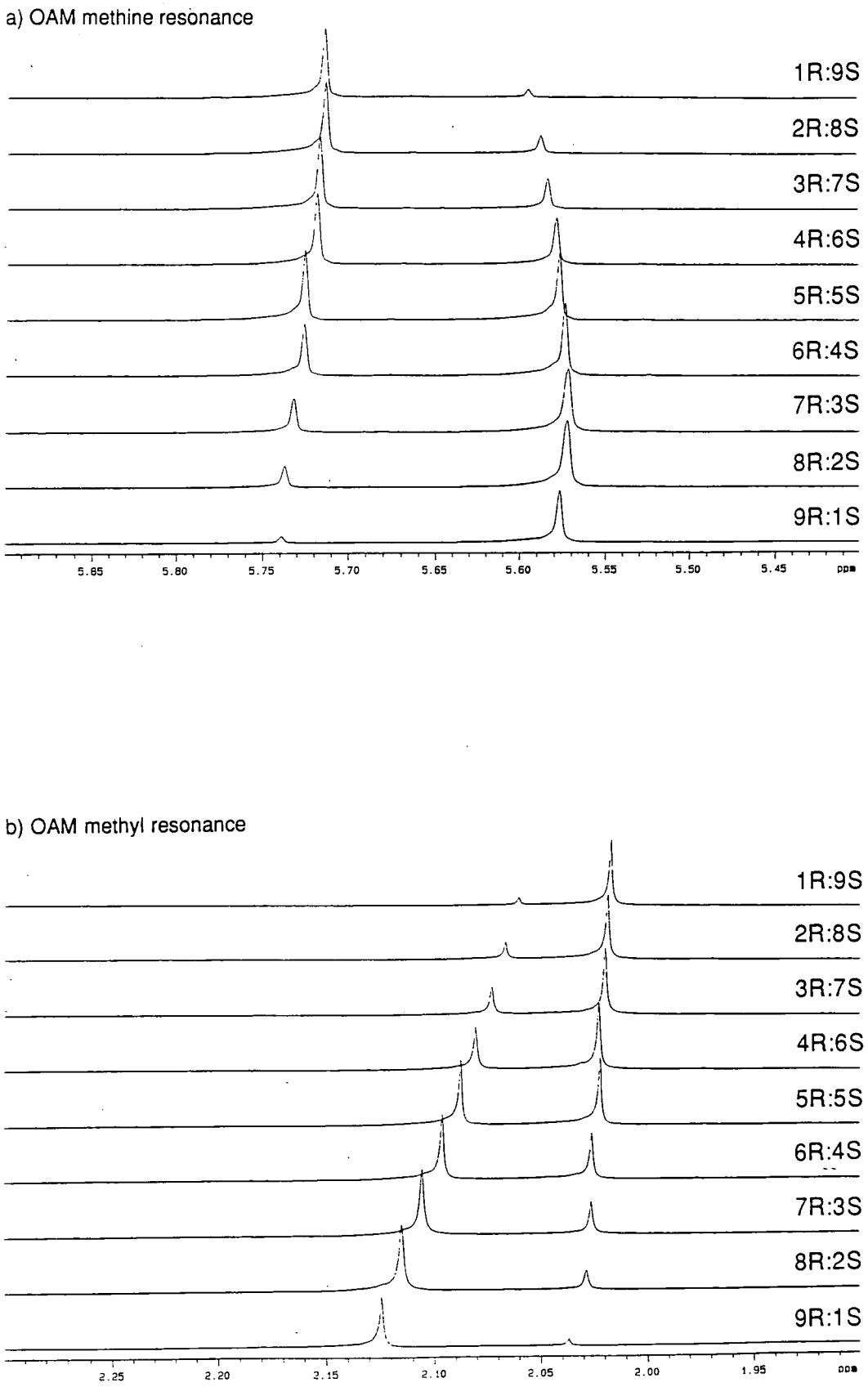
TABLE 13

The measurement of $\Delta\delta_H$ against enantiomeric purity of O-acetylmandelic acid 19

Enantiomeric Excess R-OAM	observed α-methine resonance (ppm)			observed OAc resonance (ppm)		
	Hf	Lf	$\Delta\delta_H$	Hf	Lf	$\Delta\delta_H$
0.656	5.738	5.574	0.164	2.114	2.028	0.086
0.439	5.572	5.731	0.159	2.105	2.026	0.079
0.207	5.574	5.725	0.151	2.095	2.025	0.070
0.011	5.579	5.727	0.148	2.088	2.023	0.065
-0.178	5.579	5.718	0.139	2.080	2.022	0.058
-0.385	5.585	5.717	0.132	2.072	2.019	0.053
-0.592	5.717	5.599	0.118	2.062	2.019	0.043

The effect of increasing the enantiomeric purity of S-OAM with 1S,2S-DPDAE on both the diastereotopic methine and acetyl resonances is illustrated in **figure 12**. Both diastereotopic resonances are affected by the changes in enantiomeric composition. For the methine resonance, as the enantiomeric purity of the R-OAM increases the chemical shift in the R-OAM:1S,2S-DPDAE complex shifts to lower frequency. In the case of the O-Acetyl singlet, an increase in the percentage of R-OAM in the mixture results in a shift to higher frequency of the acetyl singlet in the R-OAM:S-DPDAE complex. In the case of the acetyl signals in particular, the observed variation of $\Delta\delta_H$ with % ee of OAM is associated primarily with this differential shift which must reflect the fact that the acetyl methyl in the R-OAM:1S,2S-DPDAE complex is closer to the phenyl ring of the DPDAE, than it is in the corresponding S-OAM complex.

Figure 12
The variation in enantiomeric purity of O-Acetylmandelic acid (OAM) 19 in 1S,2S-DPDAE : O-Acetylmandelic acid complexes



3.3.4 The Effect of Temperature on $\Delta\delta_H$

Ibuprofen and 1R,2R-diphenyl-1,2-diaminoethane were mixed in d_8-toluene at 2:1 acid-base stoichiometry at a concentration of 0.1 mmol ml^{-1} w.r.t. racemic acid. Spectra were acquired at 10K intervals between 333-223K.

The shift non-equivalence for Ibuprofen resonances between 303-243K is given in **Table 14**. A plot of the logarithm of the chemical shift non-equivalence of the methine proton of Ibuprofen against reciprocal temperature is also given (**Graph 4**). The temperature dependence conforms only approximately to a simple Boltzmann distribution for which a linear plot is expected. A linear variation would have implied preferential population of lower energy conformations of the diastereoisomeric salt complexes as the absolute temperature falls. As the temperature is lowered the observed increasing shift non-equivalence can be correlated to a preferred population of a particular low energy conformation for one of the diastereoisomeric complexes in which the methyl protons spend more time, on average in the vicinity of the anisotropic phenyl group. The variation of shift non-equivalence with temperature for the methine quartet of Ibuprofen is given in **figure 13**. With decreasing temperature, the resonance due to the S-Ibuprofen:1R,2R-DPDAE complex shifts to lower frequency while that of the R-Ibuprofen:1R,2R-DPDAE is static. Again this implies that in the S-Ibuprofen:1R,2R-DPDAE complex, differential shielding occurs (via the DPDAE moiety). In addition low temperature spectra show differential line broadening between the two multiplets. This might be a consequence of the difference in free energies of activation for exchange between free and bound acids in the two diastereoisomeric salt complexes, and at low temperatures, the slower rates of exchange on the NMR timescale is apparent for the S-Ibuprofen:1R,2R-DPDAE complex. Alternatively as the exchange rate slows at lower temperatures, selective broadening may arise due to the differing frequency

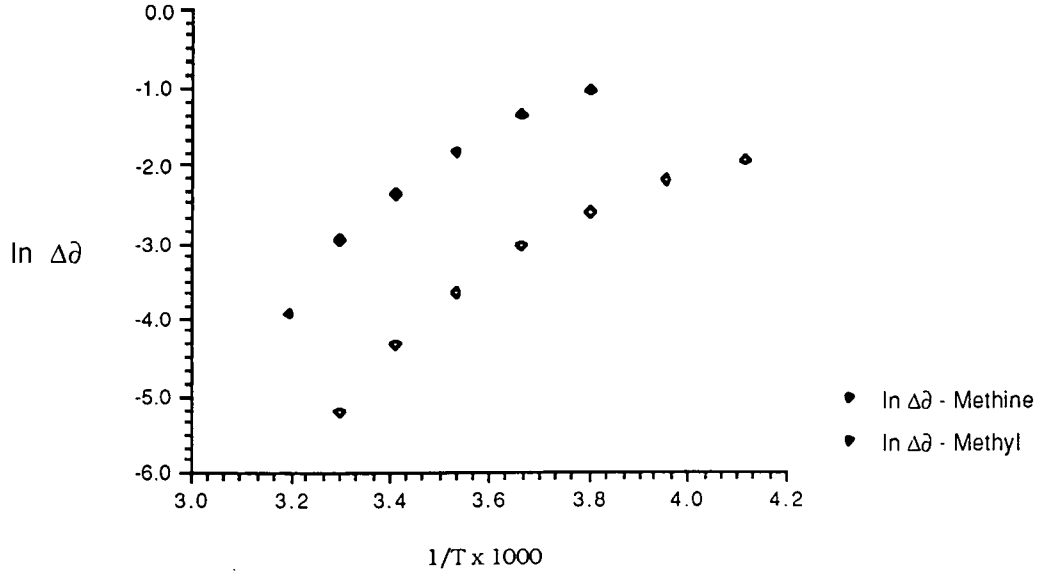
difference ($\Delta\upsilon$) between the free and complexed acid. The extent of broadening is dependent on this frequency difference and is defined for a equally populated system with two sites by **equation 8**.

$$T_2^{-1} = T_2^{-1} + \left[\frac{\upsilon_a - \upsilon_x}{2}\right]^2 \tau \quad - (8)$$

Large frequency differences. $\delta\upsilon$ give increased broadening compared to the observed natural line width T_2^{-1}. For Ibuprofen with the S-Ibuprofen:1R,2R-DPDAE complex the frequency difference between the shifts of free and bound acid is indeed larger (74.2 Hz) compared to the value for the R-RR complex (70.4 Hz).

Graph 4

A plot of ln chemical shift non-equivalence against temperature for the 1,2-DPDAE, ibuprofen diastereoisomeric complex.



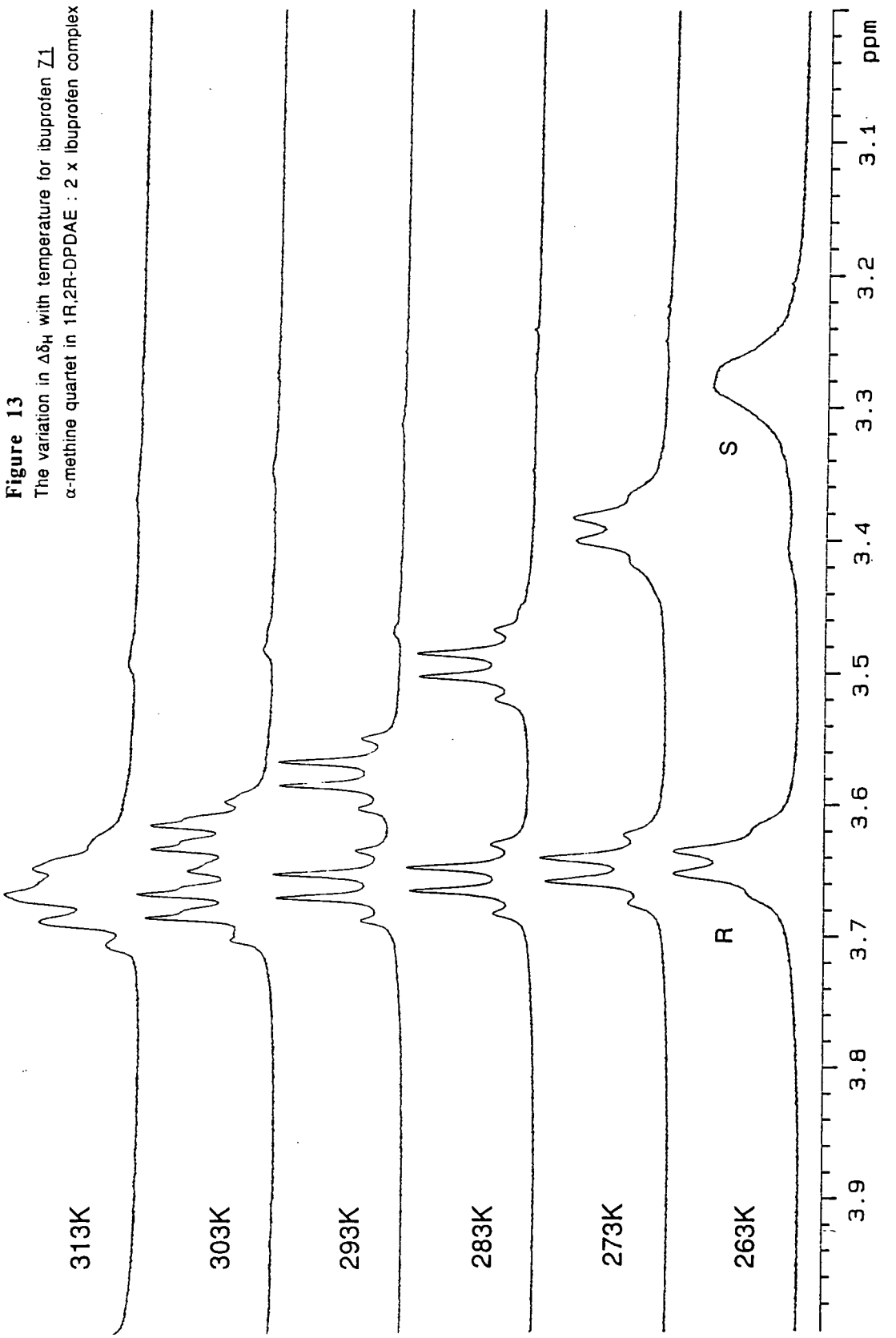


Figure 13
The variation in $\Delta\delta_H$ with temperature for ibuprofen Z1
α-methine quartet in 1R,2R-DPDAE : 2 x Ibuprofen complex

TABLE 14

The measurement of $\Delta\delta_H$ against temperature for ibuprofen 71

Temperature K	observed α-methine resonance (ppm)			observed α-methyl resonance (ppm)		
	Hf	Lf	$\Delta\delta_H$	Hf	Lf	$\Delta\delta_H$
313	3.671	3.651	0.020	_____	_____	_____
303	3.674	3.622	0.052	1.495	1.490	0.005
293	3.659	3.574	0.095	1.476	1.463	0.013
283	3.654	3.492	0.162	1.482	1.456	0.026
273	3.647	3.390	0.257	1.494	1.447	0.047
263	3.642	3.283	0.359	1.515	1.441	0.074
253	_____	_____	_____	1.538	1.428	0.110
243	_____	_____	_____	1.573	1.428	0.145

3.3.5 The Examination of the Structural Features of 1,2-Diphenyl-1,2-diaminoethane which induce Chemical Shift Non-equivalence

Given that the effectiveness of a chiral solvating agent depends on how it interacts with the solvate in solution, attempts were made to obtain structural information on intramolecular through space contacts via NOE experiments. In most of the 2:1 complexes no conclusive or misleading results were obtained. This could be due to the low molecular weight of the complex or to the rapid conformational changes of the solvated ion-pair, impairing the acquisition of reliable NOE data. Suitable crystals of (1R,2R)-1,2-diphenyl-1,2-diaminoethane mono-hydrobromide were grown for X-ray analysis to determine the conformation of the protonated CSA. **Figure 14** shows the X-ray structure, the absolute configuration agrees with that determined by polarimetry. The molecule has approximate C_2-symmetry around the C(1)-C(2) bond and around the central C-C bond fully staggered hydrogens.

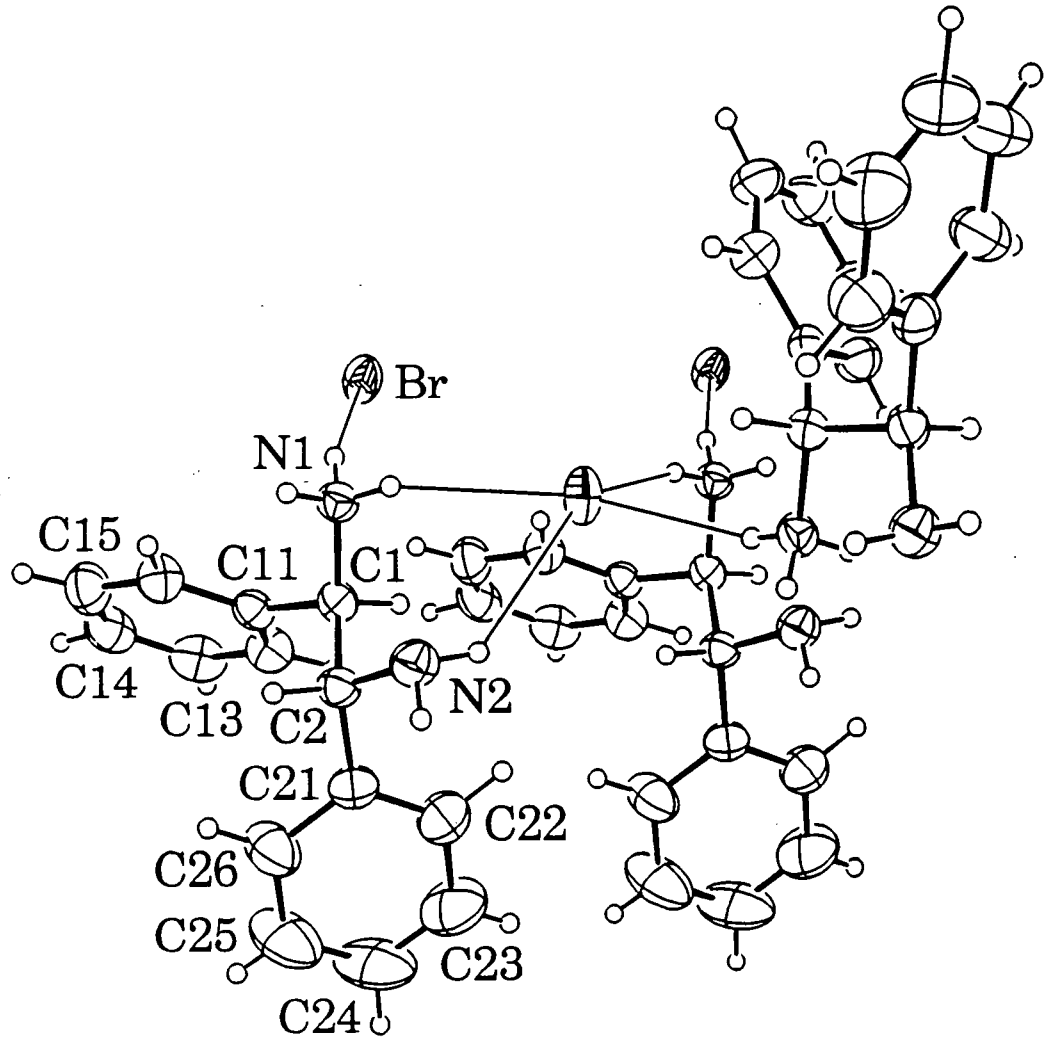
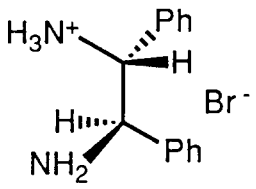


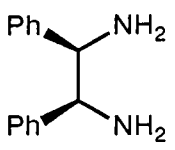
Figure 14
The crystal structure for 1R,2R-Diphenyl-diaminoethane



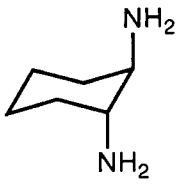
This could be considered to represent the conformation in solution, but it must be remembered that additional interactions between neighbouring groups in the crystal structure which effect conformation will not be present in solution.

The achiral diamine meso-1,2-diphenyl-1,2-diaminoethane 84 (**Figure 15**) was used to ascertain whether self recognition between the two chiral acids in the 2:1 acid:amine salt complex might have occured. The achiral diamine was mixed with Ibuprofen 71, Flurbiprofen 78 and Naproxen 79 at 0.1 mmol ml^{-1} w.r.t. chiral acid in both $CDCl_3$ and C_6D_6. The spectra displayed no measurable shift non-equivalence leading to the conclusion that the chiral acids undergo no self recognition in the diastereoisomeric salt complexes.

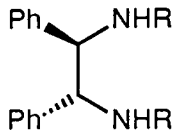
The extent of shift non-equivalence in both acid methyl and methine protons has previously been shown to be linked to the anisotropic phenyl groups of the 1,2-diamine. Replacement with non-anisotropic groups should dramatically decrease the observed $\Delta\delta_H$ value (confirmation of this premise was sought by the analysis of various chiral carboxylic acids with 1R,2R-trans-1,2-diamino-cyclohexane 85). The extent of non-equivalence for both types of proton is listed (**Table 15**). The observed $\Delta\delta_H$ values for the majority of examples are significantly smaller than for the equivalent 1,2-DPDAE complexes, and in the case of α-halo acids, no $\Delta\delta_H$ was seen at all. Although entry 3, Naproxen displayed zero shift non-equivalence in C_6D_6 at 2:1 stoichiometry, the chemical shift non-equivalence for the methyl doublets in $CDCl_3$ was 0.099 ppm (**spectrum 17**). This is almost 3 times the value for the 1,2-DPDAE salt ($\Delta\delta_H$ = 0.034, $CDCl_3$). The relative disposition of the bulky napthyl substituent in the diastereoisomeric complexes probably is responsible for inducing such large non-equivalence.



84



85



a) R = CH_2Ph
b) R = CH_2CH_3

86

Figure 15

The observation in section 2.3 that secondary mono amines CSA gave higher non-equivalence than their primary and tertiary analogues led to the synthesis of two N-substituted 1,2-DPDAE derivatives which were examined as potential CSA's. (1S,2S)-N,N'-dibenzyl-1,2-diphenyl-1,2-diaminoethane 86a and (1S,2S)-N,N'-Diethyl-1,2-diphenyl-1,2-diaminoethane 86b were mixed with Ibuprofen and 2-chloropropionic acid in $CDCl_3$, or C_6D_6. Results are summarised in **Table 16**. Mono substitution greatly reduces $\Delta\delta_H$. The largest $\Delta\delta$ was observed with 86a and 2-chloropropionic acid 82 (**Spectrum 18**, for 2-CH_3 protons in $CDCl_3$). The introduction of substituents on the 1° amine of the CSA must inhibit the selective association and is suggestive of a simple two-point hydrogen bonding interaction in the salt complexes.

TABLE 15

The measurement of $\Delta\delta_H$ with (1R,2R)-Diaminocyclohexane 85 with selected chiral carboxylic acids.

Entry	substrate[a]	observed resonance	solvent	$\Delta\delta_H$ ppm
1	71	2-H	$CDCl_3$	0.018
			C_6D_6	0.024
		$2\text{-}CH_3$	$CDCl_3$	0.014
2	78	$2\text{-}CH_3$	$CDCl_3$	0.019
			C_6D_6	0.007
		2-H	$CDCl_3$	0.018
			C_6D_6	0.019
3	79	$2\text{-}CH_3$	$CDCl_3$	0.099
4	72	$2\text{-}CH_3$	$CDCl_3$	0.002
			C_6D_6	0.002
		2-H	C_6D_6	0.009
5	19	2-OAc	$CDCl_3$	0.010
			C_6D_6	0.014

a) 2-Chloropropionic acid 82 and 2-Bromopropinoic acid 80 were tested but gave no Chemical shift non-equivalence.

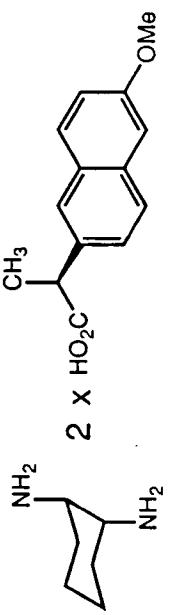
TABLE 16

The measurement of $\Delta\delta_H$ for chiral solvating agents 86a, 86b with selected chrial carboxylic acids.

