NMR Determination of Enantiomeric Purity

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Received February 14, 1991 (Revised Manuscript Received June 3, 1991)

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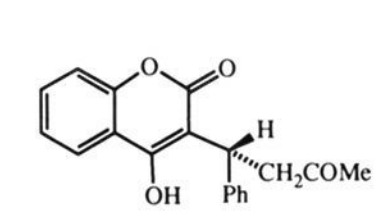
David Parker was born in Consett, England in 1956 He received a B.A. in Chemistry from the University of Oxford in 1978 and a D.Phil. in 1980. Following a NATO post-doctoral fellowship in Strasbourg (1980–1981) he was appointed to a Lectureship in Chemistry at Durham University and was promoted to a Senior Lectureship in 1989. He was the recipient of the Royal Society of Chemistry Hickinbottom Fellowship (1988–1989) and was awarded the RSC Corday-Morgan Medal and Prize for 1987. His current research interests are wide ranging, including the synthesis and complexation properties of functionalized macrocycles and their application in clinical analysis, diagnosis and therapy, chemical sensors and electroactive materials, and the measurement of enantiomeric purity using NMR and potentiometric methods of analysis.

I. Introduction

Over the past decade there has been a great surge of interest in enantioselective synthesis which has led to an increased demand for accurate, reliable, and convenient methods of measuring enantiomeric purity. At the same time the pharmaceutical industry has had to address the requirement—being imposed by regulatory authorities in Europe and the United States in particular—that they must begin to market chiral drugs as pure enantiomers. Although more than 50% of commercial drugs are chiral, less than half of these are marketed in an enantiomerically pure form and only 10% of synthetic chiral drugs are available enantiopure. Examples of the different pharmacological response of two enantiomers are quite common: (*S*)-warfarin (**1**) is six times as active as an anticoagulant as the *R* enantiomer, while (*S*)-propranolol (**2**) is an antihypertensive and antiarythmic used in the treatment of heart disease while the *R* enantiomer acts as a contraceptive. A further example is the alkaloid (−)-levorphanol (**3**) which is a potent narcotic analgesic while its enantiomer **4** has none of this activity yet is marketed (as its methyl ether) as a cough suppressant.



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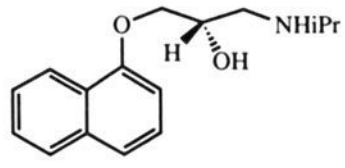

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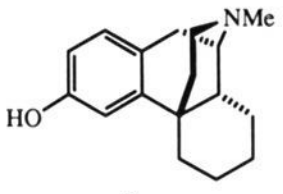

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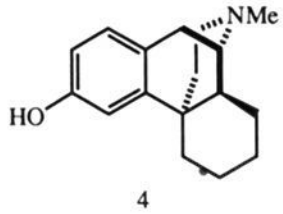

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Before the mid-1960s, the enantiomeric purity of a chiral molecule was usually assessed by using chiroptical methods. This often involved measuring the optical rotation of the sample with use of a polarimeter under defined conditions of temperature, solvent, and concentration and at a given wavelength of the incident plane-polarized light. This value was then compared to the known rotation for an enantiomerically pure sample of the same compound, measured under identical conditions. This value is commonly termed "optical purity". Provided that the measurement is carried out under rigorously controlled conditions along with appropriate calibrations, then this value may be equated with "enantiomeric purity". There are two major problems with this method of analysis. First, optical purity and enantiomeric purity are not necessarily equivalent. It has been demonstrated, for example, that optical rotation does not vary linearly with enantiomeric composition for 2-methyl-2-ethylbutandioic acid[1] in various nonpolar solvents. Although in this case diastereoselective dimerization is the likely case of the "nonideal" behavior, there are reports of nonlinear variations of optical rotation with concentration even in polar solvents.[2] A second limitation is that the literature is infected with many examples of incorrect optical rotations for compounds considered to be enantiomerically pure. For example prior to 1974, the specific rotation of enantiomerically pure (+)-3-

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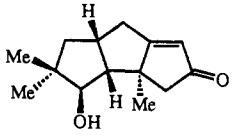
methylcyclopentene was believe to be $[\alpha]^{20}_D = +78°$. Following an independent measurement using a chiral gas chromatographic method,[3] the rotation was shown to be $[\alpha]^{20}_D = +174.5°$ for the enantiopure compound. More recently, the enone **5** has been shown to have a



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rotation of $[\alpha]^{20}_D = +34°$ (*c* 1, $CHCl_3$),[4] whereas its enantiomer has been reported to have a rotation of $[\alpha]^{20}_D = -115.4$ (*c* 0.2, $CHCl_3$).[5] There have even been reports of incorrect interpretations of literature rotations. The rotation of enantiopure *exo*-2-norbornanecarboxylic acid is $[\alpha]^{20}_D = -27.8°$ (*c* 1, EtOH).[6] Unfortunately, it was assumed[7] that this value should be $[\alpha]^{20}_D = -10.7$ (*c* 1, EtOH) so that incorrect enantiomeric purities have been reported for the asymmetric hydrocyanation of norbornene (subsequently corrected following an independent NMR analysis using a chiral derivatizing agent[8]) and for the asymmetric hydroformylation of norbornene.[9] Finally, the use of optical rotation for determination of enantiomeric purity is subject to the uncertainty of contamination with an optically active impurity. This is particularly serious if the impurities have a high rotation or a rotation of the opposite sign to that of the substrate being analyzed. Certainly sample homogeneity must be demonstrated in parallel with the measurements of rotation, and the quoted values should include error limits. Although the method is a convenient one it is a rather unsatisfactory method for determining accurate enantiomeric purity unless stringent control conditions are followed.

Given these limitations, it is necessary to use independent methods of analysis when assaying enantiomeric purity. Although rapid progress has been made in the last five years in developing sensitive and accurate GC[10] and HPLC[11] methods of analysis, many practicing organic chemists use NMR methods. Gas chromatographic methods in particular are preferred for quality control in pharmaceutical and fine chemical applications, being more precise than the NMR-base methods. The HPLC methods of chiral analysis are also used