Entry	substrate	86a			86b		
		Observed resonance	Solvent	$\Delta\delta_H$ ppm	Observed resonance	Solvent	$\Delta\delta_H$ ppm
1[a]	71	$2\text{-}CH_3$	$CDCl_3$	0.010	$2\text{-}CH_3$	$CDCl_3$	0.019
			C_6D_6	0.008		C_6D_6	-----
2	82	$2\text{-}CH_3$	$CDCl_3$	0.032	2-H	$CDCl_3$	0.027
			C_6D_6	0.037		C_6D_6	0.027

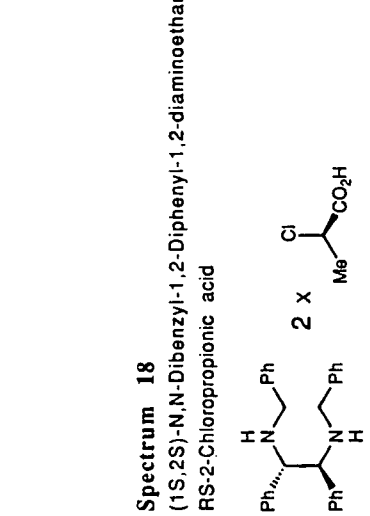
a) 0.025 mmol amine 86a

Spectrum 17
(1R,2R)-Diaminocyclohexane
RS-Naproxen

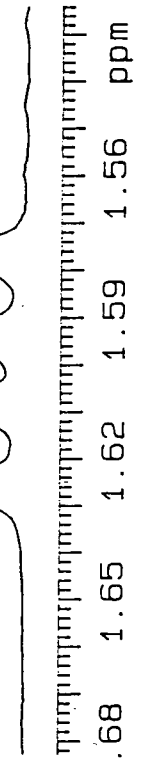


8.5 7.9

Spectrum 18
(1S,2S)-N,N-Dibenzyl-1,2-Diphenyl-1,2-diaminoethane
RS-2-Chloropropionic acid



86a 82



3.4 The Analysis of Enantiotopic Methylene Protons

Internally enantiotopic methylene hydrogens are rendered internally diastereotopic by derivatisation with a chiral substrate (**Figure 16**). Chemical shift non-equivalence may result if the preferred conformation places H_R and H_S in different magnetic environments for the majority of time in the rapidly rotating system. If all conformations are equally populated then no $\Delta\delta$ will result.

The example of 1,2-diphenyl-1,2-diaminoethane acts as a CSA for 1° carboxylic acids RCH_2CO_2H presents an unusual case in which *internal* diastereotopicity is induced by an *external* non-covalently bonded chiral reagent. No other examples of this type have been reported for 1° carboxylic acids at this time.

Several achiral carboxylic acids were studied (87-92, **figure 17**) at both 2:1 and 1:1 stoichiometry. Spectra were also acquired using samples at concentrations of 0.4 mmol ml^{-1} and 0.1 $mmol^{-1}$ respectively. The higher concentration corresponds to the optimal conditions defined with other chiral 2° acids in maximising $\Delta\delta_H$. The results are listed in **Table 17**. Maximum non-equivalence was observed with phenyl acetic acid 87 (**Spectrum 19**) and 4-bromo phenyl acetic acid 89 (**Spectrum 20**) both of which are α-aryl carboxylic acids. This corresponds to previous observations with chiral carboxylic acids. Unbranched alkyl acids and 3-phenylpropionic acid gave limited amounts of non-equivalence over the range of conditions. None of the substrates examined failed to give non-equivalence.

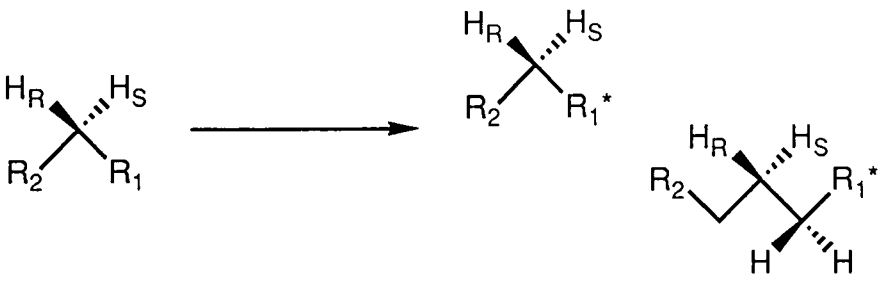
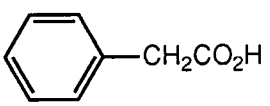


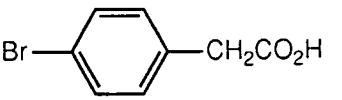
Figure 16



Phenylacetic acid
87

$CH_3CH_2CO_2H$

Propionic acid
88



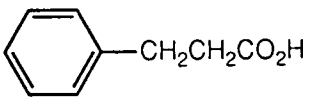
4-Bromophenylacetic acid
89

$CH_3CH_2CH_2CO_2H$

n-Butyric acid
90

$(CH_3)_2CHCH_2CH_2CO_2H$

4-Methylpentanoic acid
91



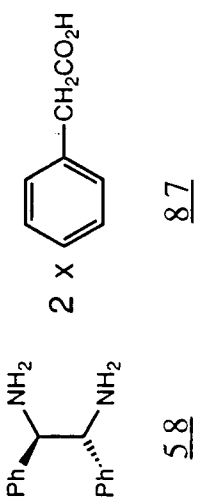
3-Phenylpropionic acid
92

Figure 17

Spectrum 19

(1R,2R)-1,2-Diphenyl-1,2-diaminoethane

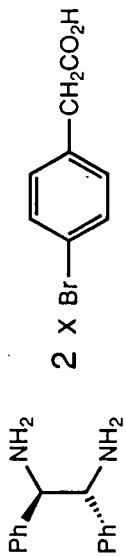
Phenylacetic acid



58 87

Spectrum 20

(1R,2R)-1,2-Diphenyl-1,2-diaminoethane
4-Bromophenylacetic acid



58 89

TABLE 17

The measurement of $\Delta\delta_H$ H_S/H_R for the achiral acids 87-92 with chiral solvating agent 1,2-DPDAE.

Entry	substrate	Solvent	$\Delta\delta_H$ ppm[a]			
			1:1 stoichiometry		2:1 stoichiometry	
			0.4 M	0.1 M	0.4 M	0.1 M
1	87	$CDCl_3$	0.051	0.048	0.136	0.056
		C_6D_6	------	------	0.031	0.016
		$C_6D_6CD_3$	------	0.012	------	0.017
2	88	$CDCl_3$	0.035	------	0.042	------
		C_6D_6	------	------	------	------
3	89	$CDCl_3$	0.060	0.063	0.130	0.082
		C_6D_6	------	------	------	------
4	90	$CDCl_3$	------	------	0.015	------
		C_6D_6	------	------	------	------
5	91	$CDCl_3$	------	------	0.035	------
		C_6D_6	------	------	------	------
6	92	$CDCl_3$	------	------	------	0.024
		C_6D_6	------	------	0.033	0.030

a) Spectra were recorded at 2:1 or 1:1 acid to amine stoichiometry at 0.4 or 0.1 mmol/ml. acid concentration at 298K

Spectra for the 2:1 complex of phenyl acetic acid with 1R,2R-DPDAE were recorded at various temperatures (**Table 18**) and the methylene resonances are shown in **Figure 18**. Both diastereotopic methylene resonances are shifted to lower frequency as the temperature falls, the low frequency doublet to a greater extent. This is in agreement with previous observations made for chiral carboxylic acids and corresponds to the pro S (or pro R) hydrogen being closer on average to the anisotopic phenyl group in the preferred conformation. Attempts to assign the prochirality of the methylene resonances (pro R and pro S) failed due to the lack of a suitable amount of chiral α deuteriated substrates. Determination of the enantiomeric purity of α deutero carboxylic acids by either ^1H or ^2H NMR is quite feasible due to the high degree of anischronicity induced in methylene protons by 1,2-DPDAE.

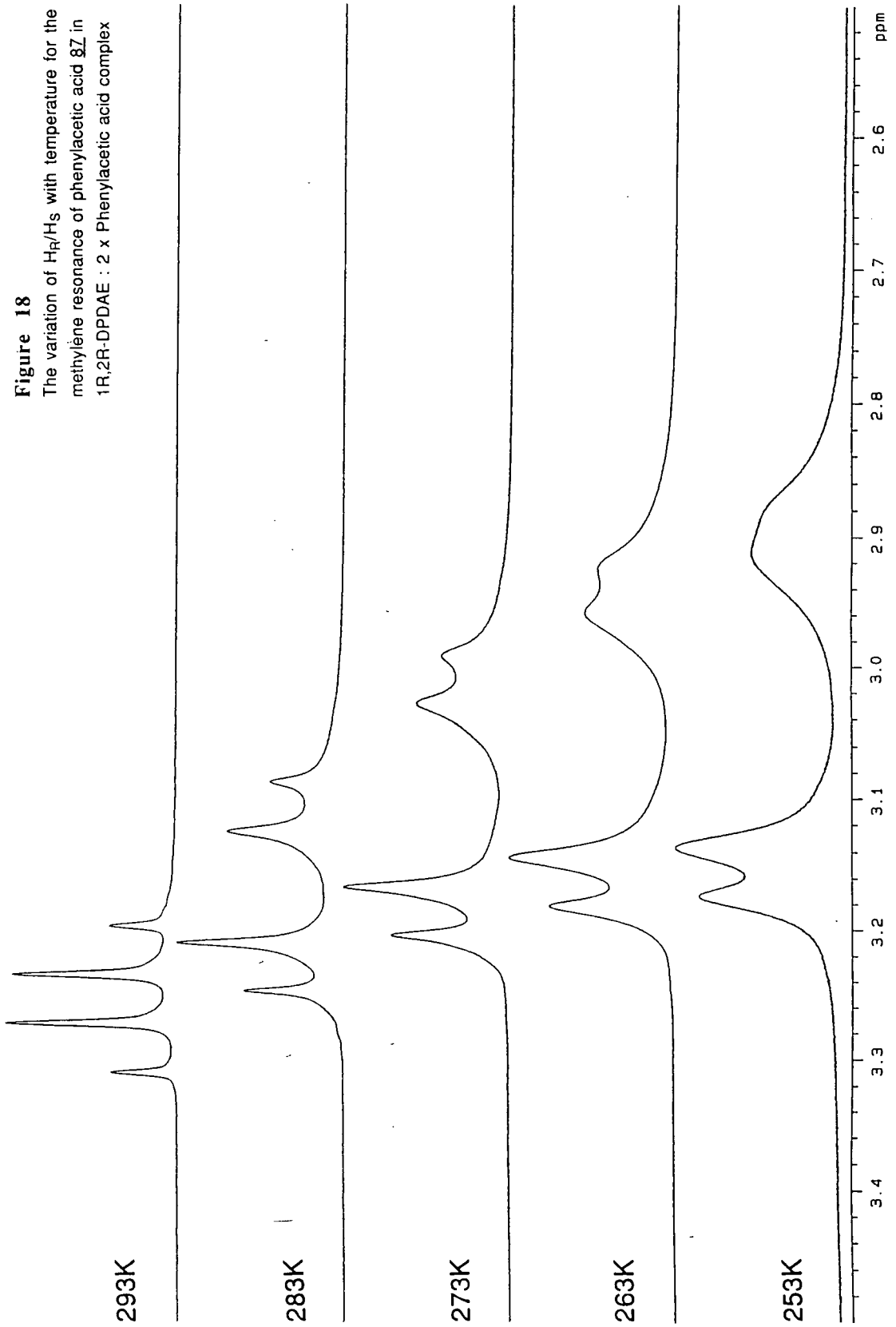


Figure 18
The variation of H_R/H_S with temperature for the methylene resonance of phenylacetic acid 8Z in 1R,2R-DPDAE : 2 x Phenylacetic acid complex

TABLE 18

The measurement of H_S/H_R for Phenylacetic acid with (1R,2R)-DPDAE at different temperatures[a].

Entry	Temperature	observed resonance		$\Delta\delta_H$
	K	H	H'	ppm
1	293	3.288	3.222	0.056
2	283	3.227	3.110	0.117
3	273	3.183	3.012	0.171
4	263	3.162	2.943	0.219

a) Spectra were recorded at 0.1 mmol/ml acid concentration at 2:1 stoichiometry acid to amine.

3.5 Applications of 1,2-Diphenyl-1,2-diaminoethane

The primary function of such a chiral solvating agent is in the non-destructive analysis of the enantiomeric composition of chiral acids. The reagent can be used to determine absolute configuration within certain limitations, If the sense of non-equivalence has been assigned previously with samples of known enantiomeric composition. The determination of substrate configuration in closely related carboxylic acids is prone to error. The conformation responsible for shift non-equivalence could alter between related acids in their rapidly reversible salt complexes. This could effect the sense as well as the value of $\Delta\delta$.

3.5.1 Enantiomeric Excess Determinations

To obtain accurate and reliable integrals for enantiomeric purity analysis the spectrum must be fully relaxed before acquisition. A typical relaxation delay of 5 x T_1 of the signal under observation is usually required. A high signal to noise ratio is also desirable which can be obtained at high field and with longer acquisition times. High sensitivity and full relaxation is essential when utilising ^{13}C satellite peaks in calibrating enantiomeric purity determinations. The sample must also remain in solution during acquisition. Degassing and filtration before acquisition is desirable to increase resolution.

Several commercially available enantiopure carboxylic acids were analysed with 1,2-DPDAE in order to determine their enantiomeric purity. The results, are listed in **Table 19** for both the R and S enantiomers in most cases.

TABLE 19

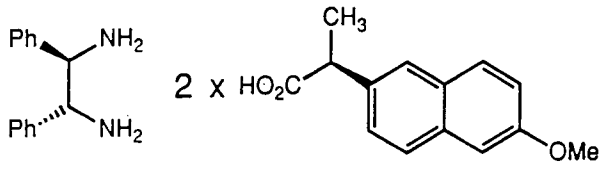
The measurement of $\Delta\delta_H$ for chiral solvating agents 86a, 86b with selected chiral carboxylic acids.

Entry	Substrate	Solvent	Observed resonance[a]	Enantiomeric composition		Enantiomeric excess
				%R	%S	%
1	71	C_6D_6	2-H[b]	99.6 1.0	0.4 99.0	99.2 98.0
2	78	C_6D_6	2-H[b]	99.4 3.7	0.6 96.2	98.8 92.6
3	79	$CDCl_3$	2-CH_3	0.6	99.4	98.8
4	70	$CDCl_3$	2-CH_3	99.0 0.1	1.0 99.9	98.0 99.8
5	82	$CDCl_3$	2-CH_3	99.8 0.2	0.2 99.8	99.6 99.6

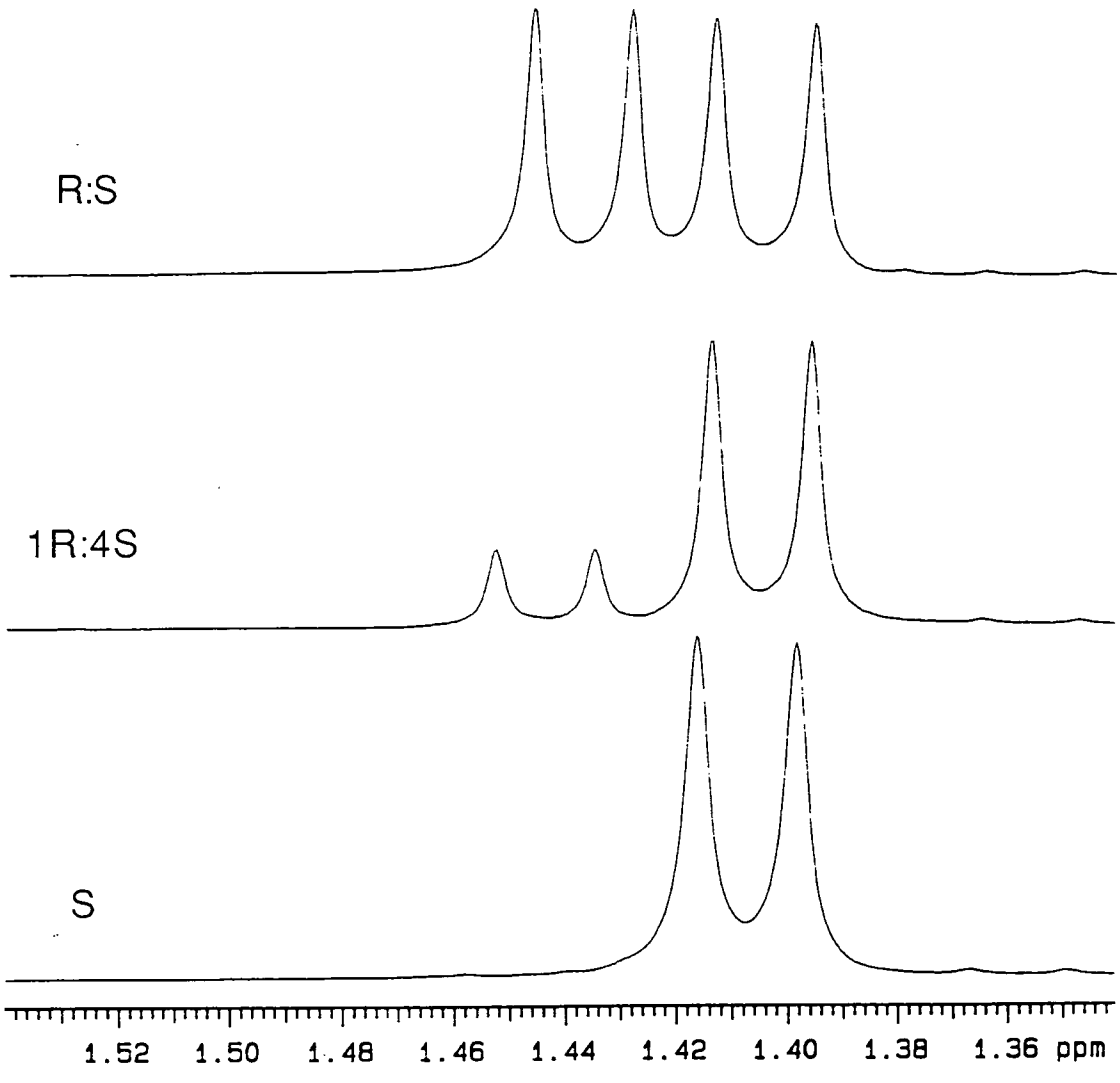
a) Enantiomeric composition derived by compairing the carbon-13 satellites of the major diastereoisomer with the resonance of the minor.
b) Enantiomeric compostion derived by comparing the major and minor diastereomeric resonances

Figure 19

The variation of enantiomeric purity for naproxen methyl resonances in 1R,2R-DPDAE : 2 x RS-Naproxen complexes



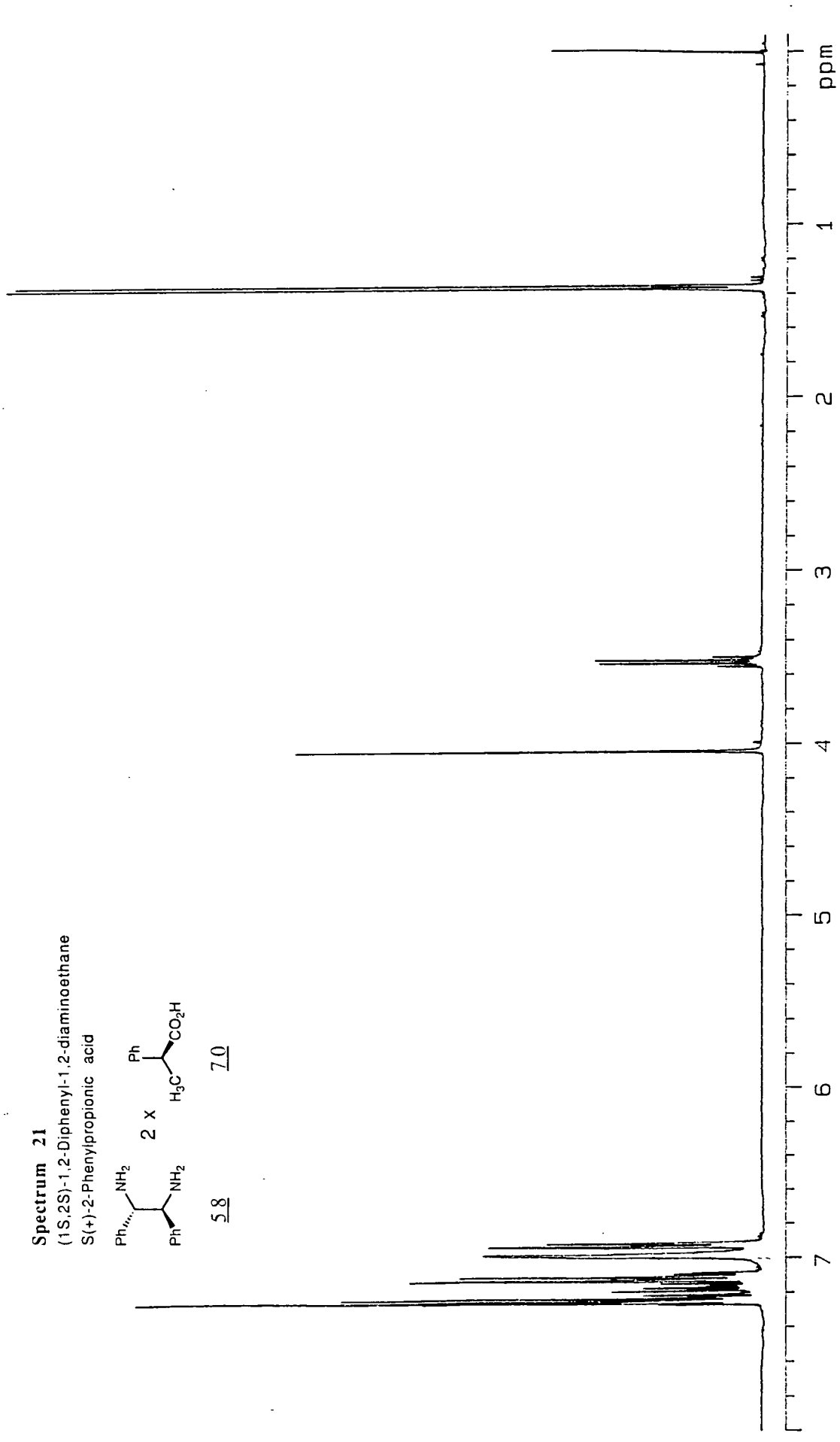
58 79



The position of the resonance due to the minor enantiomer has to be established before enantiomeric purity determinations are carried out. This avoids the danger of assigning spinning side bands or impurities to the minor enantiomer. This was usually achieved by comparing the chemical shifts of resonances due to the racemate with the enantiopure acid, although it is possible, as illustrated by **Figure 19** (a stacked plot of the methyl resonance of Naproxen at different enantiomeric purities) that the absolute peak position changes slightly with enantiomeric purity.

In the majority of cases enantiomeric excess was derived by comparing the integral of the resonance due to the minor enantiomer with the ^{13}C satellites of the resonance due to the major enantiomer, as shown in **Spectrum 21** and the related **Figure 20** for S-2-phenylpropionic acid and S,S-(-)-DPDAE. Both ^{13}C satellites and the resonance due to the minor enantiomer are shown on the same scale permitting an initial assessment of enantiomer composition. Excess determination requires a conversion factor for the ^{13}C satellite (0.54% intensity of the major enantiomer).

The values quoted in **Table 19** above 99% e.e. are approaching the limits of detection and will incur large errors due to base line noise. In practice these compounds can be considered to be essentially enantiomerically pure.


Spectrum 21
(1S,2S)-1,2-Diphenyl-1,2-diaminoethane
S(+)-2-Phenylpropionic acid
2 x
5.8
7.0
ppm
1
2
3
4
5
6
7

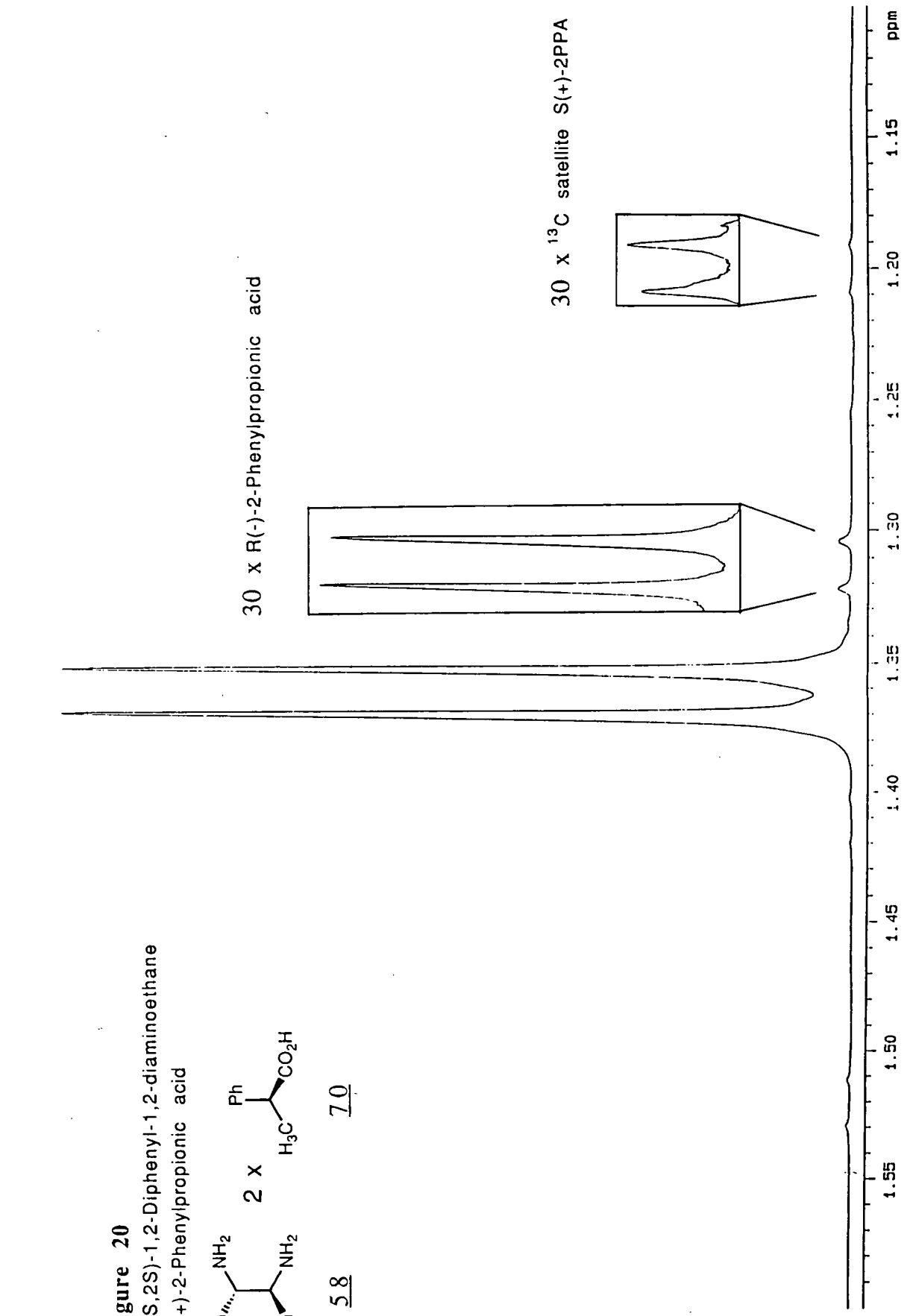


Figure 20
(1S,2S)-1,2-Diphenyl-1,2-diaminoethane
S(+)-2-Phenylpropionic acid

2 x

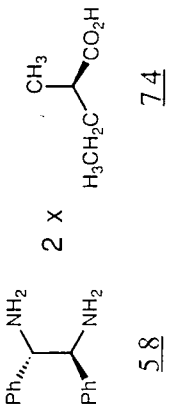
5 8 7 0

3.5.2 Determination of Absolute Configuration in 2-Methylbutyric Acid

A small (0.1 mmol) sample of chemically impure enzymatically derived 2-methylbutyric acid 74 was supplied for analysis by Dr D O'Hagan. Alternative methods of analysis are difficult due to the small amount of material available and the marginal difference in alkyl substituents around the asymmetric carbon. R and S-2-methylbutyric acid are both readily available, and a stacked plot varying the enantiomeric composition of the 2-methylbutyric acid in the presence of 1R,2R-(-)-1,2-DPDAE in $CDCl_3$ was produced to establish the absolute configuration of the diastereomeric resonances (**figure 21**). The sense of the shift non-equivalence was observed with the 2- and 3-methyl groups of the acid at 1.12 ppm (doublet), 0.92 ppm (triplet) respectively. The two groups had opposing sense in the diastereomeric complexes.

The 2-methyl butyric acid enzymatic sample was mixed with 1R,2R-DPDAE in $CDCl_3$, which had been shown to give maximum attainable $\Delta\delta_H$. Initially one resonance was observed with the methyl group indicating a sample with high enantiomeric purity. Examination of the chemical shift of this resonance seemed to indicate that the absolute configuration was R, but due to the small non-equivalence this was not totally certain. Two small amounts of racemic 2-methylbutyric acid was added to the unknown solution. In each spectrum, the resonance due to the 2-CH_3 proton (doublet) displayed both the expected major R peaks plus a minor S-resonance associated with racemate addition. To dispel the possibility that the minor enantiomer could be attributed to a chemical impurity, the 2-CH_3 resonances were decoupled from the 2-methine proton. **Figure 22** displays the decoupled resonances which are compared to racemic 2-methylbutyric acid. The lower frequency shoulders on both samples corresponds to the S-enantiomer in the racemate. This confirms that the absolute configuration is R-2-methylbutyric acid for the unknown sample.

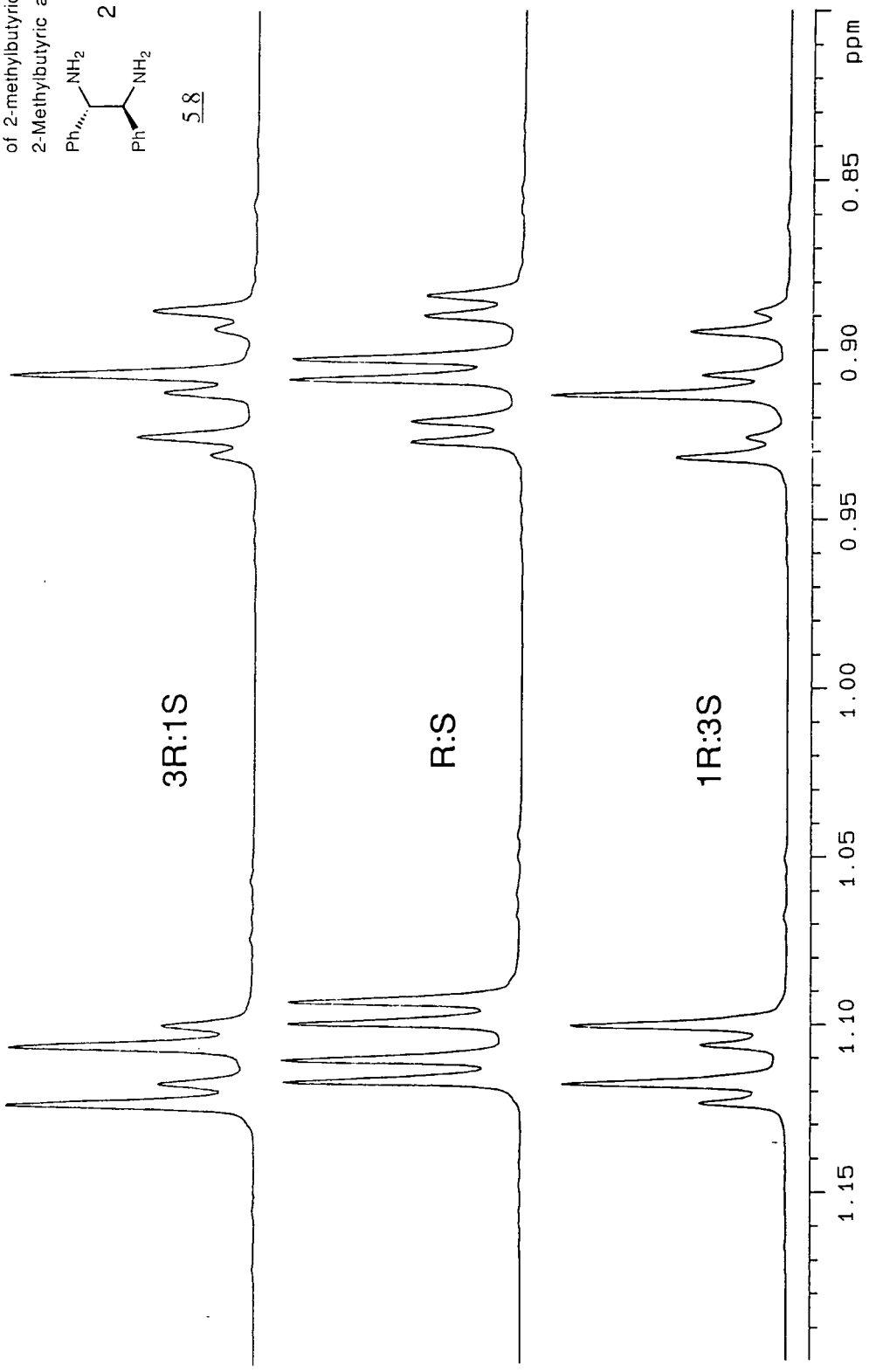
Figure 21
The variation in enantiomeric composition of 2-methylbutyric acid 7.4 in 1R,2R-DPDAE : 2-Methylbutyric acid complexes



5.8

2 x

7.4



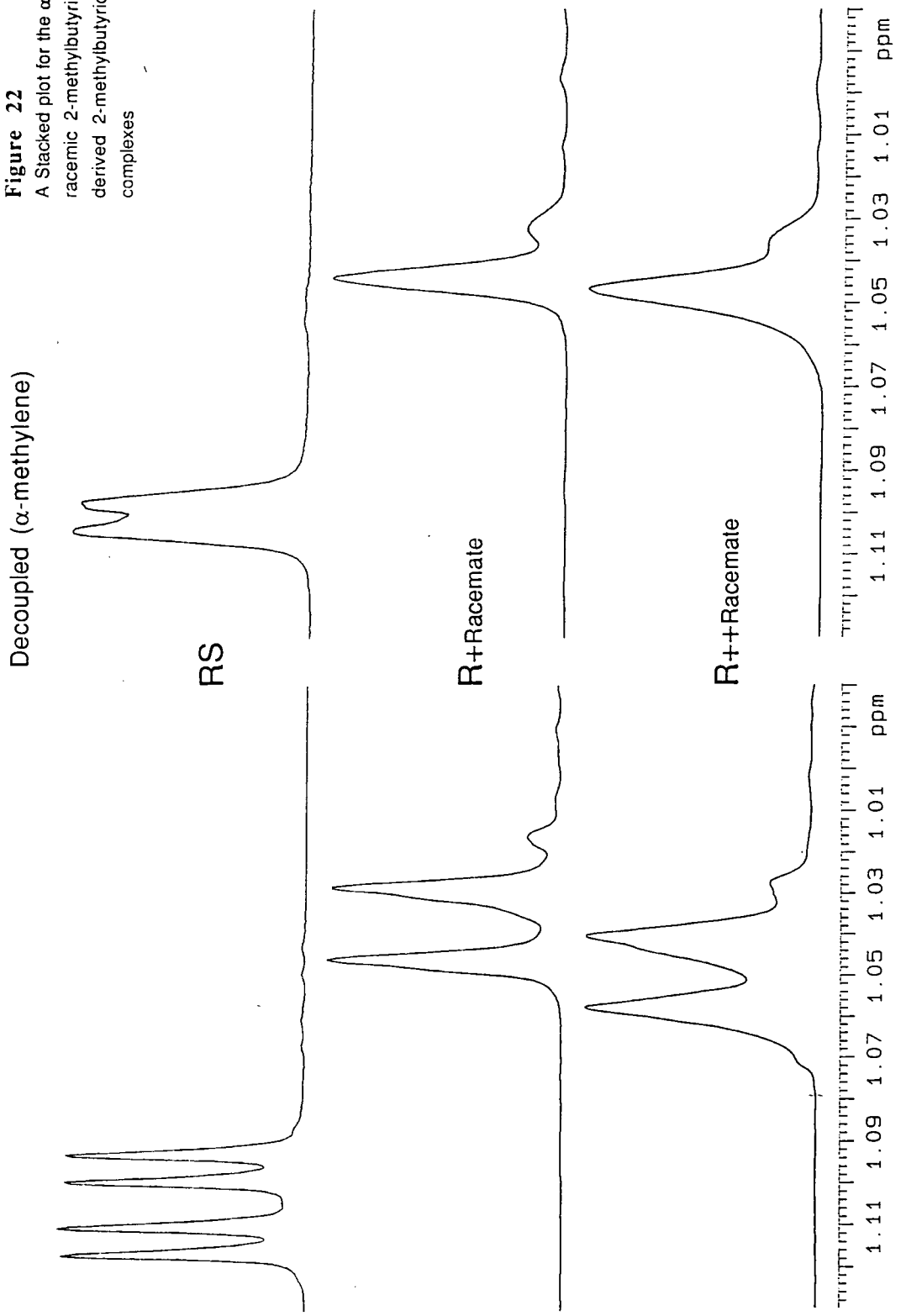


Figure 22
A Stacked plot for the α-methyl resonances of racemic 2-methylbutyric acid against enzymatically derived 2-methylbutyric acid in their 1R,2R-DPDAE complexes

3.6 Conclusions

1,2-Diphenyl-1,2-diaminoethane induces remarkably high chemical shift non-equivalence in a wide range of α-aryl and α-halo carboxylic acids under a variety of conditions. It may be prepared via a simple synthetic procedure (1,2-DPDAE is now commercially available from Fluka). In most cases the diastereoisomeric salts of 1,2-DPDAE show high solubility in both deutero-aryl and deutero-chlorinated solvents. Although selective precipitation of one diastereoisomeric complex was observed occasionally, selective precipitation of the major enantiomer in enantiomeric excess determinations was avoided by using the complementary enantiomer of the CSA. With almost all observed complexes, optimal non-equivalence was observed at 2:1 stoichiometry and 0.4 mmol ml^{-1} concentration at room temperature.

The effectiveness of 1,2-DPDAE was demonstrated by the ability to render internally enantiotopic methylene hydrogens diastereotopic for aryl and alkyl - 1° carboxylic acids. This observation has no precedent for 1° carboxylic acids.

The large observed chemical shift non-equivalence with its consistency in inducing non-equivalence in a wide variety of acids makes 1,2-DPDAE suitable for the analysis of enantiomeric excess as illustrated in Section 3.5.

To effectively develop derivatives of 1,2-DPDAE with the goal of improving non-equivalence or to make predictions of the absolute configuration for α-aryl carboxylic acid a model for the preferred conformation of complexation needs to be devised.

The following assumptions can be used to construct a model for recognition. The protonated amino groups in the 2:1 complex will probably prefer an antiperiplanar conformation to reduce columbic interactions. Both the amino

groups probably undergo hydrogen bond interactions with the carbonyl group of chiral acids. Given that the 2:1 complex displays higher non-equivalence than the 1:1 complex, this could infer that the position of both aryl rings in relation to the 2-chiral carboxylic acids is important. Furthermore, no self induced recognition was observed between the two chiral acids with the analogous achiral meso-diamine. This reaffirms the need for trans-antiperiplaner arrangement of the amino groups in the diamine. Small values of $\Delta\delta_H$ observed with acids in the presence of α-methylbenzylamine, which is effectively a subunit of 1,2-DPDAE, supports the importance of the second aryl group in the involvement of inducing non-equivalence.

The failure to observe any measurable NOE's between the acid and the diamine could suggest the absence of intermolecular interactions between the acid and diamine, so the conformation adopted is one in which the groups are not in close proximity.

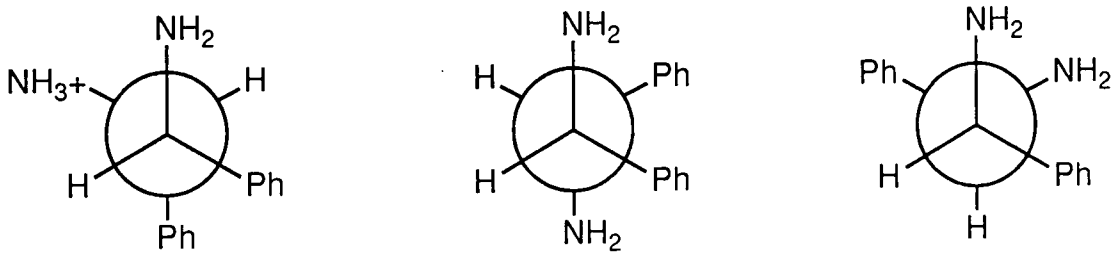
Differential shifts obtained by altering several experimental parameters with the carboxylic acid substrates suggested that frequency shifts in the NMR spectra were due to the proximity of the observed α-groups (CH_3 or H usually) to an aryl group on the CSA. This was highlighted by the fact that differential shifts were observed with temperature for the pro-S and pro-R protons of 1° carboxylic acids. In addition the selective shift of the α-methyl group occurred in *one* of the diastereoisomeric salt complexes (it moved substantially to lower frequency). This suggest that *one* of the substitutuents α to the CO_2H group is in proximity to the aryl group in the preferred conformation.

The crystal structure for 1R,2R-diphenyl-1,2-diaminoethane mono-hydrobromide suggests a conformation in which both amino and phenyl groups are gauche. This may be represented by the Newman projection **Figure 23ai**. This conformation would minimise steric repulsions between the functional groups, bringing in close proximity the ammonium and amine groups which can undergo dipolar interactions reducing the energy of this conformation.

Models for 1:1 and 2:1 complexation can be devised encompassing all the above points (**Figure 23**). In the case of 1:1 complexation the proposed model resembles the crystal structure (**Figure 23ai**) where complexation could be considered to occur by a chelating interaction between the 1,2-diamine and the carboxylic functionality **Figure 23b**. The low observed non-equivalence is in agreement with the model in which the anisotropic phenyl groups of the diamine are relatively remote from the chiral carboxylic acid. The 1:1 model agrees with the crystal structure, but suffers from a lack of sufficient experimental observations.

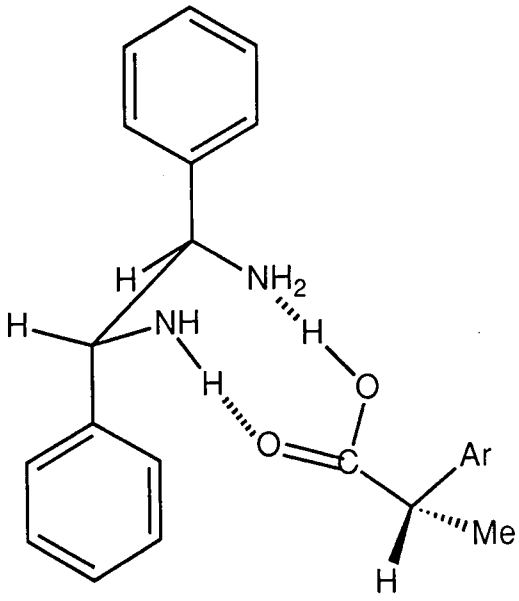
A more rigorous investigation of 2:1 complexation should yield a better description of the solvation complex. The low energy conformation **Figure 23ai** proposed as the principle conformer involved in 1:1 complexation could play a similar role in 2:1 complexation, although the behaviour of the protonated amine functionalities must be taken into account. The increase in steric repulsion between the amines due to protonation or hydrogen bonding in the 2:1 complex would tend to disfavour a conformation placing the amine groups in close proximity. Also, the 2:1 complex would prefer a conformation which reduced the columbic interactions between the charged groups. The conformer depicted by **Figure 23aii** places the amine groups antiperiplanar and is the only conformer which satisfies the above points. A proposed model based on this conformation is illustrated by

Figure23c It is assumed that the aryl group of the acid effectively plays no part in the molecular interactions within the complex. The 1,2-DPDAE complex has C_2 symmetry, the methine protons of the amine are also pointing away from the complex and are effectively isolated. Diastereomeric interactions arise between the 2° aryl group of 1,2-DPDAE and the α-substituents as depicted in **Figure 23**. The anisotropy of the phenyl ring leads to a larger shift in the position of the α-substituent resonance and a lesser effect is seen with the other α-substituent, which is more remote with respect to the phenyl ring.



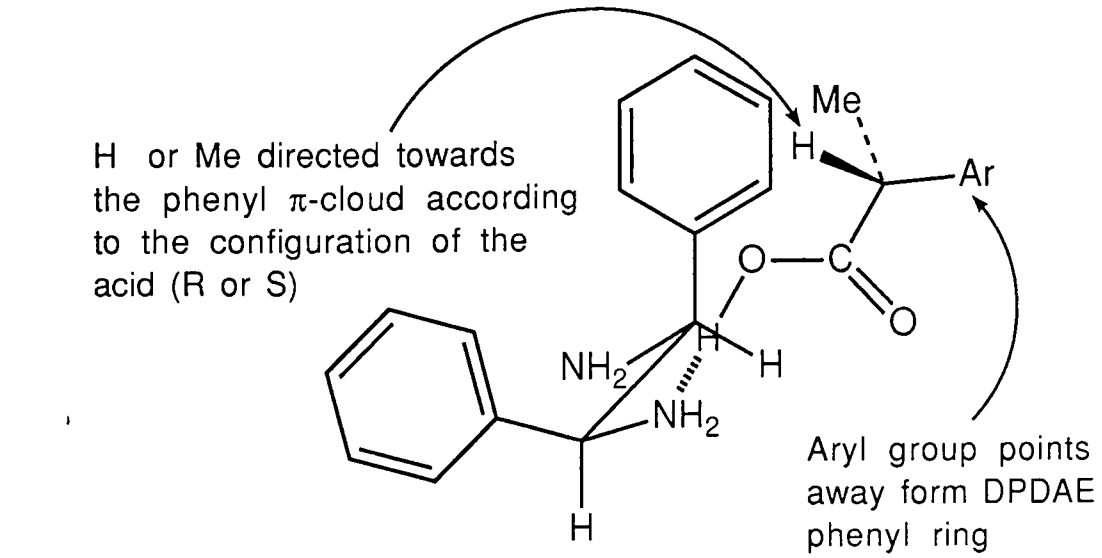
i ii iii

a



b

Figure 23


H or Me directed towards the phenyl π-cloud according to the configuration of the acid (R or S)
Me
H
Ar
O
C
O
H
H
NH2
NH2
H
Aryl group points away form DPDAE phenyl ring
Only one interaction between the amino group of DPDAE and the Chiral acid is shown for clarity

C

Figure 23

CHAPTER 4

Oganometallic Chiral Derivatising Agents

4.1 The Chiral Derivatising Agent η^2-Ethene Platinum-DIOP

The zero valent platinum complex 35 and the palladium analogue 93 have been shown to be effective chiral derivatising agents for electron poor and strained η^2-donors [69, 91, 92]. The versatility of DIOP-Pt°-ethene (**Spectrum 22**) as a chiral derivatising agent is shown in this chapter by the breath of enantiomeric purity determinations that may be made on chiral alkynes, enones, and norbornene derivatives.

The derivatisation may be carried out in an aprotic solvent or in situ under argon in the NMR tube. The reaction proceeds by displacement of the bound ethene by the substrate. Binding of the chiral η^2-donor may occur via the Re or Si face (**Figure 24**). In the constitutional isomers formed, loss of C_2 symmetry leads to chemically non-equivalent phosphorus atoms. With racemic olefins two diastereoismers may be formed in equal amounts for each constitutional isomer. The resulting pair of diasteroisomers can be analysed by proton-decoupled ^{31}P NMR spectroscopy. Platinum(195) with a nuclear spin of $\frac{1}{2}$ and 30% natural abundance will couple to the phosphorus atoms to give additional high and low frequency satellites.

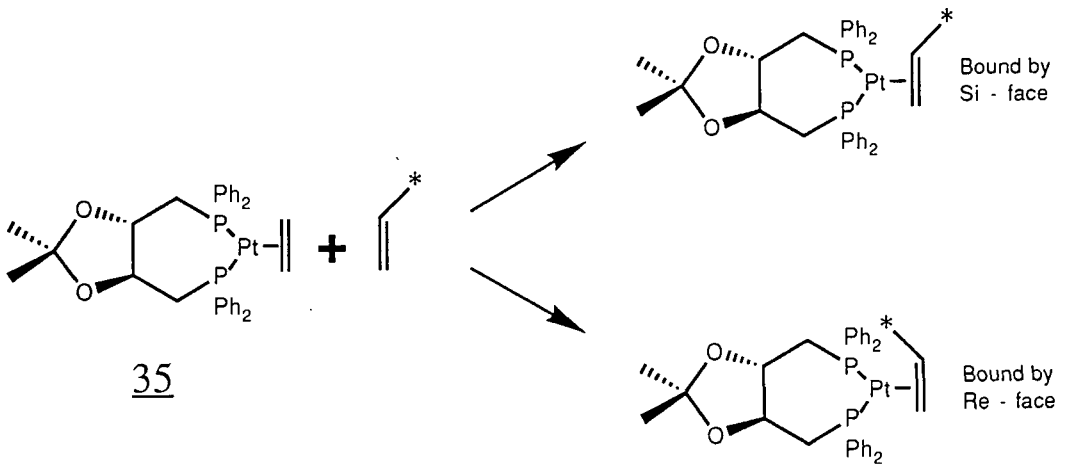


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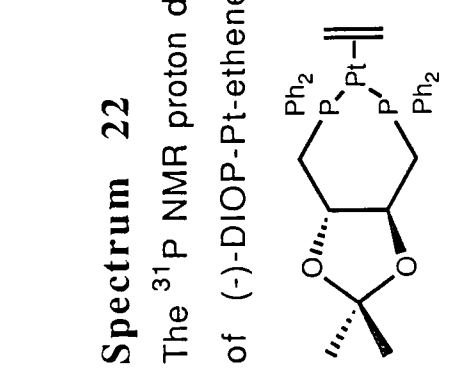
Figure 24

Spectrum 22

The ^{31}P NMR proton decoupled spectrum of (-)-DIOP-Pt-ethene



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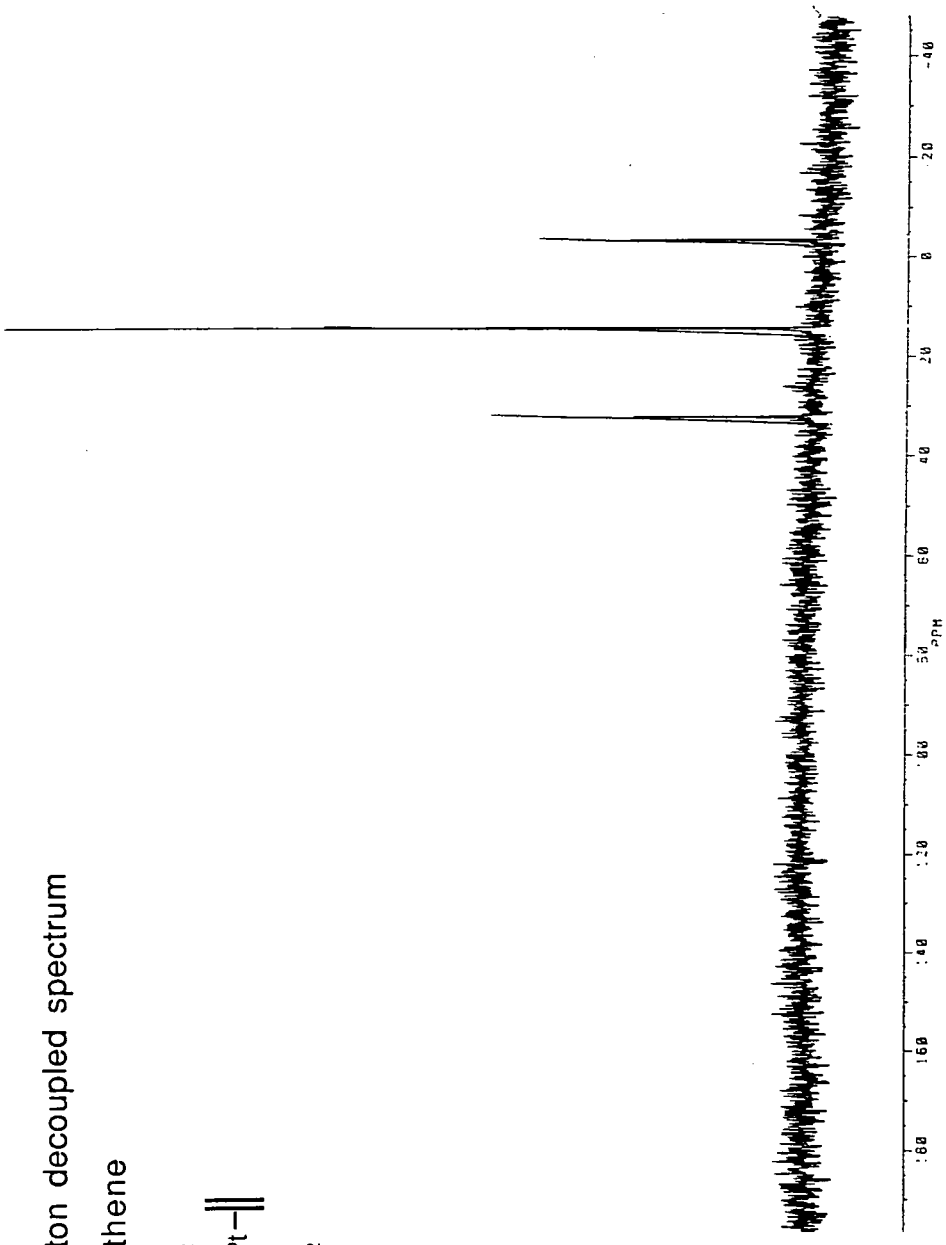

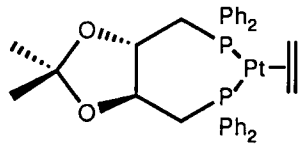

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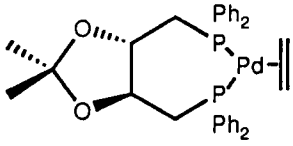

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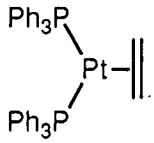

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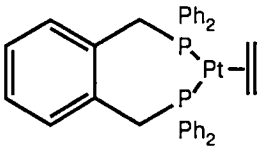

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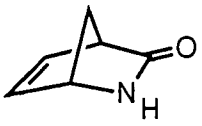

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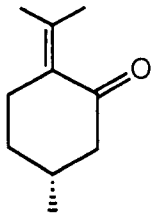

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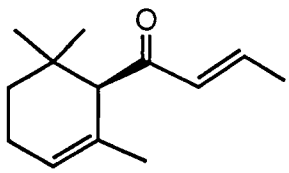

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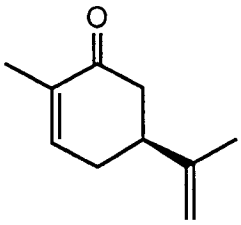

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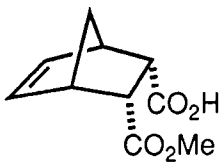

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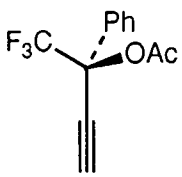


100

This gives a possible total of 12 pairs of resonances in the ^{31}P NMR spectrum of complexes of racemic olefins. The phosphorus-phosphorus coupling constant is sensitive to chemical environment, with typical values of 60 Hz. The values can be used to distinguish diastereoisomers and constitutional isomers. In the alkene complexes with remote chiral centres, pairs of constitutional isomers will have similar phosphorus couplings.

The assignment of diastereoisomeric resonances is aided by analysing both enantiopure and enantiomerically enriched samples. This also establishes whether derivatisation is stereoselective (i.e. whether kinetic resolution may be occurring.) or facially selective. Enantiomeric purity is obtained by comparing two sets of unperturbed resonances in the ^{31}P NMR spectrum.

The CDA 35 was used to determine the enantiomeric purity of selected chiral cyclohexene and norbornene derivative, and results are summarised in **Table 20**. The bicyclic lactam 96, 2-aza-bicyclo[2.2.1]hept-5-en-3-one was selectively bound to the platinum by the more open *exo* face. This is illustrated in the ^{31}P NMR spectrum in which two diastereoisomeric second order doublets may be distinguished corresponding to the bound (+) and (-) enantiomers (**Figure 25a**). The different appearance of the high and low frequency satellites (**Figure 25b**) is due to the non-equivalence (anisogamy) of platinum-phosphorus coupling constants. The minor diastereoisomeric resonance due to the (+)-lactam is present in both the main and the satellite peaks of supposedly enantiopure (-)-bicyclic lactam. Integration of these resonances gave an enantiomeric purity of 98% (± 0.2%).

Pulegone 97 and the norbornene derivative 77 also undergo face selective complexation. In the case of 77, diastereomeric resonances due to the racemate display no chemical shift non-equivalence in the ^{31}P NMR spectrum, so that enantiomeric excess could not be determined.

The enone Damascone 98 whose S-enantiomer is a powerful fragrance undergoes non-selective complexation with the platinum complex to yield Si and Re bound constitutional isomers for each enantiomer, (**Figure 26**). For each sample of R and S damascone complexes no resonance due to the opposite enantiomer of damascone was seen. The enantiomeric purity is

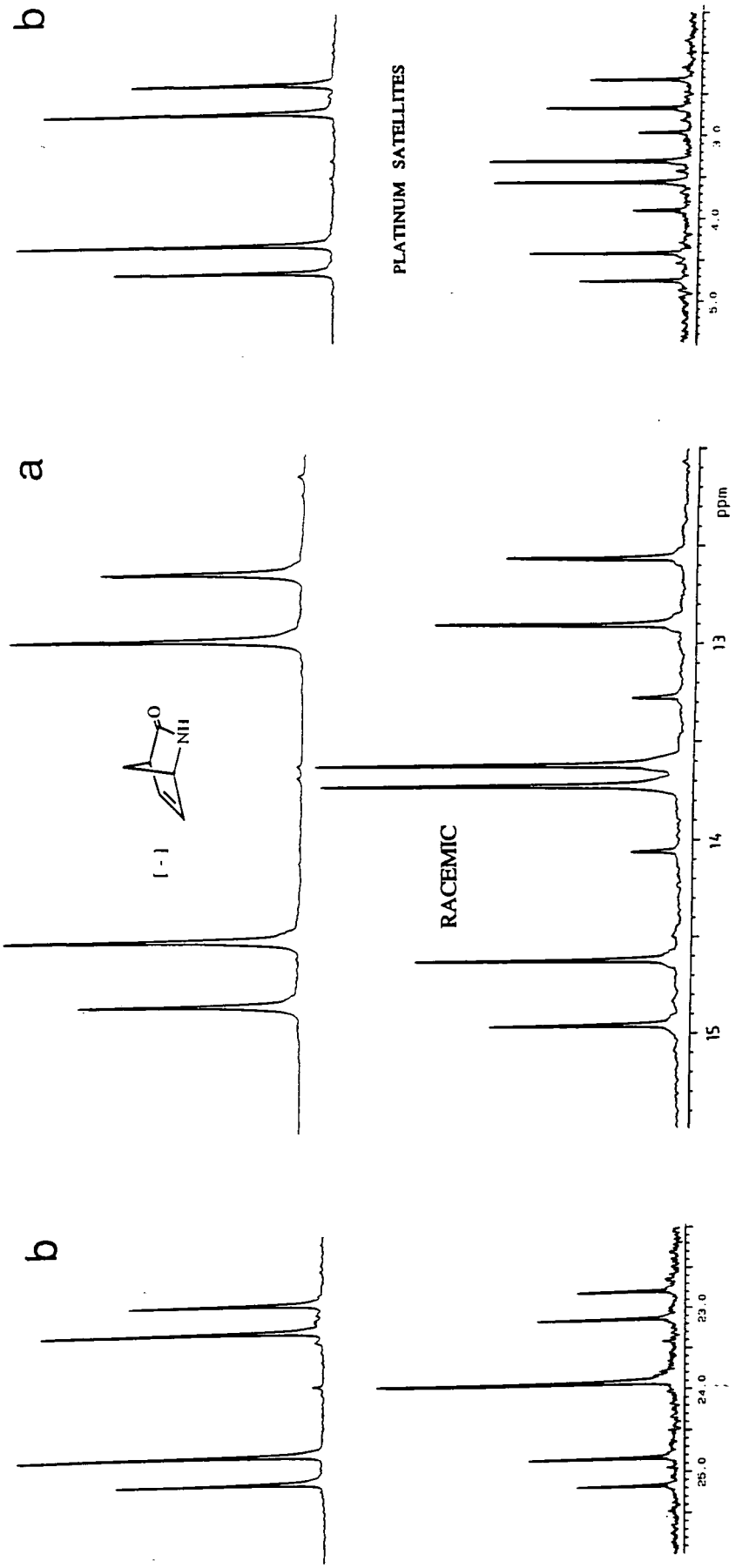


Figure 25

^{31}P NMR spectra of 2-aza-bicyclo[2.2.1]hept-5-en-3-one 8Z derivatives with (-)-DIOP-Pt-ethene

Figure 26

The ^{31}P NMR spectra of damascone derivatives of (-)-DIOP-Pt-ethene

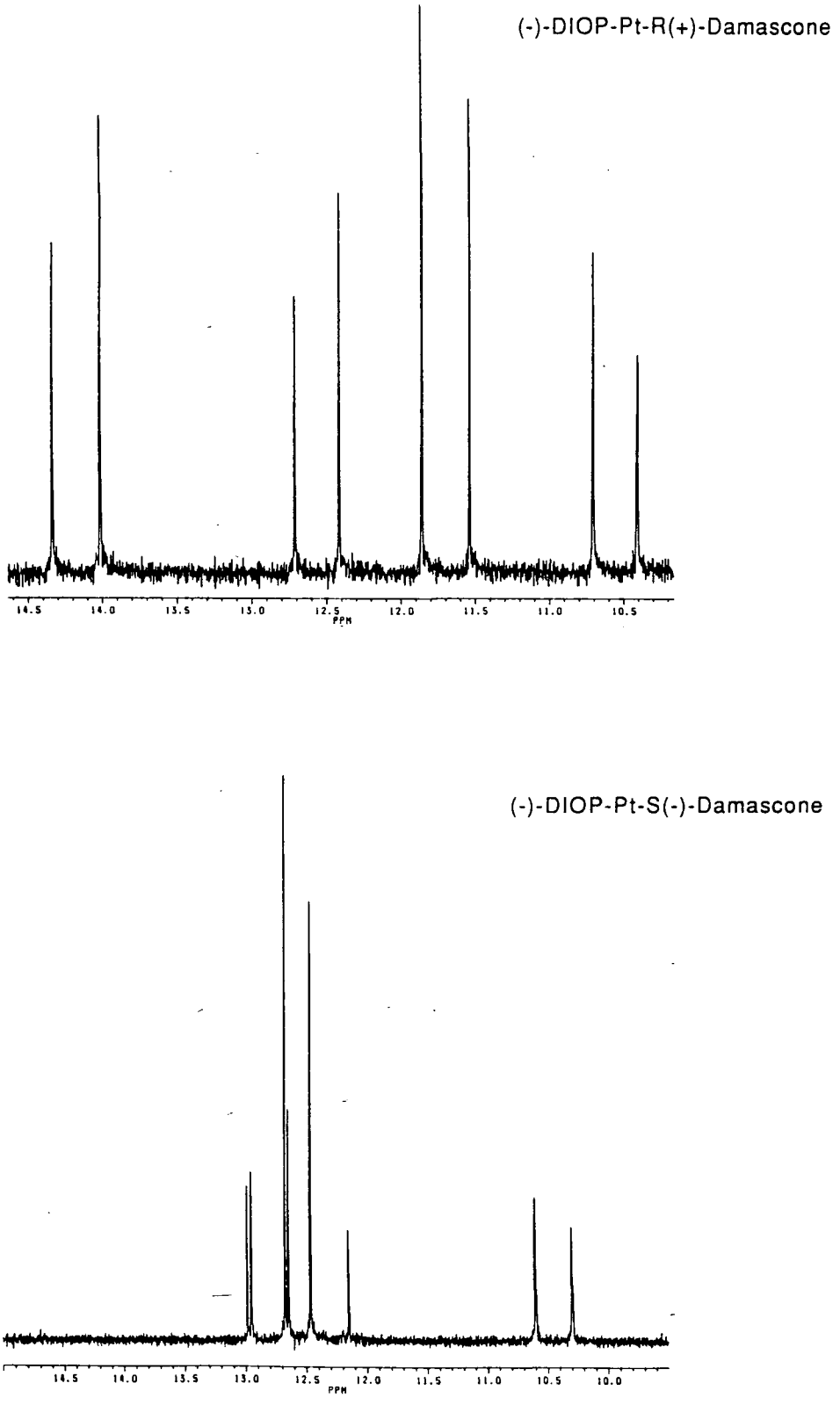


Table 20

^{31}P NMR data and enantiomeric excess for chiral alkene derivatives of η^2 - ethene Platinuim DIOP

Entry	Substrate	δ_{Pa} ppm	δ_{Pb} ppm	J_{Pa-Pb} Hz	J_{Pt-Pa} Hz	J_{Pt-Pb} Hz	% e.e.
1	[-]-96	14.77	12.73	55	3301	3313	98.6 ±0.2 %
	[+]-96	13.80	13.51	55	3595	3094	a
2	R-97	14.36	11.14	60	3381	3419	> 98
3	R-98[c]	14.17	11.68	65	3523	3571	> 99.7
		12.55	10.55	60	3815	3835	
	S-98[c]	12.82	12.30	63	3668	3854	> 99.7
		12.79	10.44	62	3493	3728	
4	77	15.06	13.58	71	3472	2443	b
5	99[c]	13.77	9.88	65	3409	3881	96
		12.50	10.75	65	3537	3938	
6	R-100[d]	10.73	1.27	38	3494	3449	b
	S-100[e]	10.68	1.24	39	3481	3481	b

a) Data from racemate.
b) Unable to determine enantiomeric excess due to absence of observable $\Delta\delta$.
c) Constitutionally isomeric species related by binding of the Si or Re face.
d) ^{19}F NMR spectrum displayed non-equivalence $\Delta\delta = 0.737$, high frequency singlet ee = 85.6 %
e) ^{19}F NMR spectrum displayed non-equivalence $\Delta\delta = 0.739$, low frequency singlet ee = 69.8 %

therefore at least 99.7%, in agreement with values deduced from optical rotation measurements [182]

The chiral alkyne 100 bound non-selectively to the platinum-DIOP moiety to produce one pair of diastereoisomeric resonances for each enantiomer. For each diastereomeric complex, the minor enantiomeric complex could not be distinguished from the major enantiomer in the ^{31}P NMR spectrum. The diastereomeric complexes did display chemical shift non-equivalence in their

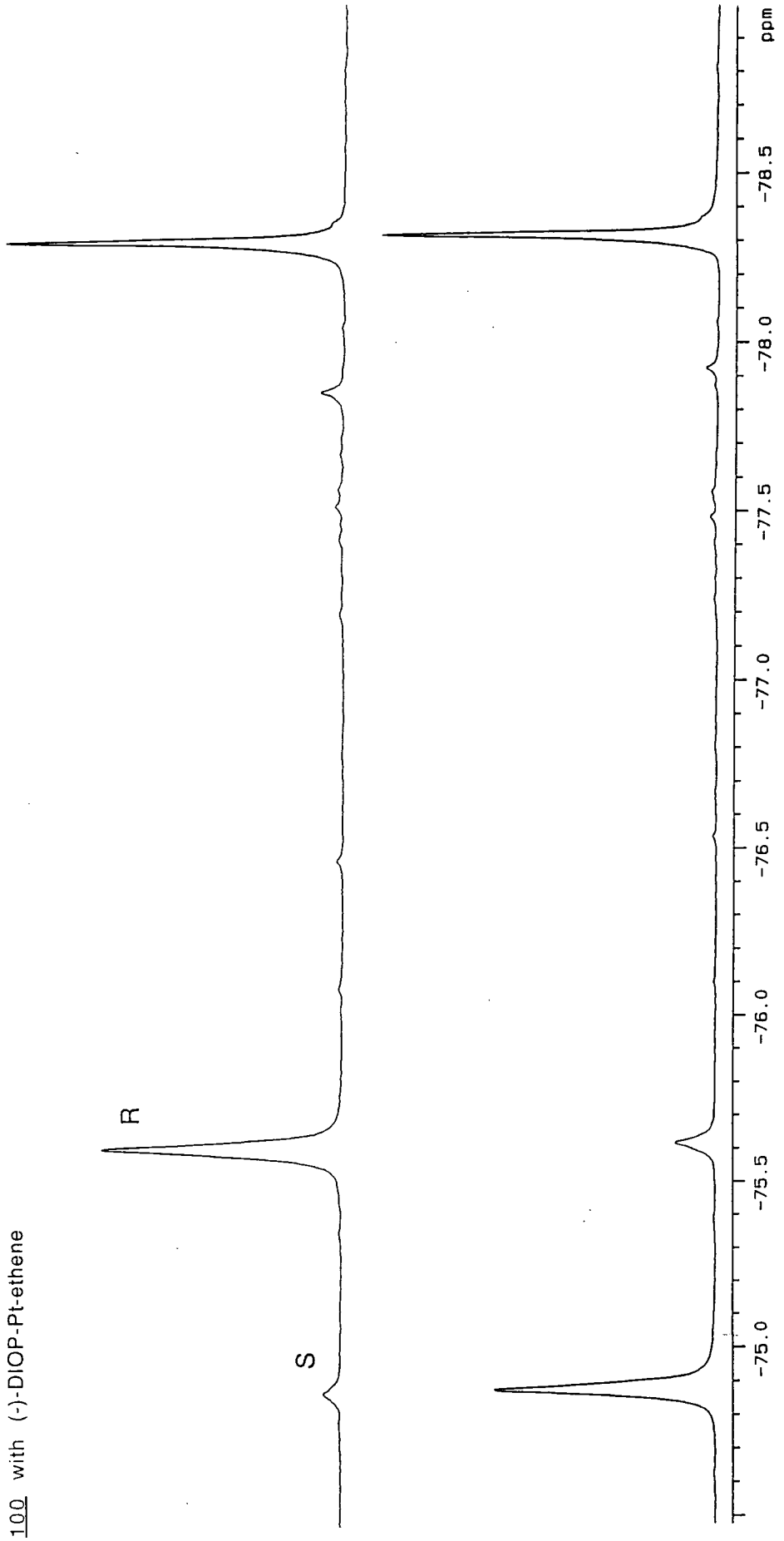


Figure 27
The ^{19}F NMR spectra of R and S chiral alkyne
100 with (-)-DIOP-Pt-ethene

^{19}F NMR spectra. The ^{19}F resonance for both the *R* and *S* complex is shown in **Figure 27**. The observed chemical shift non-equivalence was large ($\Delta\delta$ = 0.739 ppm, C_6D_6, 293K) and both of the samples analysed possessed moderate enantiomeric purity.

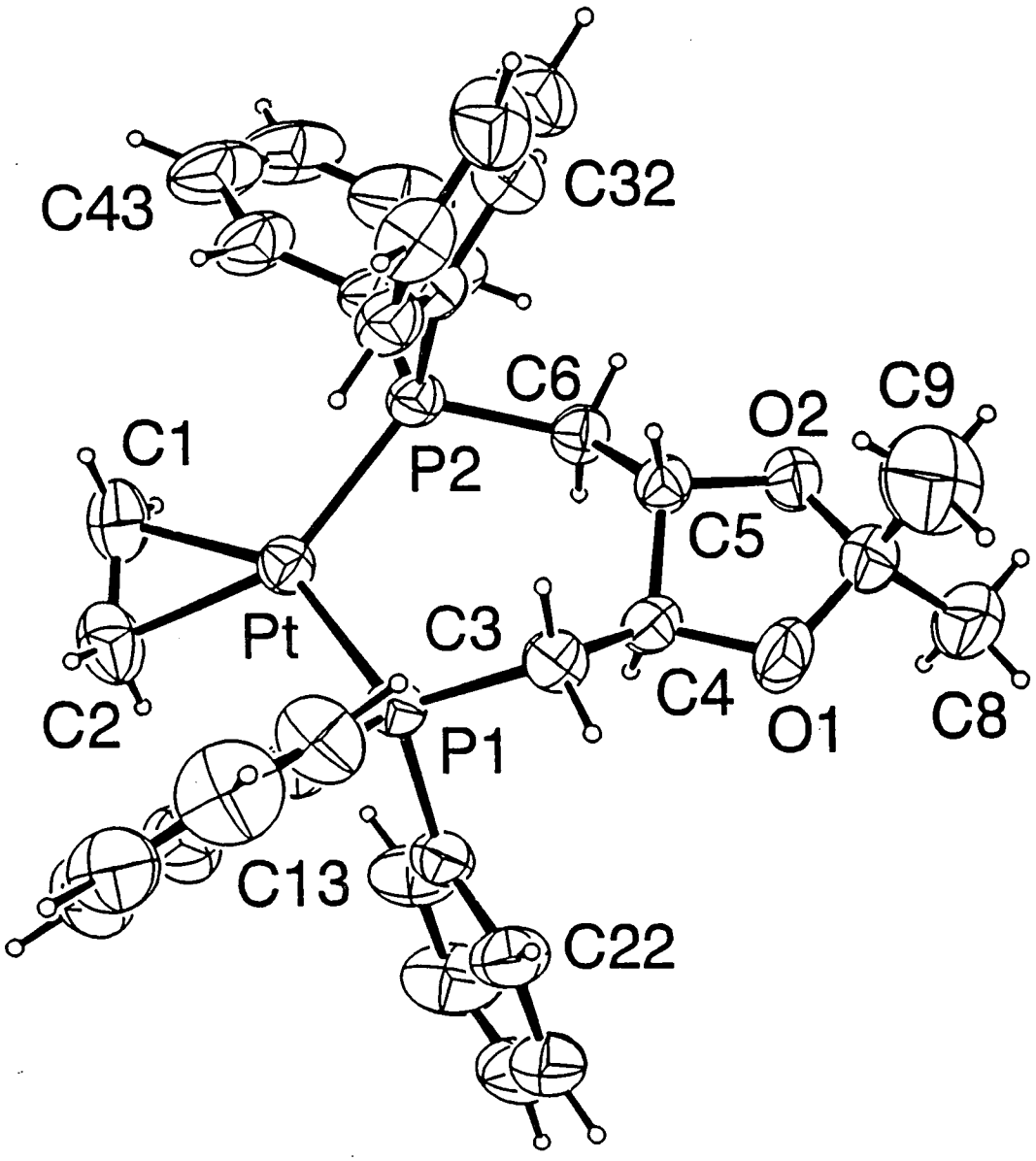
Crystals of η^2-ethene platinum DIOP Suitable for X-ray crystallography were obtained from a dimethylsulphoxide solution. A representation of the molecular structure deduced from the X-ray crystallographic data is shown in **Figure 28**, and **Table 21** highlights some of the significant geometric parameters.

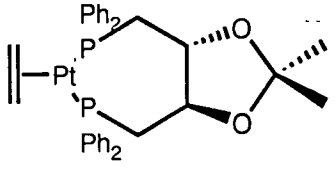
The structure is similar to that of the analogous palladium complex [183] The ethene carbon-carbon bond length may be related to the π-donor ability of the d^{10} metal. The greater the electron donation from the metal the longer the C-C bond length will be. The ethene bond lengths for the platinum complex 35, the Palladium complex 93, and in free ethene are 1.402(9), 1.366(11) and 1.337(2) Å respectively. This compares to 1.434(13) and 1.45(2) Å for the bis(triphenylphosphine) 93 and the seven-ring chelating biphosphine 95 [184, 185].

These values may therefore be related to the degree of π-donation from the metal to the LUMO of the ethene. Π-donor ability correlates to the relative order of energy promotion. from the $(n-1)d^{10}$ state to the $(n-1)d^9$ np state of the metal species, this increases from nickel, platinum and palladium by 1.72, 3.28 and 4.23 eV [186] . Metals with greater electron availability would be expected to from stronger metal-olefin bonds, hence more stable alkene complexes. Platinum coordination geometry is trigonal and approximately planar with a dihedral angle of 4.9(4)° between PPtP and CPtC planes, similar

Figure 28

The crystal structure for (-)-DIOP-Pt-ethene





35

to that found in structures 93, 94, 95. The PPtP chelate bite angle is 105.25(4)°, similar to that of the palladium complex 93 and in the seven-ring chelate complex 95. Attempts were made to synthesise the analogous η^2-ethene nickel-DIOP, but this proved to be unsuccessful. The synthesis was attempted in a similar manner to the formation of the platinum complex, but the final step, the reductive addition of ethene to zero valent nickel failed to yield the expected product. NMR Analysis of the reaction mixture was further complicated by the presents of the paramagnetic nickel(II) ion, indicative of incomplete reduction.

Table 21.

Select geometric data for Pt complex 35

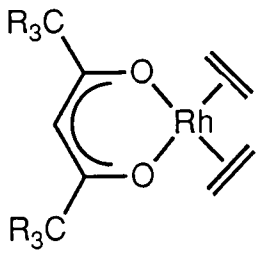
Bond distances Å		Bond angles Degrees	
Pt-P(1)	2.261(4)	P(1)-Pt-P(2)	105.25(4)
Pt-P(2)	2.254(1)	C(1)-Pt-C(2)	38.9(3)
Pt-C(1)	2.109(5)	P(1)-Pt-C(2)	108.8(2)
Pt-C(2)	2.100(5)	P(2)-Pt-C(1)	107.1(2)
C(1)-C(2)	1.402(9)	P.Pt.P-C.Pt.C[a]	4.9(4)

a) Dihedral angle.

4.2 The Analysis of Rhodium(I) Acetylacetone Diethene Derivatives as Reagents to Induce Self Recognition

With previous observations with the achiral reagent PCl_3 and related compounds (see Section 1.2.1.3), we would expect, in principle that two chiral alkenes bound to an achiral metal centre would also produce two sets of diastereomeric complexes (two *meso* forms and a pair of *enantiomers*).

The square planar d^8 rhodium(I) acetylacetonate diethylene complex 101a, has previously been used in conformational studies of its alkene derivatives [187]. The achiral di-ethene complex and it's fluorinated analogue 101b .were reacted with 2 equivalents of a chiral η^2-donor then the ^{19}F and ^1H spectra recorded in order to observe the presence of self recognition. The rhodium complex was dissolved in dry, degassed THF under Argon. Two equivalences of the unsaturated chiral substrate was introduced to the solution which displaced the bound ethene. The solvent was removed under reduced pressure and the residue dissolved in a suitable NMR solvent, usually CD_2Cl_2. For the the derivatives tested 102a-d, non - equivalence was not observed in the ^1H or ^{19}F spectra, and in the majority of cases, the reaction did not proceed as expected.

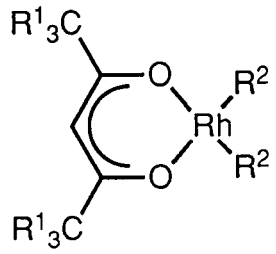


a) R = H
b) R = F

101

The possible cause of the incomplete or failed reactions may be related to the high steric demand in the alkene substituents examined. Also the analysis of the spectra is complicated by the possibility of Si or Re binding for each diastereomer and of slow interconversion (on the NMR time scale) of the rotameric isomers resulting from relatively free rotation about the metal-carbon bond.

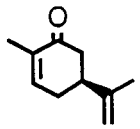
Although the reagent did not work with the reagents tested, it could still induced chemical shift non-equivalence with less bulky reagents, however in the free rotating system (about the M-C bond) the different conformations adopted by these complexes would complicate their spectra.

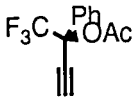


102

a) R^2  ,R1 = H, F

b) R^2  ,R^1 = H, F

c) R^2  ,R^1 = H, F

d) R^2  ,R^1 = H, F

CHAPTER 5

Experimental

5.1 Instrumentation

5.1.1 NMR Spectroscopy

Proton NMR spectra were recorded on a Bruker AC 250 Spectrometer with 8K data points, a Varian VR 400S with 64K data points, and a Bruker AMX 500 Spectrometer with 64K data points. All chemical shifts are quoted against TMS standard at 0 ppm.

Phosphorus 31 NMR spectra were recorded on a Bruker AC 250 with 8K data points and a Varian with 128K data points. Manipulation of data and acquisition parameters was carried out where necessary.

Solvents

Chloroform-d, 99.8 atom % D Aldrich 22,578-9

Benzene-d_6, 100 atom % D Aldrich 17,587-0

Benzene-d_6, 100 atom % D Aldrich 23,697-7

Benzene-d_6, 100 atom % D Aldrich 29,616-9

Pyridine-d_5, 99 atom %D Aldrich 15,232-3

Deuterium oxide 99 atom % D 26,979-4

Toluene-d_8 99+ atom % D 15,199-8

Methyl Sulphoxide-d_6 99.9 atom % D Aldrich 23, 692-6

Limits of Detection

Bruker AC 250 Spectrometer - single pulse (90°)

S/N 50:1 (0.1% ethylbenzene)

Varian VR 400S Spectrometer - single pulse (90°)

S/N 120:1 (0.1% ethylbenzene)

Bucker AMX 500 Spectrometer - single pulse (90°)

S/N (0.1 % ethylbenzene)

5.1.2 Mass Spectroscopy

Mass spectra were recorded on a VG 7070E Spectrometer operating in chemical ionisation, electron impact or desorption chemical ionisation mode.

5.1.3 X-ray Crystallography

Data collection and processing was carried out on a CAD4 diffractometer. Enraf Nonius CAD4 software was used for data collection and cell refinement utilising least squares analysis. Data processing parameters are given in the appendix.

5.2 Experimental Chapters 2, 3

5.2.1 Chiral Solvating Agents

Unless otherwise stated, these compounds were used as received:-

R (+)- N,N-Dimethyl-1-Phenethylamine - Aldrich 24,207-1

S (-)- N,N-Dimethyl-1-Phenlethylamine - Aldrich 24,206-3

RS-N,N-Dimethyl-1-(Naphthyl) ethylamine (5.2.7)

RS-N,N-Dimethyl-2-Phenyl Glycine Methyl ester (5.2.6)

(IR,2S)-Ephedrine - Aldrich 13,491-0

(IR,2R)-N-methyl ephedrine - Aldrich 28,777-6

(IS,2S)-Pseudoephedrine - Aldrich 28,763-6

(IS,2S)-Methyl Pseudoephedrine - Aldrich 29,004-1

RS-Benzyl-Phenethylamine (5.2.8)

RS-N-methyl-1-Phenethylamine (5.2.9)

S-2-(Anilinomethyl)-Pyrrolidine - Merck 818236

S-Proline t-Butyl ester - Sigma P-7769

S-Prolinamide - Sigma P-6675

S-Proline p-nitroanilide from

S-Proline p-Nitroanilide trifluoroacetic acid salt - Sigma P-5267

S-Proline N-Methylamide (5.2.10)

(1R,2R)/(1S,2S)-1,2-Diphenyl-1,2-Diaminoethane (5.2.11)

(1R,2R)/1S,2S)-N,N'-Dibenzyl-1,2 Diphenyl-1,2 Diaminoethane (5.2.13)

(1R,2R)/1S,2S)-N,N'-Diethyl-1,2-Diphenyl-1,2-Diaminoethane (5.2.14)

(1R,2S)-1,2-Diphenyl-1,2-Diaminoethane (5.2.15)

5.2.2 Solutes

RS-Mandelic acid 99+% - Aldrich 24,121-0

(-)-Camphanic acid - Merck 364404

(+)-Camphanic acid - Merck 52260

3-Phenybutyric acid - Aldrich 11,680-7

2-Phenylpropionic acid - Aldrich P3,170-1

Ibuprofen - Sigma 1-4883

Ketoprofen - Sigma F-8514

RS-α-Methoxy-α-(trifluoromethyl) phenylacetic acid - Aldrich 15,655-8

R-0-Acetylmandelic acid - Aldrich 25,303-0

S-0-Acetylmandelic acid - Aldrich 25,302-2

2-Bromopropionic acid - Fluka 18170

2-Chloropropionic acid - Fluka 26158

R-Hexahydromandelic acid - Fluka 52550

S-Hexahydromandelic acid - Fluka 52545

(+)-0,0-Dibenzoyl-L-Tartaric acid - Fluka 33610

(-)-0,0-Dibenzoyl-L-Tartaric acid - Fluka 33620

(±)-Cis-endo-bicyclo[2,2,1]-6/5-methoxycarbonyl-hepta-2-ene-5/6-oic acid

Trans-Cyclohexane-1,2-dicarboxylic acid - Fluka 28975

RS-Naproxen (5.2.3)

Flurbiprofen - Sigma F-8714

2-Fluorobutanoic acid (5.2.4)

Phenylacetic acid - Aldrich P1,662-1

Propionic acid - Aldrich 24,035-4

4-Bromophenylacetic acid - Aldrich 13,867-3

n-Butyric acid - Aldrich B10,350-0

4-methylpentanoic acid - Aldrich 27,782-7

RS-2-Methylbutyric acid - Aldrich 19,307-0

3-Phenylpropionic acid - Aldrich 13,523-2

5.2.3 RS-Naproxen (Racemisation Method) (79)

(S)-Naproxen (5.47 g, 23.75 mmol) was dissolved in 2.5M NaOH solution (5.0 g in 50 ml EtOH), then heated under reflux for 3 days. The solvent was removed under reduced pressure. The residue was dissolved in water (20 ml) then acidified to pH 0 with 6M HCl, The free acid was extracted into chloroform, dried over magnesium sulphate, filtered, and the solvent removed under reduced pressure. The product was recrystallised from chloroform /hexane (1:4) to yield a white crystalline solid (3.20 g, 58.5%).

Found %: C, 73.0 ; H, 6.1. calculated for $C_{14}H_{18}O_3$: C, 73.0 ; H, 6.2

δ_H ($CDCl_3$) 7.64-7.03 (7H, M, Nap), 3.84 (1H, q , J = 7.1Hz, CH), 1.58 (3H, d, J = 7.1Hz, $-CH_3$)

$[\alpha]_D^{20} = 0°$ (c 1.0, $CDCl_3$)

5.2.4 Fluorobutanioc Acid (83)

Methyl-2-Fluorobutanoate[a] (0.27 g, 2.54 mmol) was dissolved in 6M HCl (20 ml), the solution was refluxed for 5 hours, cooled and the free acid extracted into dichloromethane (3 x 10 ml), dried over magnesium sulphate and the solvent removed under reduced pressure to give a colourless oil (0.18 g, 70.1%).

δ_H ($CDCl_3$) 4.94 (1H, ddd, J = 7.8Hz, J = 6.4Hz, J = 48.9Hz, HCF), 2.06-1.93 (2H, m, $-CH_2$), 1.08 (3H, t, J = 7.5Hz, $-CH_3$)

a. Received July 1991, from Dr D. O'Hagan, Department of Chemistry, University of Durham.

5.2.5 The Formation of Diastereomeric Salts for NMR Analysis.

The CSA (0.10 mmol, solid, liquid or solution of known molarity) was added to its complementary solute (0.10 mmol, 1:1 molar ratio) in a suitable deuterated solvent (1 ml; chloroform-d, benzene-d_6, benzene-d_6+ pyridine-d_5, toluene-d_8). The solution was filtered, degassed and the ^{1}H NMR spectrum recorded.

In the case of 1,2-diphenyl-1,2-diaminoethane, maximum non-equivalence was observed with a 2:1 acid/amine molar ratio (0.05 mmol diamine, 0.10 mmol complementary reagent).

5.2.6 N,N'-Dimethyl-2-phenylglycine methyl ester [188] (61)

(R) or (S)-Phenylglycine (13.61 g, 90 mmol) was dissolved in aqueous formaldehyde (14.6 ml, 180 mmol in 270 ml H_2O). To the solution a catalytic amount of palladium on activated carbon (5%, 6.65 g) was added and the mixture was subjected to hydrogenation for 6 hours (H_2, 35lbs per sq inch).

The solution was filtered and the solvent was removed under reduced pressure. The product was recrystallised from acetone/ethanol (1:1) to yield a white crystalline solid (8.39 g, 52%). Mpt 255-256° C (lit. Mpt 257° C) [188]

Found % : C, 68.2 ; H, 7.9 ; O, 16.6 ; N, 7.3. calculated for $C_{11}H_{15}NO_2$: C, 68.4 ; H, 7.9 ; N.7.3 ; O, 16.6

δ_H (D_2O) 7.52 (5H, s, Ph), 4.61 (1H, s, CH), 3.01, 2.54 (6H, d, $N(CH_3)_2$)

m/e (NH_3, CI) 203 (M^+ + 10), 185 (M^+ + 8), 181 (M^+ + 12), 180 (M^+ + 13)

(R) or (S)-N,N'-Dimethyl-2-phenylglycine (8 g, 45 mmol) was dissolved in methanol (500 ml) and cooled to 0° C. A solution of Diazomethane [189] in ether/methanol (2.90 g, 68 mmol, 0° C) was added dropwise over 15 minutes. The solution was kept at 0° C for 30 minutes, and then the solvent and excess diazomethane was removed under reduced pressure. The ester was extracted into ether (3 x 10 cm^3), the solvent removed under reduced pressure and the product purified by distillation (50-60° C, 0.02 mm Hg) to give a colourless oil (3.88 g, 45%).

δ_H ($CDCl_3$) 7.45-7.25 (5H,m,Ph), 3.87 (1H,s,CH), 3.70 (3H,s,OCH_3), 2.25 (6H,s,$N(CH_3)_2$)
m/e (NH_3,CI) 195 ($M^+ + 2$), 194 ($M^+ + 1$)

5.2.7 N,N'-Dimethyl-1-(1-Naphthyl)ethylamine [190] (62)

(R) or (S)-1-(1-Naphthyl) ethylamine (1 g, 5.84 mmol) was added to dilute acetic acid (5M, 80 ml) and formaldehyde (2 ml, 24.66 mmol). Palladium on activated carbon (5%, 2 g) was added to the solution prior to hydrogenation (H_2, 34.9 lbs per sq inch, 6 h, 20°C).

The solution was filtered, the pH raised to 12 (KOH solution) and the resultant free amine was extracted into chloroform (2 x 10 cm^3). The combined organic extracts were dried over anhydrous potassium carbonate, the solution was filtered and the solvent removed under reduced pressure to yield a colourless oil (592 mg, 51%).
m/e (SMI) $C_{14}H_{17}N$ Found : 199.12448, (mmv 11.6). Calculated : 199.2950
δ_H ($CDCl_3$) 8.33-7.17 (7H, m, Ar), 3.92 (1H, q, J = 6.6 Hz NCH), 2.20 (6H, s, $N(CH_3)_2$), 1.40 (3H, d, J=6.6 Hz, CH_3)
m/e (NH_3, CI) 201 ($M^+ + 2$), 200 ($M^+ + 1$)

5.2.8 N-Benzyl-Phenethylamine [191] (63a)

(R) or (S)-α-methylbenzylamine (1.92 ml, 1.81 g, 15 mmol) was mixed with dry ethanol (10 ml) under nitrogen. Benzaldehyde (4.57 ml, 4.77 g, 45 mmol) was slowly added to the solution which was then stirred for 30 minutes.

The resultant imine was cooled to 0° C, a solution of sodium borohydride in ethanol (1.13 g, 30 mmol in 10 ml EtOH) was gradually introduced. The solution was allowed to reach room temperature and was then stirred for 15 hours. An excess of ethanol (5 ml) was added to the solution which was stirred for a further 30 minutes.

The solvent was removed under reduced pressure, the residue was dissolved in water, acidified to pH 2 (HCl solution) then washed with ether (3 x 10 ml). The pH of the aqueous solution was raised to 12 (KOH solution) and the free amine extracted into dichloromethane (3 x 20 ml). The solution was dried over magnesium sulphate, filtered and the solvent removed under reduced pressure to yield a colourless oil (2.49 g, 78.5%).

δ_H ($CDCl_3$) 7.59-7.41 (10H, m, 2Ph), 4.26 (1H, q, J_{ax} = 6.6 Hz, NCH), 3.87, 3.80 (2H, q, $J_{aa'}$ = 13.3 Hz), 1.84 (1H, s, NH), 1.57 (3H, d, J_{ax} = 6.6Hz, CH_3)

m/e (NH_3, CI), 212 ($M^+ + 1$), 213 ($M^+ + 2$)

5.2.9 N-Methyl-1-Phenethylamine [22, 191, 192] (63b)

(R) or (S) -α-methylbenzylamine (1.93 ml, 1.83 g, 16 mmol) was mixed with dry toluene (84 ml) and pyridine (11 ml) then cooled to 0° C. Isobutylchloroformate (5.84 ml, 6.12 g, 45 mmol) was dissolved in dry toluene (14 ml). This was slowly added to the amine solution over 20 minutes. The solution was allowed to reach room temperature then was stirred for 2 hours.

2M sodium hydroxide (75 ml) solution was added to the solution. The two immiscable layers were stirred vigorously together for 3 hours. The aqueous layer was removed then washed with toluene (3 x 15 ml). The organic solution and washings were combined and dried over magnesium sulphate and the solvent was removed by reduced pressure. The produce was recrystallised from hexane (1.94 g, 55.2%).

Found % : C, 71.1 ; H, 8.9 ; N, 6.0. calculated for $C_{13}H_{19}NO_2$: C, 71.0 ; H, 8.7 ; N.6.3.

δ_H ($CDCl_3$) 7.33-7.27 (5H,m,Ph), 4.93 (1H,s,NH), 4.84 (1H,s,NCH), 3.84, 3.83, 3.81, 3.80 (2H, dd, $J_{aa'}$ = 2.2 Hz, J_{ax} 6.59 Hz, CH_2O), 1.89, 1.87, 1.84. (1H, J = 5.0 Hz, J = 6.6 Hz, $CHMe_2$), 1.49, 1.46 (3H, d, J = 6.6 Hz, CH_3), 0.90, 0.88 (6H, d, J = 5.1 Hz, $C(CH_3)_2$)

m/e (NH_3, CI) 222 (M^+ + 1), 301 (M^+ +18).

(R) or (S)-N-Isobutyl-1-phenethylamine (1.01 g, 4.6 mmol) was dissolved in dry, degassed tetrahydrofuran (7 ml). Lithium aluminium hydride (0.54 g, 14.2 mmol) was dissolved in dry, degassed THF under nitrogen and cooled to 0° C, the amine solution was slowly added over a 30 minute period. The solution was allowed to warm to room temperature then refluxed for 3 hours.

The solution was cooled and excess $LiAlH_4$ removed by the addition of water (0.5 ml) then 2M NaOH (0.5 ml). The solution was filtered and the solvent removed by reduced pressure, the residue was dissolved in water, acidified and washed with ether (3 x 5 ml). After the pH of the solution was raised to 12 (KOH solution), the free amine was extracted into chloroform (3 x 10 ml). The solution was dried over magnesium sulphate, filtered, and the solvent removed under reduced pressure to yield a colourless oil (80° C, 12 mmHg, 0.36 g, 59.4%).

m/e (SMI) $C_9H_{13}N$ Found : 135.08740, (mmv 17.4). Calculated : 135.2084

δ_H 7.17 (5H,s,Ph), 3.38 (1H, q, J_{ax} = 6.5 Hz, NCH), 2.10 (3H,s,NCH_3), 1.17 (3H, d, J_{ax} = 6.5 Hz, CH_3), 0.91 (1H, b, NH).

m/e (NH_3, CI) (M^+ + 1) 136, (M^+ - 16) 120

5.2.10 L-Proline-N-Methylamide [193] (66d)

L-Proline methylester hydrochloride (1.05 g, 6.4 mmol) was dissolved in methanol (10 ml). The solution was cooled to -78° C. Methylamine was condensed into the proline solution. The mixture was stirred for 5 hours. The solution was left to warm to room temperature, and the solvent removed under reduced pressure. The residue was dissolved in ether, filtered, and the solvent removed under reduced pressure to give a colourless solution. The solution was distilled under reduced pressure (80° C, 0.1 mmHg, 0.55 g, 67.4%).

δ_H ($CDCl_3$) 3.84 (1H, dd, J_{aa} = 9.3 Hz, J_{ae} 5.5 Hz, CHCO), 3.55 (1H,s,NHMe), 3.12 (1H, b, NH), 3.11-2.92 (2H, m, CH_2), 2.88, 2.86 (3H, s,s', $NHCH_2$), 2.19 (1H, dt, J = 7.5 Hz, $J_{HH'}$ = 19.7 Hz, CH_a), 1.95 (1H, dt, J = 6.5 Hz, $J_{HH'}$ = 19.3 Hz, CH_e), 1.75 (2H, quin, J = 6.9 Hz, CH_2)

m/e (NH_3, CI) 129 (M^+ + 1), 70 (M^+ - 58)

5.2.11 (RS)-1-1,2-Diphenyl-1,2-diaminoethane [194] (58)

Benzil (78.22 g, 0.37 mmol) was mixed with cyclohexanone (39.3 ml, 37.2 g, 0.38 mmol), ammonium acetate (296.5 g, 3.84 mmol) and acetic acid (741 ml). The solution was refluxed for one hour, then allowed to cool slightly before it was poured into water (1l). The solution was stirred for 2 hours then left for 15 hours. The resulting crystals were removed by filtration, washed with water (3 x 200 ml). The product was recrystallised from methanol/water (4:1) to yield a yellow solid (86.8 g, 81%).

Found % : C 83.8 ; H 7.0 ; N 9.1 ; calculated for $C_{20}H_{20}N_2$: C 83.8 ; H 7.0 ; N 9.7

δ_H ($CDCl_3$) 7.52-7.32 (5H, m, Ph), 1.97-1.92 (1H,m,CH_2C), 1.84-1.68 (2H, m, CH_2CH_2)

5-Spirocyclohexyl-2,3-diphenylisoimidazole (40 g, 138.7 mmol) was dissolved in THF (200 ml) and cooled to -78° C. Ammonia was condensed into the solution (250 ml) then lithium (4 g, 576.4 mmol) was added in small amounts. The solution was stirred under a nitrogen atmosphere for 2 hours. Ammonium chloride (40 g,747.8 mmol) was added to the solution before being allowed to reach room temperature. Water (200 ml) was stirred with the organic layer for 30 minutes, the aqueous phase was separated then washed with ether (3 x 50 ml). The combined washing and organic layer was washed with sodium chloride solution (3 x 30 ml) then dried over anhydrous magnesium sulphate, filtered then the solvent volume reduced to 150 ml.

2M HCl (200 ml) was added to the solution, the phases were stirred vigorously for 2 hours. The organic layer was removed then washed with water (3 x 30 ml). The combined aqueous solution and washings was basified with NaOH (pH 14). The free amine was extracted into dichloromethane (3 x 60 ml)

dried, filtered, and the solvent removed under reduced pressure to yield a colourless solid (24.18 g, 81.4%). Mpt 82-83° C (lit. Mpt 83° C) [194]

δ_H ($CDCl_3$) 7.30 (5H, s, Ph), 4.10 (1H, s, CH), 1.60 (2H, s, NH_2)

5.2.12 Resolution of Racemic-1,2-Diphenyl-1,2-diaminoethane [195] (58)

(RS)-1,2-diphenyl-1,2-diaminoethane (4.30 g, 20.0 mmol) was dissolved in 35 ml of dry ethanol upon heating. S-mandelic acid (6.10 g, 40.1 mmol) was dissolved in the hot solution which was left to cool forming crystals of the salt. The precipitate was removed by filtration and recrystallised twice from ethanol (50 ml, 30 ml) then dried (3.49 g, 67.3%) Mpt 156-157° C (lit 164-165° C) $[\alpha]_D^{20}$ = + 122.0° (lit 126.9°, c 1.51, MeOH) [195]. The washings were combined and saved.

The (1S,2S) DPDAE (S)MA salt (3.49 g, 6.73 mmol) was dissolved in water (40 ml) basified with NaOH (pH14). The free amine was extracted into ether (3 x 10 ml), the solution was dried, filtered then the solvent removed under reduced pressure to yield a white precipitate. The product was recrystallised from ether/hexane (1:1) (0.94 g, 65.4%) Mpt 79.5-80.5° C (lit 80° C) [195] $[\alpha]_D^{20}$ = 104.1° (lit 106.5°, c 1.0, MeOH) [195]

The saved washing's ((1R,2R) DPDAE (S)MA) solvent was removed under reduced pressure. The free amine was obtained as above. The impure (1R,2R)DPDAE (1.8 g, 8.43 mmol) was dissolved in ethanol (50 ml) upon heating. R-Mandelic acid (2.57 g, 16.9 mmol) was dissolved in the hot solution then the solution was left for crystal formation. The crystals were filtered and dried (3.55 g, 81.3%).

mpt 158-159° C (lit 164-165° C) [195], $[\alpha]_D^{20}$ = 15.70° (lit 126.9°, c 1.4, MeOH) [92]

The free (1R,2R) DPDAE was obtained from (1R,2R) DPDAE (R)MA as described above.
(1.20 g, 66.7%) mpt 80-80.5° C (lit 80° C) [195] $[\alpha]_D^{20}$ = 95.7° (lit 106-5°, c 1.0, MeOH) [195]

The enantiomeric purity of the resolved amine was checked by ^1H NMR using R-O-acetylmandelic acid as a Chiral solvating agent (C_6D_6, $\Delta\delta$ = 0.077 ppm). No minor resonance was seen for the complementry enantiomer. The resolved amines are essentially pure with an enantiomeric execess > 99.7% (limit of detection).

5.2.13 N,N'-Dibenzoyl-1,2-diphenyl-1,2-diaminoethane [196] (86a)

(R) or (S)-1,2-diphenyl-1,2-diaminoethane (0.28 g, 1.29 mmol) was dissolved in dry chloroform (30 ml) with triethylamine (0.45 ml, 0.32 g, 3.24 mmol). The solution was cooled to 0° C and benzoyl chloride (0.5 ml, 0.54 g, 3.84 mmol) added dropwise over 10 minutes. The solution was allowed to reach room temperature, the precipitate was removed by filtration, and washed with 1M HCl (3 x 10 ml) then washed with water (3 x 20 ml). The white solid was dried under reduced pressure (0.37 g, 67.3%). Sublimes 168-170° C.

Found % : C, 79.9 ; H, 5.8 ; N, 6.4 calculated for $C_{28}H_{24}N_2O_2$: C, 79.9 ; H 5.8 ; N, ; 6.6
m/e (NH_3, CI) 421 (M^+ + 1), 212 (M^+ - 208), 106 (M^+ - 314)

(R) or (S)-N,N'-Dibenzoyl-1,2-diphenyl-1,2-diaminoethane (0.37 g, 0.87 mmol) was mixed with tetrahydrofuran (20 ml) and lithium aluminium hydride (0.36 g, 9.49 mmol) at 0° C under nitrogen. The solution was allowed to reach room temperature then heated to reflux for 4 days. The solution was cooled and excess $LiAlH_4$ removed by the addition of water and 4M NaOH.(0.36 ml

H_2O, 1.2 ml 4M NaOH, 2 x 1 ml H_2O). The solvent was removed under reduced pressure and the residue was mixed with HCl solution (pH 1, 20 ml) The solution was filtered and the pH was raised to 12 (KOH solution). The free amine was extracted into dichloromethane (3 x 10 ml), dried over potassium carbonate, filtered, and the solvent removed under reduced pressure to yield a colourless oil (0.18 g, 51.2%).

The product was purified by column chromatography (Al_2O_3, 2% Hexane in dichloromethane) $R_f = 0.37$.

δ_H ($CDCl_3$) 7.30-7.03 (10H, m, 2Ph), 3.71 (1H, s, CH), 3.68, 3.65, 3.50, 3.47 (2H, dd, J_{aa} = 13.4 Hz, CH_2), 2.21 (1H, b, NH).

5.2.14 N,N'-Diethyl-1,2-diphenyl-1,2-diaminoethane [197] (86b)

(R) or (S)-1,2-Diphenyl-1,2-diaminoethane (0.44 g, 2.06 mmol) was dissolved in dry dichloromethane (20 ml) with triethylamine (1.84 ml, 1.32 g, 13.2 mmol). The solution was cooled to 0° C under Nitrogen and acetyl chloride (1 ml, 14.1 mmol) was added dropwise over 15 minutes, the reaction was left to warm to room temperature then stirred for 2 hours. 1M HCl (10 ml) was added to the solution which was stirred for a further 30 minutes. The organic and aqueous layers were separated, and the aqueous layer washed with dichloromethane. The organic layer and combined washing were dried over potassium carbonate, filtered and the solvent removed under reduced pressure to yield a white solid (0.53 g, 86.3%). Recrystallisation from methanol/water (1:1 v:v) gave a colourless solid (0.44 g, 72.0%) Mpt 130-133°C.

Found % : N, 8.3 ; C, 67.4 ; H, 6.8 Cal. for $C_{18}H_{20}N_2O_2$: C, 73.0 ; N, 9.5 ; H, 6.8
m/e (NH_3, CI) 297 ($M^+ + 1$), 269 ($M^+ - 28$), 105 ($M^+ - 191$).

(R) or (S)-N,N'-Acetyl-1,2-diphenyl-1,2diaminoethane (0.44 g, 72.0%) was mixed with THF (20 ml) and $LiAlH_4$ (0.35 g, 9.18 mmol) at 0° C under Nitrogen. The solution was allowed to reach room temperature then refluxed for 2 days. The solution was cooled and water, 4M NaOH (0.6 ml H_2O, 2.4 ml 4M NaOH, 2 x 1 ml H_2O) was added. The solvent was removed under reduced pressure. To the residue 1M HCl solution (30 ml) was added. The solution was filtered and the pH raised to 12 (KOH solution). The free amine was extracted into dichloromethane (3 x 10 ml), dried over magnesium sulphate, filtered and the solvent removed under reduced pressure to yield a white solid (0.25 g, 62.8%).

δ_H ($CDCl_3$) 7.31-7.00 (5H, m, Ph), 3.96 (1H, s, CH), 2.69-2.36 (2H, m, CH_2), 1.19 (3H, t, J = 7.1 Hz, CH_3).
m/e (NH_3, CI) 269 (M^+ + 1), 134 (M^+ - 134), 106 (M^+ - 162).

5.2.15 meso-1,2-Diphenyl-1,2-Diaminoethane [198] (84)

Benzaldehyde (100 ml, 104.7 g, 986.6 mmol) was mixed with ammonium acetate (66.9 g, 86.1 mmol) and the solution was heated under reflux for 3 hours, then allowed to cool to room temperature. The precipitate was collected by filtration, washed with ethanol (3 x 20 ml) and dried under reduced pressure to yield N-benzoyl-N'-benzylidine-Meso-1,2-Diphenyl-1,2-Diaminoethane as a white solid (47.3 g, 47.4%) Mpt 257-258° C, (lit 259° C) [198]

δ_H (DMSO-d6) 8.81 (1H, d, J = 9.2 Hz, NCPh), 7.14 (1H, s, NHCO), 6.76-6.28 (22H, m, 4Ph), 4.76 (1H, t, J = 9.40, HCNHCO), 3.94 (1H, d, J = 9.6 Hz, HCNC)
m/e (NH_3, CI) 405 (M^+ + 1), 210 (M^+ - 194), 106 (M^+ - 298)
Found % : N, 6.8 ; C, 83.8 ; H, 6.0 Cal. for $C_{28}H_{24}N_2O$: N, 6.9 ; C, 83.1 ; H, 6.0

N-benzoyl-N'-benzylidine-Meso-1,2-Diphenyl-1,2-Diaminoethane (10.0 g, 24.7 mmol) was dissolved in 6M sulphuric acid (100 cm^3). The solution was steam distilled for 7 hours on (until the distillate was no longer acidic). The solution was cooled, filtered and neutralised with ammonia solution (33% w/v). The free amine was extracted into ether (3 x 20 ml), dried over magnesium sulphate, filtered and the solvent removed under reduced pressure. The diamine was recrystallised from Hexane to yield a white crystalline solid (2.3 g, 44%) Mpt 118-119° C, (lit 120° C) [198]

δ_H ($CDCl_3$) 7.41-7.30 (5H, m, Ph), 4.03 (1H, s, CH), 1.41 (2H, s, NH_2)
m/e (NH_3, CI) 213 ($M^+ + 1$), 196 ($M^+ - 16$), 106 ($M^+ - 106$)
Found % : N, 13.0 ; C, 79.0 ; H, 7.6 Cal. for $C_{14}H_{16}N_2$: N, 13.2 ; C, 79.2 ; H, 7.6

5.2.16 The Formation of (1R, 2R)-1,2-Diphenyl-1,2-Diaminoethane Monohydrobromide Crystals for X-ray Analysis.

(1R, 2R)-1,2-DPEDA (30.8 mg, 0.145 mmol) was dissolved in iso-propylalcohol (1 ml) containing 2-Bromopropionic acid (21.4 mg, 0.140 mmol). Iso-propylether vapour was allowed to diffuse into the solution over 3 days during which time crystals suitable for X-ray analysis formed.
(See appendix for desposition data)

δ_H ($CDCl_3$) 7.18-7.17 (3H, m, o,p-Ph), 6.98-6.97 (2H, m, m-Ph),
4.41 (1H, s, CH).

5.2.17 The Attempted crystallisation of 1,2 diphenyl-1,2-diaminoethane salts for X-ray analysis.

Several unsuccessful attempts were made to grow crystals of 1,2-DPDAE carboxylate salts suitable for X-ray analysis. A summary of the reagents and methods used follows.

Vapour diffusion

1 Equivalent of the acid (0.1 mmol) was added to 0.5 equivalents of 1R,2R-DPDAE (0.5 mmol). The dicarboxylate salt was dissolved in a minimum volume of the polar solvent (0.5 ml), filtered and placed in a vapour diffusion chamber containing isopropyl ether as the vapour diffusing agent. The chamber was left until crystal formed or an equilibrium was reached.

Polar solvent - Isopropyl alcohol

Reagents	
α-Bromopropionic acid	Crystals formed
S-Naproxen	No crystals
R(+)/S(-)-2-Chloropropionic acid	No Crystals
R(-)/S(+)-2-Phenylpropionic acid	No Crystals
R/S-Mandelic acid	No Crystals

Polar solvent - Acetronitrile

Reagents	
S-Naproxen	Crystals Formed
R(+)/S(-)-2-Chloropropionic acid	No Crystals

Crystallisation from constant volume

1 Equivalent of the acid was added to 0.5 equivalents of 1R,2R-DPDAE. The dicarboxylate salt was dissolved in a minimum of the polar solvent (1.0 ml), filtered and placed in a sealed container.

Polar solvent - Dichloromethane

Reagents	
R(+)/S(-)-2-Chloropropionic acid (0.1 mmol)	Crystals (fine needles)
α-Bromophenylacetic acid (0.1, 0.2, 0.3 mmol)	No Crystals
4-Bromophenylacetic acid (0.1 mmol)	No Crystals
(0.4 mmol)	Crystals formed
2-Bromopropionic acid (0.1, 0.4, 0.5 mmol)	Crystals formed

Polar solvent - Benzene

Reagents	
α-Bromophenylacetic acid (0.1 mmol)	No Crystals
4-Bromophenylacetic acid (0.1, 0.3, 0.5 mmol)	Crystals formed
2-Bromopropionic acid (0.1, 0.3, 0.5 mmol)	Crystals formed

5.3 Experimental Chapter 4

5.3.1 The Formation of Diastereomeric Complexes for NMR Analysis.

(R,R)-DIOP-Pt^{0}-C_2H_4 (15 mg, 0.02 mmol) was dissolved in dry, degassed tetrahydrofuran (1.5 ml). The solid η^2-donor (0.02mmol) was dissolved in dry, degassed THF (1.5 ml).

The η^2-donor solution or liquid was added by syringe to the platinum complex. The solution was stirred for 10 minutes with concomitant evolution of ethene. The THF was removed under reduced pressure, the residue dissolved in deutero-benzene (0.5 ml) and the NMR spectrum recorded.

5.3.2 η^2-donors

(R,R)-DIOP-Pt^{0}-(RS)-Damascone[a] (98).
R-Enantiomer- δ_P (C_6D_6) Pa 14.17 (J_{Pa-Pb} 65 Hz, J_{Pa-Pt} 3523 Hz), Pb 11.68 (J_{Pb-Pa} 65 Hz, J_{Pb-Pt} 3571 Hz), Pa' 12.55 ($J_{Pa'-Pb'}$ 60 Hz, J_{Pa-Pt} 3815 Hz), Pb' 10.55 ($J_{Pb'-Pa'}$ 60 Hz, $J_{Pb'-Pt}$ 3835 Hz)
S-Enantiomer- δ_P (C_6D_6) Pa 12.82 (J_{Pa-Pb} 63 Hz, J_{Pa-Pt} 3668 Hz), Pb 12.30 (J_{Pb-Pa} 63 Hz, J_{Pb-Pt} 3854 Hz), Pa' 12.79 ($J_{Pa'-Pb'}$ 62 Hz, J_{Pa-Pt} 3493 Hz), Pb' 10.44 ($J_{Pb'-Pa'}$ 62 Hz, $J_{Pb'-Pt}$ 3728 Hz)

(R,R)-DIOP-Pt^{0}-(RS)-2-aza bicyclo [2.2.1] hept-5-en-3-one[b] (96).
[-]-Enantiomer δ_P (C_6D_6) Pa 14.77 (J_{Pa-Pb} 55 Hz, J_{Pa-Pt} 3301 Hz) Pb 12.73 (J_{Pb-Pa} 55 Hz, J_{Pb-Pt} 3313 Hz)
[+]-Enantiomer δ_P (C_6D_6) Pa 13.80 (J_{Pa-Pb} 55 Hz, J_{Pa-Pt} 3595 Hz) Pb 13.51 (J_{Pb-Pa} 55 Hz, J_{Pb-Pt} 3094 Hz)

(R,R)-DIOP-Pt°-(R)-Pulegone[c] (97)

Palegone was added in large excess to a solution of DIOP-platinum ethane (15 mg, 0.02 mmol) in tetrahydrofuran (1.5 ml). Excess palegone was removed after 5 days at room temperature.

R-Enantiomer- δ_P (C_6D_6) Pa 14.36 (J_{Pa-Pb} 60 Hz, J_{Pa-Pt} 3381 Hz), Pb 11.14 (J_{Pb-Pa} 60 Hz, J_{Pb-Pt} 3919 Hz)

(R,R)-DIOP-Pt°-(±)-Cis-endo-bicyclo[2,2,1]-6/5-methoxycarbonyl-hepta-2-ene-5/6-oic acid[d] (77)

Racemate- δ_P (C_6D_6) Pa 15.06 (J_{Pa-Pb} 71 Hz, J_{Pa-Pt} 3472 Hz), Pb 13.58 (J_{Pb-Pa} 71 Hz, J_{Pb-Pt} 3443 Hz)

(R,R)-DIOP-Pt°-(RS)- 1,1,1-Trifluoro-2-acetoxy-2-phenylbut-3-yne (100).

R-enantiomer- δ_P (C_6D_6) Pa 10.73 (J_{Pa-Pb} 38 Hz, J_{Pa-Pt} 3494 Hz), Pb 1.27 (J_{Pb-Pa} 39 Hz, J_{Pb-Pt} 3449 Hz)

S-enantiomer- δ_P (C_6D_6) Pa 10.68 (J_{Pa-Pb} 39 Hz, J_{Pa-Pt} 3481 Hz), Pb 1.24 (J_{Pb-Pa} 39 Hz, J_{Pb-Pt} 3481 Hz)

δ_F (C_6D_6) 74.88 (1H, s, (s)-CF_3), 75.62 (1H, s, (R)-CF_3), 78.32 (xH, s, free-CF_3)

a). Received January 1989 from Fehr, C.
Fehr, C.; Galindo, J. J. Am. Chem. Soc., 1988, 110, 6909.

b). Received April 1990 from Roberts, S. M. Department of Chemistry, Exeter University.

c). Compound obtained from Fluka 82569

d). Received January 1990, from J. Gopal, J. Department of Chemistry, Durham University.

5.3.3 (R,R)-2,3-0-Isopropylidene-2,3-Dihydroxy-1,4-Bis (Diphenyl phosphino) Butane Dichloro Platinum (II) ((R,R)-DIOP-$Pt^{II}Cl_2$) [199]

$Pt(^tBu\ CN)_2Cl_2$ [a] (90 mg, 0.21 mmol) was dissolved in dry, degassed chloroform (3 cm^3) under nitrogen, (R,R)-DIOP [b] (102 mg, 0.21 mmol) was dissolved in dry degassed chloroform then transferred by steel cannula to the platinum complex. The solution was stirred for 20 minutes. The volume of dichloromethane was reduced by a quarter, then methanol (0.5 cm^3) was added. A precipitate formed which was collected by filtration, washed with methanol (3 x 0.5 ml) and dried under reduced pressure (106 mg, 67%).

δ_P ($CDCl_3$) 17.0 ppm ($J_{P\text{-}Pt}$ 3513 Hz)

a - Bis (trimethylacetonitrile) dichloroplatinum(II).

b - (R, R)-2,3-0-Isopropylidene-2,3-dihydroxyl-1,4-bis(diphenyl-phosphino)butane.

5.3.4 (R,R)-2,3-0-Isopropylidene-2,3-Dihydroxy-1,4-bis(diphenylphosphino) butane Platinum (0)-ethene ((R,R)-DIOP-Pt^0-C_2H_4) [199] (35)

(R,R)-DIOP-$Pt^{II}Cl_2$ (191 mg, 0.25 mmol) was dissolved in dry, degassed dichloromethane (4 ml) and dry, degassed ethanol (4 ml) was added. The solution was degassed with ethene and cooled to -78° C under nitrogen.

Sodium borohydride (22.7 mg, 0.60 mmol) was dissolved in dry ethanol (4 ml) and degassed with ethene then cooled to -78° C. The sodium borohydride solution was transferred by steel cannula to the platinum complex. Ethene was bubbled through the solution for 30 minutes.

The solution was allowed to warm to room temperature, and at the first signs of darkening the complex was transferred to the dry degassed ethanol (15 ml). The solution was left for 15 minutes while the product precipitated. The product was filtered, washed with ethanol (3 x 5 ml) then dried under reduced pressure (144 mg, 80%).

δ_P (C_6D_6) 14.39 ppm ($J_{P\text{-}Pt}$ 3589 Hz)

5.3.5 The Formation of (R,R)-DIOP-Pt°-C_2H_4 Crystals for X-ray Analysis

(R,R)-DIOP-Pt°-C_2H_4 (22.1 mg, 0.03 mmol) was dissolved in 0.7 ml of DMSO and THF (2 ml). The THF was removed under reduced pressure, the solution filtered, degassed and left under nitrogen for 3 days for the crystals to form (See appendix for deposition data).

δ_P (C_6D_6) 14.53 ppm ($J_{P\text{-}Pt}$ 3588 Hz)

APPENDICES

Appendix 1
Deposition Data

1.1 (R,R)-DIOP-Pt^0-C_2H_4 (35)

Bond distances (Å)

Pt-P(1)	2.261(1)	C(12)-C(13)	1.390(8)
Pt-P(2)	2.254(1)	C(13)-C(14)	1.350(11)
Pt-C(1)	2.109(5)	C(14)-C(15)	1.356(10)
Pt-C(2)	2.100(5)	C(15)-C(16)	1.384(8)
P(1)-C(3)	1.839(4)	C(21)-C(22)	1.398(7)
P(1)-C(11)	1.827(5)	C(21)-C(26)	1.374(7)
P(1)-C(21)	1.823(4)	C(22)-C(23)	1.404(9)
P(2)-C(6)	1.843(5)	C(23)-C(24)	1.364(12)
P(2)-C(31)	1.831(4)	C(24)-C(25)	1.347(11)
P(2)-C(41)	1.834(4)	C(25)-C(26)	1.386(8)
O(1)-C(4)	1.437(5)	C(31)-C(32)	1.392(6)
O(1)-C(7)	1.437(6)	C(31)-C(36)	1.395(6)
O(2)-C(5)	1.433(5)	C(32)-C(33)	1.375(9)
O(2)-C(7)	1.401(6)	C(33)-C(34)	1.372(9)
C(1)-C(2)	1.402(9)	C(34)-C(35)	1.373(9)
C(3)-C(4)	1.525(6)	C(35)-C(36)	1.388(7)
C(4)-C(5)	1.521(6)	C(41)-C(42)	1.384(7)
C(5)-C(6)	1.521(6)	C(41)-C(46)	1.371(8)
C(7)-C(8)	1.494(9)	C(42)-C(43)	1.373(9)
C(7)-C(9)	1.530(10)	C(43)-C(44)	1.376(14)
C(11)-C(12)	1.377(7)	C(44)-C(45)	1.358(13)
C(11)-C(16)	1.396(7)	C(45)-C(46)	1.399(8)

Bond angles (°)

P(1)-Pt-P(2)	105.25(4)	O(2)-C(7)-C(9)	109.7(5)
P(1)-Pt-C(1)	147.5(2)	C(8)-C(7)-C(9)	113.7(6)
P(1)-Pt-C(2)	108.8(2)	P(1)-C(11)-C(12)	125.0(4)
P(2)-Pt-C(1)	107.1(2)	P(1)-C(11)-C(16)	116.9(4)
P(2)-Pt-C(2)	145.9(2)	C(12)-C(11)-C(16)	118.2(5)
C(1)-Pt-C(2)	38.9(3)	C(11)-C(12)-C(13)	120.3(5)
Pt-P(1)-C(3)	118.7(1)	C(12)-C(13)-C(14)	120.7(6)
Pt-P(1)-C(11)	111.8(2)	C(13)-C(14)-C(15)	120.1(5)
Pt-P(1)-C(21)	118.6(2)	C(14)-C(15)-C(16)	120.6(6)
C(3)-P(1)-C(11)	104.0(2)	C(11)-C(16)-C(15)	120.1(6)
C(3)-P(1)-C(21)	100.2(2)	P(1)-C(21)-C(22)	121.2(4)
C(11)-P(1)-C(21)	101.3(2)	P(1)-C(21)-C(26)	120.5(4)
Pt-P(2)-C(6)	115.8(2)	C(22)-C(21)-C(26)	118.3(5)
Pt-P(2)-C(31)	118.3(1)	C(21)-C(22)-C(23)	119.5(6)
Pt-P(2)-C(41)	115.6(2)	C(22)-C(23)-C(24)	120.4(6)
C(6)-P(2)-C(31)	100.5(2)	C(23)-C(24)-C(25)	120.1(5)
C(6)-P(2)-C(41)	102.5(2)	C(24)-C(25)-C(26)	120.8(6)
C(31)-P(2)-C(41)	101.7(2)	C(21)-C(26)-C(25)	120.9(5)
C(4)-O(1)-C(7)	109.5(3)	P(2)-C(31)-C(32)	121.1(4)
C(5)-O(2)-C(7)	107.0(3)	P(2)-C(31)-C(36)	120.1(3)
Pt-C(1)-C(2)	70.2(3)	C(32)-C(31)-C(36)	118.7(5)
Pt-C(2)-C(1)	70.9(3)	C(31)-C(32)-C(33)	119.8(7)
P(1)-C(3)-C(4)	112.0(3)	C(32)-C(33)-C(34)	121.2(6)
O(1)-C(4)-C(3)	107.5(4)	C(33)-C(34)-C(35)	120.0(5)
O(1)-C(4)-C(5)	101.7(3)	C(34)-C(35)-C(36)	119.6(5)
C(3)-C(4)-C(5)	117.5(4)	C(31)-C(36)-C(35)	120.7(4)
O(2)-C(5)-C(4)	101.9(3)	P(2)-C(41)-C(42)	117.3(4)
O(2)-C(5)-C(6)	106.0(4)	P(2)-C(41)-C(46)	124.5(4)
C(4)-C(5)-C(6)	119.4(4)	C(42)-C(41)-C(46)	118.2(5)
P(2)-C(6)-C(5)	114.2(3)	C(41)-C(42)-C(43)	121.2(7)
O(1)-C(7)-O(2)	105.6(4)	C(42)-C(43)-C(44)	120.1(7)
O(1)-C(7)-C(8)	110.0(5)	C(43)-C(44)-C(45)	119.8(5)
O(1)-C(7)-C(9)	108.6(6)	C(44)-C(45)-C(46)	120.0(7)
O(2)-C(7)-C(8)	109.0(5)	C(41)-C(46)-C(45)	120.7(6)

Final atomic parameters (x10^4, x10^5 for Pt, P1 and P2) and equivalent isotropic thermal parameters B_{iso} (Å^2)

	x	y	z	B_{iso}*
Pt	11720(1)	25000	23296(1)	2.950(8)
P1	15593(10)	7467(10)	32113(8)	3.05(4)
P2	-9080(11)	30380(10)	22221(9)	3.03(4)
O1	-773(4)	98(4)	4880(3)	5.9(2)
O2	-2073(3)	1759(3)	4530(3)	4.1(1)
C1	1856(6)	3792(5)	1503(5)	5.1(3)
C2	2869(5)	2959(6)	1961(5)	5.3(3)
C3	195(4)	53(4)	3550(4)	3.5(2)
C4	-290(4)	864(4)	4242(3)	3.4(2)
C5	-1497(4)	1651(4)	3733(4)	3.1(2)
C6	-1297(5)	2931(4)	3422(4)	3.2(2)
C7	-1920(5)	641(5)	5026(4)	4.5(2)
C8	-1673(7)	841(8)	6143(5)	7.6(4)
C9	-3132(10)	-149(8)	4506(8)	9.1(6)
C11	2090(5)	-439(4)	2517(3)	3.7(2)
C12	1338(5)	-1425(5)	2070(5)	5.1(3)
C13	1833(8)	-2271(6)	1549(5)	6.7(4)
C14	3042(7)	-2124(6)	1451(4)	6.1(3)
C15	3797(6)	-1154(7)	1875(5)	6.1(3)
C16	3336(6)	-301(6)	2405(5)	5.1(3)
C21	2880(4)	699(4)	4454(3)	3.4(2)
C22	3186(6)	-366(6)	5024(5)	5.1(3)
C23	4168(6)	-354(7)	5998(5)	6.5(3)
C24	4838(6)	682(8)	6379(5)	6.3(3)
C25	4558(7)	1703(6)	5821(5)	6.6(3)
C26	3592(6)	1718(5)	4858(4)	5.1(2)
C31	-2303(4)	2191(3)	1351(3)	3.2(2)
C32	-3612(4)	2542(9)	1181(3)	4.4(2)
C33	-4640(5)	1836(6)	590(5)	5.8(3)
C34	-4403(6)	786(6)	156(5)	5.5(3)
C35	-3121(6)	429(4)	302(4)	4.7(3)
C36	-2070(5)	1132(4)	895(4)	3.8(2)
C41	-1378(4)	4593(4)	1814(4)	3.7(2)
C42	-1305(6)	4943(5)	872(5)	5.5(3)
C43	-1577(7)	6105(7)	528(6)	7.1(4)
C44	-1932(7)	6947(6)	1120(7)	7.5(4)
C45	-2021(7)	6623(5)	2043(7)	7.1(4)
C46	-1760(6)	5434(5)	2386(5)	5.4(3)

*B_{iso} is the mean of the principal axes of the thermal ellipsoid.

Crystal data

$C_{33}H_{36}PtO_2P_2$. M 721.68; monoclinic, $a = 10.666(2)$, $b = 11.105(3)$, $c = 13.818(3)$ Å, $\beta = 109.45(2)°$, $V = 1543.3(6)$ Å^3, $D_c = 1.553$ gcm^{-3}, $Z = 2$, μ(Mo-K_α) = 47.2 cm^{-1}, $F(000) = 715.85$. Space group $P2_1$. Crystal dimensions $0.49 \times 0.36 \times 0.33$ mm.

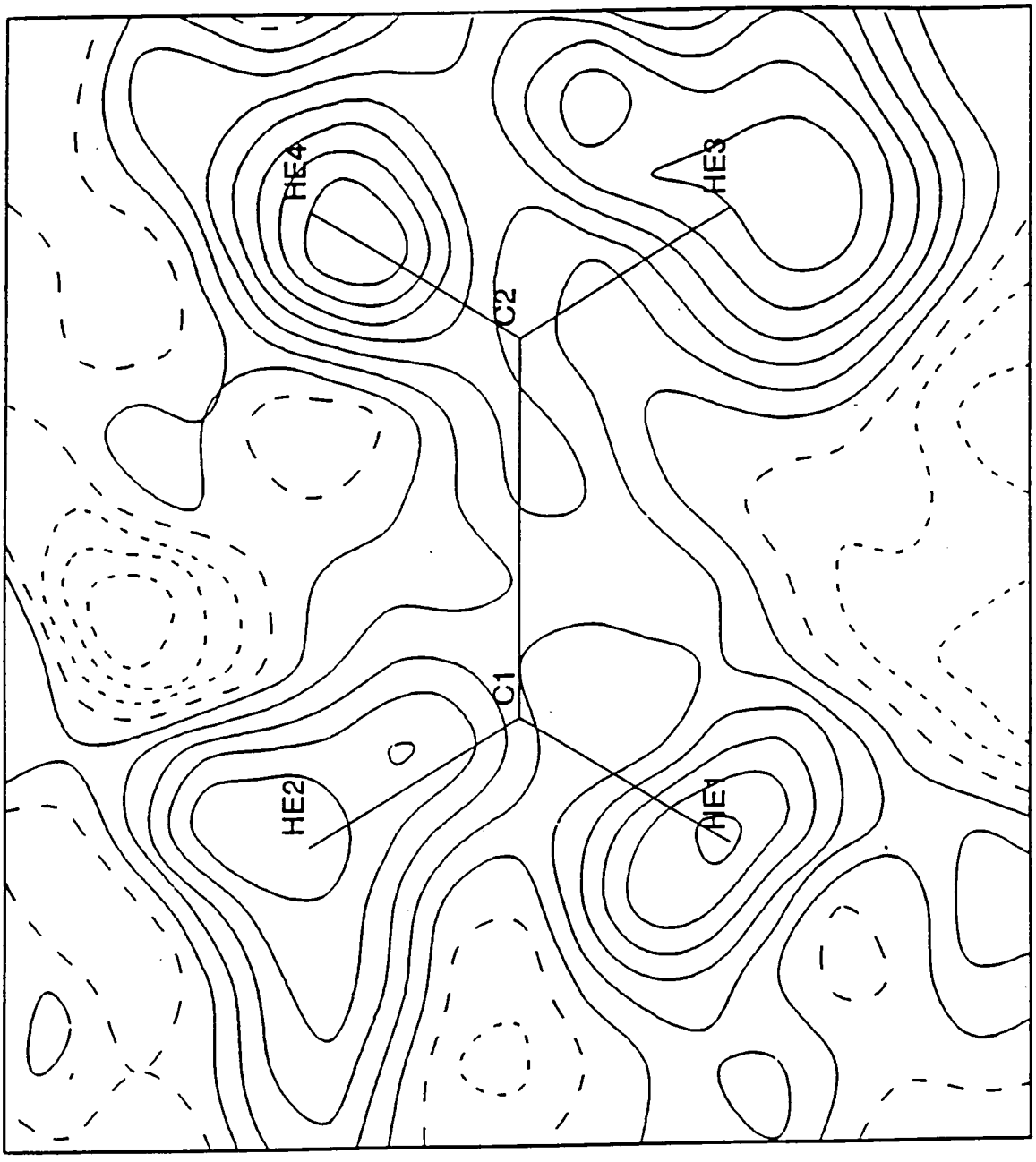
Data collection and processing

Intensity data were collected with a CAD4 diffractometer by the $\omega/2\theta$-scan method with $\omega = 0.6 + 0.35 \tan\theta$, to a maximum $2\theta = 53.8°$. Cell data were determined by a least squares analysis of the setting angles of 25 reflections with $20 < 2\gamma < 38°$. The range of indices was h −13 to 12, k −14 to 14, l −17 to 17. 6492 Unique reflections were collected. Data were corrected for absorption Lorentz and polarisation effects and during refinement for secondary extinction. The 5901 reflections with $I > 3\sigma(I)$ were used in structure solution and refinement.

Structure analysis and refinement

The structure was solved by the heavy-atom method and refined by full-matrix, least-squares calculations. All non-hydrogen atoms were allowed anisotropic motion, with hydrogen atoms positioned geometrically (C–H 0.95 Å) and included (as riding atoms) in the structure factor calculations with an overall B_{iso} of 5 Å^2. The final cycle of refinement included 343 variable parameters and converged to $R = 0.021$, $R_w = 0.026$. The absolute configuration was established unequivocally by refinement of a $\delta f''$ multiplier. All calculations were performed on a PC 386 system with the NRCVAX suite of programs

Electrostatic potentials for the planar ethene ligand.



1.2 1R,2R-1,2-Diphenyl-1,2-diaminoethane Monohydrobromide

$$U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
Br	0.37639 (3)	0.00000	0.994824 (15)	0.04367 (12)
N(1)	0.1306 (3)	0.3485 (3)	0.03900 (13)	0.0333 (8)
N(2)	0.1801 (5)	0.6511 (3)	0.12321 (18)	0.0409 (13)
C(1)	0.1918 (4)	0.3495 (3)	0.14472 (18)	0.0320 (10)
C(11)	0.0964 (3)	0.20056 (24)	0.19176 (16)	0.0333 (9)
C(12)	0.2225 (4)	0.1178 (3)	0.26511 (17)	0.0445 (11)
C(13)	0.1358 (5)	−0.0166 (5)	0.31114 (17)	0.0522 (14)
C(14)	−0.0736 (5)	−0.0690 (4)	0.28361 (19)	0.0526 (13)
C(15)	−0.1995 (4)	0.0112 (6)	0.21076 (17)	0.0501 (13)
C(16)	−0.1146 (4)	0.1471 (3)	0.16541 (18)	0.0419 (11)
C(2)	0.1209 (3)	0.5154 (4)	0.18564 (13)	0.0342 (9)
C(21)	0.2086 (4)	0.53170 (25)	0.29143 (15)	0.0382 (11)
C(22)	0.4186 (5)	0.5824 (4)	0.31980 (21)	0.0566 (15)
C(23)	0.4930 (7)	0.6004 (5)	0.4159 (3)	0.0771 (20)
C(24)	0.3557 (7)	0.5679 (7)	0.48433 (22)	0.091 (3)
C(25)	0.1472 (6)	0.5179 (9)	0.45749 (20)	0.088 (3)
C(26)	0.0730 (4)	0.4976 (7)	0.36117 (16)	0.0602 (14)

Fractional atomic coordinates and equivalent isotropic thermal parameters (Å^2)

Geometric parameters (Å, °)

N(1)—C(1)	1.489 (3)	C(15)—C(16)	1.395 (4)
N(2)—C(2)	1.469 (4)	C(2)—C(21)	1.528 (3)
C(1)—C(11)	1.517 (3)	C(21)—C(22)	1.377 (4)
C(1)—C(2)	1.535 (4)	C(21)—C(26)	1.380 (3)
C(11)—C(12)	1.391 (3)	C(22)—C(23)	1.383 (4)
C(11)—C(16)	1.384 (3)	C(23)—C(24)	1.370 (6)
C(12)—C(13)	1.395 (4)	C(24)—C(25)	1.363 (7)
C(13)—C(14)	1.376 (4)	C(25)—C(26)	1.388 (4)
C(14)—C(15)	1.376 (4)		
N(1)—C(1)—C(11)	110.97 (21)	N(2)—C(2)—C(1)	109.00 (19)
N(1)—C(1)—C(2)	108.89 (20)	N(2)—C(2)—C(21)	115.35 (23)
C(11)—C(1)—C(2)	112.71 (20)	C(2)—C(21)—C(22)	122.10 (21)
C(1)—C(11)—C(12)	119.11 (21)	C(2)—C(21)—C(26)	119.32 (21)
C(1)—C(11)—C(16)	121.84 (21)	C(1)—C(2)—C(21)	110.54 (21)
C2—C1—C11—C12	−98.0 (2)	C1—C2—C21—C22	81.4 (2)
C2—C1—C11—C16	80.3 (2)	C1—C2—C21—C26	−99.7 (3)
N1—C1—C2—N2	−44.3 (2)	H1—C1—C2—H2	−173 (2)
C11—C1—C2—C21	64.3 (2)		
Br—N(1)^{i}	3.346 (2)	Br—N(1)^{iii}	3.359 (2)
Br—N(1)^{ii}	3.279 (2)	Br—N(2)^{iii}	3.560 (3)

Symmetry codes: (i) $-x, y-\frac{1}{2}, 1-z$; (ii) $x, y, 1+z$; (iii) $1-x, y-\frac{1}{2}, 1-z$.

Crystal data

$C_{14}H_{17}N_2^+.Br^-$
$M_r = 293.20$
Monoclinic
$P2_1$
$a = 6.1749\ (4)$ Å
$b = 8.0494\ (4)$ Å
$c = 14.0057\ (5)$ Å
$\beta = 96.078\ (4)°$
$V = 692.23\ (6)$ Å^3
$Z = 2$
$D_x = 1.407$ Mg m^{-3}

Mo $K\alpha$ radiation
$\lambda = 0.70930$ Å
Cell parameters from 25 reflections
$\theta = 15.00–20.00°$
$\mu = 2.92$ mm^{-1}
$T = 293$ K
Plate
$0.12 \times 0.25 \times 0.55$ mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: empirical
$T_{min} = 0.3107$, $T_{max} = 0.5302$
2997 measured reflections
2866 independent reflections

2578 observed reflections $[I_{rel} > 3.0\sigma(I_{rel})]$
$R_{int} = 0.008$
$\theta_{max} = 26.91°$
$h = 0 — 7$
$k = -10 — 10$
$l = -17 — 17$
3 standard reflections
frequency: 120 min
intensity variation: 2.5%

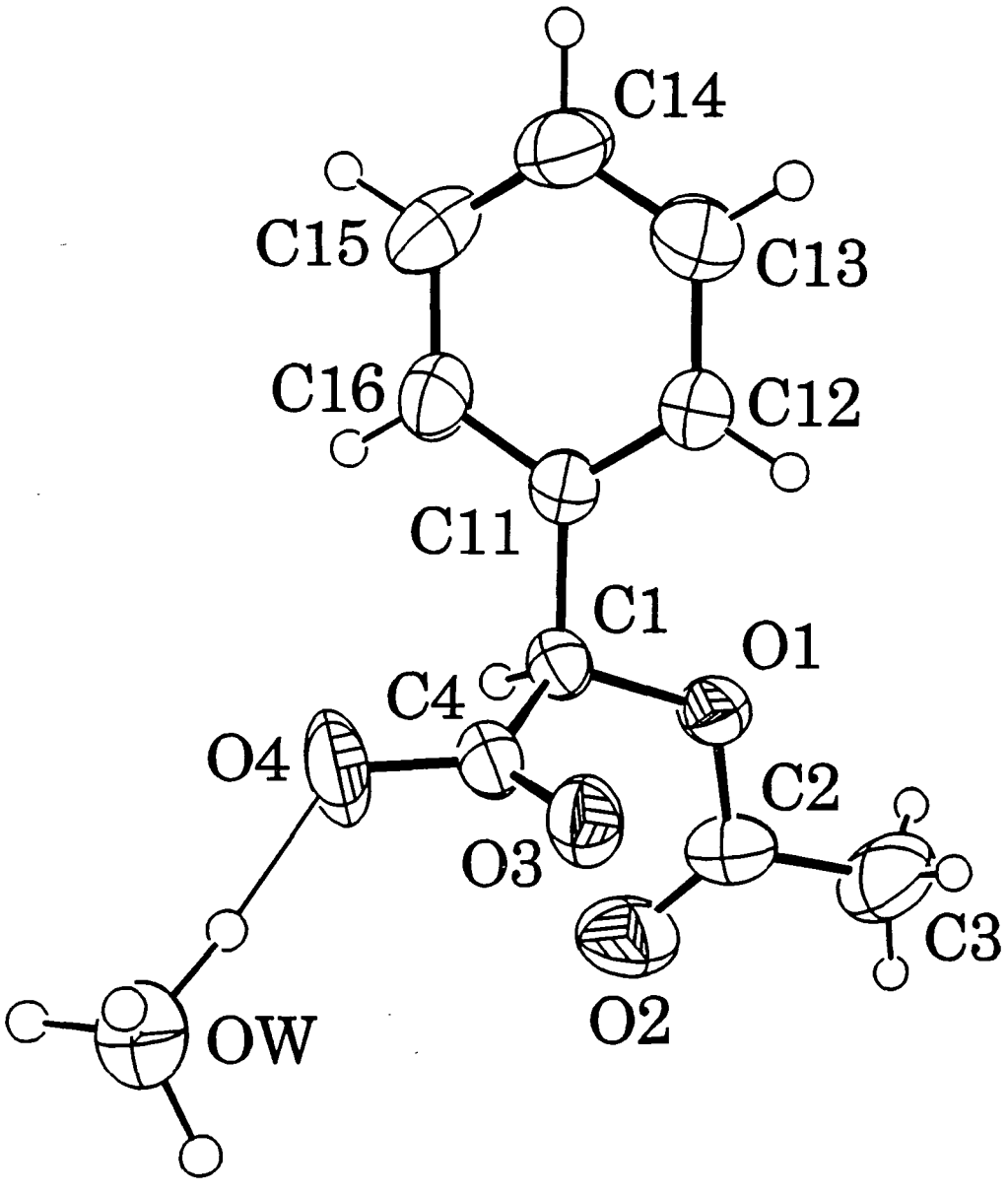
Refinement

Refinement on F
Final $R = 0.021$
$wR = 0.026$
$S = 1.09$
2578 reflections
222 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F)+0.0004F^2]$
$(\Delta/\sigma)_{max} = 0.003$

$\Delta\rho_{max} = 0.42$ e Å^{-3}
$\Delta\rho_{min} = -0.30$ e Å^{-3}
Extinction correction: Larson (1970)
Extinction coefficient: 3075 (389)
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Table 2.2B)

1.3 Oxonium (R)-O-Acetylmandelate

Crystal structure



Fractional atomic coordinates and equivalent isotropic thermal parameters (Å^2)

$$U_{eq} = \tfrac{1}{3}\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
O(1)	0.72312 (18)	0.24910	0.73775 (12)	0.0457 (7)
O(2)	0.48918 (24)	0.0515 (5)	0.65104 (17)	0.0764 (12)
O(3)	0.86806 (20)	0.0492 (4)	0.58554 (12)	0.0470 (8)
O(4)	0.8980 (3)	−0.2502 (4)	0.68155 (16)	0.0787 (14)
O(W)	0.84868 (23)	−0.5338 (4)	0.51118 (15)	0.0603 (10)
C(1)	0.82823 (25)	0.0561 (4)	0.76964 (16)	0.0389 (10)
C(2)	0.5539 (3)	0.2254 (5)	0.67886 (20)	0.0531 (13)
C(3)	0.4592 (4)	0.4352 (6)	0.6535 (3)	0.0777 (18)
C(4)	0.8652 (3)	−0.0576 (4)	0.66919 (18)	0.0426 (11)
C(11)	1.0032 (3)	0.1224 (4)	0.84925 (16)	0.0378 (10)
C(12)	1.0803 (3)	0.3199 (4)	0.84185 (19)	0.0477 (11)
C(13)	1.2419 (3)	0.3736 (5)	0.91500 (24)	0.0614 (15)
C(14)	1.3269 (3)	0.2329 (6)	0.99679 (22)	0.0617 (14)
C(15)	1.2507 (3)	0.0351 (6)	1.00337 (21)	0.0632 (14)
C(16)	1.0890 (3)	−0.0198 (5)	0.93026 (19)	0.0496 (12)
HOW(1)	0.728	−0.506	0.449	0.0707
HOW(2)	0.964	−0.512	0.480	0.0707
HOW(3)	0.847	−0.678	0.550	0.0707
HOW(4)	0.854	−0.420	0.580	0.0707

Bond lengths (Å), bond angles (°) and contact distances (Å)

O(1)—C(1)	1.451 (3)	O(4)—C(4)	1.234 (4)
O(1)—C(2)	1.326 (3)	C(1)—C(4)	1.531 (3)
O(2)—C(2)	1.211 (4)	C(1)—C(11)	1.510 (3)
O(3)—C(4)	1.246 (3)	C(2)—C(3)	1.496 (5)
C(1)—O(1)—C(2)	117.09 (17)	O(2)—C(2)—C(3)	126.01 (23)
O(1)—C(1)—C(4)	111.70 (17)	O(3)—C(4)—O(4)	125.69 (23)
O(1)—C(1)—C(11)	106.85 (20)	O(3)—C(4)—C(1)	118.94 (23)
C(4)—C(1)—C(11)	110.27 (16)	O(4)—C(4)—C(1)	115.29 (21)
O(1)—C(2)—O(2)	122.1 (3)	C(11)—C(16)—C(15)	120.1 (3)
O(1)—C(2)—C(3)	111.9 (3)		
C2—O1—C1—C4	67.7 (2)	C11—C1—C4—O3	−92.3 (2)
C2—O1—C1—C11	−171.6 (2)	C11—C1—C4—O4	84.6 (2)
C1—O1—C2—O2	−1.0 (1)	O1—C1—C11—C12	−31.1 (1)
C1—O1—C2—C3	178.7 (2)	O1—C1—C11—C16	149.8 (2)
O1—C1—C4—O3	26.4 (1)	C4—C1—C11—C12	90.5 (2)
O1—C1—C4—O4	−156.7 (3)	C4—C1—C11—C16	−88.6 (2)
OW—O(2)^i	2.902 (3)	OW—O(3)	2.763 (3)
HOW(1)—O(2)^i	1.85	HOW(3)—O(3)	1.76
OW—O(3)^i	2.794 (2)	OW—O(4)	2.722 (3)
HOW(2)—O(3)^i	1.74	HOW(4)—O(4)	1.62
O1—C1—C4—O4	−156.7 (3)	C4—C1—C11—C16	−88.6 (2)
OW—O(2)^i	2.902 (3)	OW—O(3)	2.763 (3)
HOW(1)—O(2)^i	1.85	HOW(3)—O(3)	1.76
OW—O(3)^i	2.794 (2)	OW—O(4)	2.722 (3)
HOW(2)—O(3)^i	1.74	HOW(4)—O(4)	1.62

Symmetry codes: (i) $-x, \frac{1}{2}+y, -z$.

Crystal data

$H_3O^+.C_{10}H_9O_2^-$
$M_r = 212.20$
Monoclinic
$P2_1$
$a = 7.6772\ (6)$ Å
$b = 6.2628\ (5)$ Å
$c = 12.4889\ (8)$ Å
$\beta = 104.879\ (6)°$
$V = 580.34\ (7)$ Å^3
$Z = 2$
$D_x = 1.214$ Mg m^{-3}

Mo $K\alpha$ radiation
$\lambda = 0.70930$ Å
Cell parameters from 25 reflections
$\theta = 10.00–20.00°$
$\mu = 0.09$ mm^{-1}
$T = 293$ K
Block
0.60 × 0.30 × 0.10 mm
Colourless

Data collection

Nonius CAD-4 diffractometer
$\theta/2\theta$ scan
Absorption correction: none
2511 measured reflections
2426 independent reflections
1893 observed reflections [$I_{net} > 3.0\sigma(I_{net})$]

$R_{int} = 0.005$
$\theta_{max} = 26.91°$
$h = -9 \rightarrow 9$
$k = 0 \rightarrow 7$
$l = 0 \rightarrow 15$
3 standard reflections
frequency: 120 min
intensity variation: none

Refinement

Refinement on F
Final $R = 0.039$
$wR = 0.055$
$S = 1.24$
1893 reflections
135 parameters
$w = 1/[\sigma^2(F)+0.0012F^2]$
$(\Delta/\sigma)_{max} = <0.001$

$\Delta\rho_{max} = 0.12$ e Å^{-3}
$\Delta\rho_{min} = -0.18$ e Å^{-3}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Table 2.2B)

Appendix 2
List of spectra and figures

2.1 List of Spectra

1. R-N,N-Dimethyl-2-phenylglycine methyl ester (61)
   (±)-Camphanic acid (20) ^{1}H NMR, 400 MHz, $CDCl_3$

2. R-N,N-1-(1-Naphthyl)ethylamine (62)
   (±)-Camphanic acid (20) ^{1}H NMR, 400 MHz, $CDCl_3$

3. S-N-Methyl-1-Phenylethylamine (63b)
   RS-Mandelic acid (68) ^{1}H NMR, 250 MHz, $CDCl_3$

4. (1S,2R)-(+)-Ephedrine (64a)
   RS-3-Phenylbutyric acid (69) ^{1}H NMR, 400 MHz, C_6D_6

5. (1S,2R)-(+)-N-Methylephedrine (64b)
   RS-Phenylpropionic acid (70) ^{1}H NMR, 400 MHz, C_6D_6

6. (1S,2S)-(+)-Pseudoephedrine (65a)
   RS-3-Phenylbutyric acid (69) ^{1}H NMR, 400 MHz, C_6D_6

7. (1S,2S)-(+)-N-Methyl pseudoephedrine (65b)
   RS-3-Phenylbutyric acid (69) ^{1}H NMR, 400 MHz, C_6D_6

8. S-2-(Anilinomethyl)-pyrrolidine (67)
   Ketoprofen (72) ^{1}H NMR, 250 MHz, $CDCl_3$

9. L-Proline p-Nitroanilide (66c)
   MTPA (11) ^{1}H NMR, 250 MHz, C_6D_6

10. 1,2-Diphenyl-1,2-diaminoethane (58) ^{1}H NMR, 250 MHz, $CDCl_3$

11. (1S,2S)-1,2-Diphenyl-1,2-diaminoethane (58)
    RS-O-Acetylmandelic acid (19) ^{1}H NMR, 400 MHz

12. (1R,2R)-1,2-Diphenyl-1,2-diaminoethane (58)
    RS-Hexahydromandelic acid (73) ^{1}H NMR, 250 MHz, $CDCl_3$

13. (1R,2R)-1,2-Diphenyl-1,2-diaminoethane (58)
    (±)-Trans-cyclohexane-1,2-dicarboxylic acid (76)
    ^{1}H NMR, 500 MHz, C_6D_6

14. (1R,2R)-1,2-Diphenyl-1,2-diaminoethane (58)
    RS-Ibuprofen (71) ^{1}H NMR, 400 MHz, $CDCl_3$

15. (1R,2R)-1,2-Diphenyl-1,2-diaminoethane (58)
    RS-α-Bromophenylacetic acid (81) ^{1}H NMR, 400 MHz, C_6D_6

16. (1S,2S)-1,2-Diphenyl-1,2-diaminoethane (58)
    RS-Chloropropionic acid (82) ^{1}H NMR, 250 MHz, $CDCl_3$

17. (1R,2R)-Diaminocyclohexane (85)
    RS-Naproxen (79) ^{1}H NMR, 500 MHz, $CDCl_3$

18. (1S,2S)-N,N-Dibenzyl-1,2-diphenyl-1,2-diaminoethane (86a)
    RS-2-Chloropropionic acid (82) ^{1}H NMR, 500 MHz, C_6D_6

19. (1R,2R)-1,2-Diphenyl-1,2-diaminoethane (58)
    Phenylacetic acid (87) ^{1}H NMR, 400 MHz, $CDCl_3$

20. (1R,2R)-1,2-Diphenyl-1,2-diaminoethane (58)
    4-Bromophenylacetic acid (89) ^{1}H NMR, 500 MHz, $CDCl_3$

21. (1S,2S)-1,2-Diphenyl-1,2-diaminoethane (58)
    S(+)-2-Phenylpropionic acid (70) ^{1}H NMR, 400 MHz, $CDCl_3$

22. (-)-DIOP-Pt-ethene (35) ^{31}P NMR, 101 MHz, C_6D_6

2.2 List of Figures

11. A stacked plot of the variation of Chemical shift non-equivalence against stoichiometry for 1R,2R-DPDAE : RS-Bromopropionic acid
^1H NMR, 400 MHz, $CDCl_3$

12. A stacked plot of the variation of shift non-equivalence against the variation in enantiomeric purity of O-Acetylmandelic acid (19) in 1S,2S-DPDAE : O-Acetylmandelic acid complexes
^1H NMR, 400 MHz, $CDCl_3$

13. A stacked plot of the variation in shift non-equivalence with temperature for the 1R,2R-DPDAE : Ibuprofen complex
^1H NMR, 400 MHz, $C_6D_5CD_3$

14. The crystal structure for 1R,2R-Diphenyldiaminoethane mono-hydrobromide

15. Diphenyldiaminoethane analogues

16. Enantiotopic groups rendered diastereotopic by the introduction of a chiral centre

17. Achiral carboxylic acids with enantiotopic methylene protons

18. The variation of H_R/H_S with temperature for phenylacetic acid 87
^1H NMR, 400 MHz, $CDCl_3$

19. A stacked plot of the methyl resonances of naproxen 79 at different enantiomeric purities for DPDAE : naproxen complexes
^1H NMR, 400 MHz, $CDCl_3$

20. A spectrum of S(+)-2-phenylpropionic acid 70 : DPDAE complex with expanded R(-)-2-phenylpropionic acid and S(+)-2-phenylpropionic acid ^{13}C satellite resonances

^{1}H NMR, 400 MHz, $CDCl_3$

21. A stacked plot for the varying enantiomeric composition of 2-methylbutyric acid 74 in 1R,2R-DPDAE : 2-methylbutyric acid complexes

^{1}H NMR, 400 MHz, $CDCl_3$

22. A stacked plot for the a-methyl resonances of racemic 2-methylbutyric acid against enzymatically derived 2-methylbutyric acid in their 1R,2R-DPDAE complexes

^{1}H NMR, 400 MHz, $CDCl_3$

23. a) Newman projections for 1R,2R-1,2-diphenyl-1,2-diaminoethane
b) A model for 1:1 complexation of 1,2-diphenyl-1,2-diaminoethane
c) A model for 2:1 complexation of 1,2-diphenyl-1,2-diaminoethane

24. The binding of chiral η^2-donors to DIOP-Pt°-ethene

25. The Decoupled ^{31}P spectra of 2-aza-bicyclo[2.2.1]-5-en-3-one 96 derivatives with (-)-DIOP-Pt°-ethene

^{31}P NMR, 202 MHz, C_6D_6

26. The Decoupled ^{31}P spectra of damascone derivatives of (-)-DIOP-Pt°-ethene

^{31}P NMR, 101 MHz, C_6D_6

27. The ^{19}F NMR spectra of the R and S chiral alkyne 1,1,1-trifluoro-2-acetoxy-2-phenylbut-3-yne 100

^{19}F NMR, 376 MHz, C_6D_6

28. The crystal structure for (-)-DIOP-Pt°-ethene

Appendix 3

UNIVERSITY OF DURHAM

Board of Studies in Chemistry

COLLOQUIA, LECTURES AND SEMINARS GIVEN BY INVITED SPEAKERS

1st October 1989 to 31st July 1990

(* indicates lectures attended by the author)

Palmer, Dr. F. (University of Nottingham) 17.10.89

Thunder and Lightning

Floriani, Prof. C. (University of Lausanne) 25.10.89

Molecular Aggregates - A Bridge Between Homogeneous and Heterogeneous Systems

Badyal, Dr. J. P. S. (University of Durham) 01.11.89

Breakthroughs in Heterogeneous Catalysis

Greenwood, Prof. N. N. (University of Leeds) 09.11.89

Novel Cluster Geometries in Metalloborane Chemistry

Bercaw, Prof. J. E. (California Institute of Technology) 10.11.89 *

Synthetic and Mechanistic Approaches to Ziegler - Natta Polymerization of Olefins

Becher, Dr. J. (University of Odense) 13.11.89

Synthesis of New Macrocyclic Systems Using Heterocyclic Building Blocks

Parker, Dr. D. (University of Durham) 16.11.89

Macrocycles, Drugs and Rock 'n' Roll *

Cole-Hamilton, Prof. D. J. (University of St. Andrews) 29.11.89

New Polymers from Homogeneous Catalysis

Hughes, Dr. M. N. (King's College, London) 30.11.89

A Bug's Eye View of the Periodic Table

Graham, Dr. D. (B. P. Research Centre) 04.12.89

How Proteins Adsorb to Interfaces

Powell, Dr. R. L. (ICI) 06.12.89

The Development of C.F.C. Replacements *

Butler, Dr. A. (University of St. Andrews) 07.12.89

The Discovery of Penicillin : Facts and Fancies *

Klinowski, Dr. J. (University of Cambridge) 13.12.89

Solid-State NMR Studies of Zeolite Catalysts

Huisgen, Prof. R. (Universität München) 15.12.89

Recent Mechanistic Studies of [2 + 2] Additions *

Perutz, Dr. R. N. (University of York) 24.01.90

Plotting the Course of C-H Activations with Organometallics

Dyer, Dr. U. (Glaxo) 31.01.90

Synthesis and Conformation of C-Glycosides

Holloway, Prof. J. H. (University of Leicester) 01.02.90

Noble Gas Chemistry

Thompson, Dr. D. P. (University of Newcastle upon Tyne) 07.02.90

The Role of Nitrogen in Extending Silicate Crystal Chemistry

Lancaster, Rev. R. (Kimbolton Fireworks) 08.02.90

Fireworks - Principles and Practice *

Lunazzi, Prof. L. (University of Bologna) 12.02.90

Application of Dynamic NMR to the Study of Conformational Enantiomerism *

Sutton, Prof. D. (Simon Fraser University, Vancouver) 14.02.90

Synthesis and Applications of Dinitrogen and Diazo Compounds of Rhenium and Iridium

Crombie, Prof. L. (University of Nottingham) 15.02.90

The Chemistry of Cannabis and Khat *

Bleasdale, Dr. C. (University of Newcastle upon Tyne) 21.02.90

The Mode of Action of some Anti - Tumour Agents

Clark, Prof. D.T. (ICI Wilton) 22.02.90

Spatially Resolved Chemistry (using Nature's Paradigm in the Advanced Materials Arena)

Thomas, Dr. R. K. (University of Oxford) 28.02.90

Neutron Reflectometry from Surfaces

Stoddart, Dr. J. F. (University of Sheffield) 01.03.90

Molecular Lego *

Cheetham, Dr. A. K. (University of Oxford) 08.03.90

Chemistry of Zeolite Cages

Powis, Dr. I. (University of Nottingham) 21.03.90

Spinning Off in a Huff : Photodissociation of Methyl Iodide

Bowman, Prof. J. M. (Emory University) 23.03.90

Fitting Experiment with Theory in Ar-OH

German, Prof. L. S. (Soviet Academy of Sciences) 09.07.90

New Syntheses in Fluoroaliphatic Chemistry : Recent Advances in the Chemistry of Fluorinated Oxiranes

Platanov, Prof. V.E. (Soviet Academy of Sciences, Novosibirsk 09.07.90

Polyfluoroindanes : Synthesis and Transformation

Rozhkov, Prof. I. N. (Soviet Academy of Sciences, Moscow) 09.07.90

Reactivity of Perfluoroalkyl Bromides

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COLLOQUIA, LECTURES AND SEMINARS GIVEN BY INVITED SPEAKERS

1st August 1990 to 31st July 1991

Macdonald, Dr. W.A. (ICI Wilton) 11.10.90

Materials for the Space Age

Bochmann, Dr. M. (University of East Anglia) 24.10.90

Synthesis, Reactions and Catalytic Activity of Cationic Titanium Alkyls

Soulen, Prof. R. (South Western University, Texas) 26.10.90

Preparation and Reactions of Bicycloalkenes

Jackson, Dr. R.F.W. (University of Newcastle upon Tyne) 31.10.90

New Synthetic Methods : α-Amino Acids and Small Rings *

Logan, Dr. N. (University of Nottingham) 01.11.90

Rocket Propellants

Kocovsky, Dr. P. (University of Uppsala) 06.11.90

Stereo-Controlled Reactions Mediated by Transition and Non-Transition Metals *

Gerrard, Dr. D. (British Petroleum) 07.11.90

Raman Spectroscopy for Industrial Analysis

Scott, Dr. S.K. (University of Leeds) 08.11.90

Clocks, Oscillations and Chaos *

Bell, Prof. T. (SUNY, Stoney Brook, USA) 14.11.90

Functional Molecular Architecture and Molecular Recognition *

Pritchard, Prof. J. (Queen Mary & Westfield College) 21.11.90

Copper Surfaces and Catalysts

Whitaker, Dr. B.J. (University of Leeds) 28.11.90

Two-Dimensional Velocity Imaging of State-Selected Reaction Products

Crout, Prof. D. (University of Warwick) 29.11.90

Enzymes in Organic Synthesis

Pringle, Dr. P.G. (University of Bristol) 05.12.90

Metal Complexes with Functionalised Phosphines

Cowley, Prof. A.H. (University of Texas) 13.12.90

New Organometallic Routes to Electronic Materials

Alder, Dr. B.J. (Lawrence Livermore Labs., California) 15.01.91

Hydrogen in all its Glory

Sarre, Dr. P. (University of Nottingham) 17.01.91

Comet Chemistry *

Sadler, Dr. P.J. (Birkbeck College London) 24.01.91

Design of Inorganic Drugs : Precious Metals, Hypertension & HIV

Sinn, Prof. E. (University of Hull) 30.01.91

Coupling of Little Electrons in Big Molecules : Implications for the Active Sites of Metalloproteins and other Macromolecules

Lacey, Dr. D. (University of Hull) 31.01.91

Liquid Crystals

Bushby, Dr. R. (University of Leeds) 06.02.91

Biradicals and Organic Magnets

Petty, Dr. M.C. (Durham University) 14.02.91

Molecular Electronics *

Shaw, Prof. B.L. (University of Leeds) 20.02.91

Syntheses with Coordinated, Unsaturated Phosphine Ligands

Brown, Dr. J. (University of Oxford) 28.02.91

Can Chemistry Provide Catalysts Superior to Enzymes?

Dobson, Dr. C.M. (University of Oxford) 06.03.91

NMR Studies of Dynamics in Molecular Crystals

Markam, Dr. J. (ICI Pharmaceuticals) 07.03.91

DNA Fingerprinting

Schrock, Prof. R.R. (M.I.T.) 24.04.91

Metal-Ligand Multiple Bonds and Metathesis Initiators

Hudlicky, Prof. T. (Virginia Polytechnic Institute) 25.04.91

Biocatalysis and Symmetry Based Approaches to the Efficient Synthesis of Complex Natural Products

Brookhart, Prof. M.S. (University of North Carolina) 20.06.91

Olefin Polymerizations, Oligomerizations and Dimerizations Using Electrophilic Late Transition Metal Catalysts

Brimble, Dr. M.A. (Massey University, New Zealand) 29.07.91

Synthetic Studies Towards the Antibiotic Griseusin-A

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COLLOQUIA, LECTURES AND SEMINARS GIVEN BY INVITED SPEAKERS

1st October 1991 to 31st July 1992

Burton, Prof. D.J. (University of Iowa, USA) 12.9.91

Fluorinated Organometallic Reagents

Adcock, Prof. J.L. (University of Tennessee, USA), 12.9.91

Aerosol Direct Fluorination

Salthouse ,Dr. J.A. (Manchester University), 17.10.91

Son et Lumiere - a Demonstration Lecture *

Keeley, Dr. R. (Metropolitan Police Forensic Science), 03.10.91

Modern Forensic Science

Johnson, Dr. B.F.G. (Edinburgh University), 06.11.91

Cluster-Surface Analogies

Butler, Dr. A.R. (St. Andrews University), 07.11.91

Traditional Chinese Herbal Drugs: a Different Way of Treating Disease

Koch, Prof. H. F. (Ithaca College, USA), 8.11.91

Relative Leaving Abilities of fluoride Ion Versus Proton Transfer, in the Neutralisation of Carbanions, Generated in Alcohols

Gani, Prof. D. (St. Andrews University), 13.11.91

The Chemistry of PLP-Dependant Enzymes

More OFerrall, Dr. R. (University College, Dublin), 20.11.91

Some Acid-Catalysed Rearrangements in Organic Chemistry *

Ward, Prof. I.M. (Leeds University), 28.11.91

The Science & Technology of Orientated Polymers

Grigg, Prof. R. (Leeds University), 04.12.91

Palladium Catalysed Cyclisation and Ion Capture Processes

Smith, Prof. A.L. (ex-Unilever), 05.12.91

Soap, Detergents and Black Puddings

Cooper, Dr. W.D. (Shell Research), 11.12.91

Colloid Science, Theory, and Practice

Snyder, Mr. C.E. (U.S. Air Force, Ohio), 09.01.92

Perfluoropolyethers

Long, Dr. N.J. (Exeter University), 16.01.92

Metallocenophanes-Chemical Sugar-tongs

Harris, Dr. K.D.M. (St Andrews University), 22.01.92

Understanding the Properties of Solid Inclusion Compounds

Holmes, Dr. A. (Cambridge University), 29.01.92

Cycloaddition Reactions in the Service of the Synthesis of Piperidine and Indolizidine Natural Products

Anderson, Dr. M. (Shell Research, Sittingbourne), 30.01.92

Recent Advances in the Safe and Selective Chemical Control of Insect Pests *

Fenton, Dr. D.E. (Sheffield University), 12.02.92

Polynuclear Complexes of Molecular Clefts as Models for Copper Biosites

Saunders, Dr. J. (Glaxo Group Research Limited), 13.02.92

Molecular Modelling in Drug Discovery *

Thomas, Prof. E.J. (Manchester University), 19.02.92

Application of Organo-Stannanes to Organic Synthesis

Vogel, Prof. E. (University of Cologne), 20.02.92

Porphyrins: Molecules of Interdisciplinary Interest.

Nixon, Prof. J.F. (University of Sussex), 25.02.92

Phosphaalkynes, New Building Blocks in Inorganic and Organometallic Chemistry

Hitchman, Prof. M.L. (Strathclyde University), 26.02.92

Chemical Vapour Deposition

Billingham, Dr. N.C. (University of Sussex), 05.03.92

Degradable Plastics - Myth or Magic *

Fielding, Dr. H.C. (ICI, Chemicals & Polymers), 10.03.92

Fluoropolymer Membranes

Thomas, Dr. S.E. (Imperial College, London), 11.03.92

Recent Advances in Organoiron Chemistry

Hann, Dr. R.A. (ICI Imagedata), 12.03.92

Electronic Photography - An Image of the Future.

Maskill, Dr. H. (Newcastle University), 18.03.92

Mechanistic Studies of Organic Group Transfer Reactions

Knight, Prof. D.M. (Durham University), 07.04.92

Interpreting Experiments: The Beginning of Electrochemistry

Marhold, Dr. A. (Bayer Co., Leverkusen), 30.04.92

Fluorine Chemistry in the Bayer Company

Gehert, Dr. J-C. (Ciba Geigy, Basel), 13.05.92

Some Aspects of Industrial Agrochemical Research

RESEARCH CONFERENCES

Smith Kline & French Research Symposium

Chirality in Drug Design and Synthesis

Cambridge University 27-28 March 1990

RSC Autumn Meeting

University of York 24-26 September 1991

Appendix 4
References

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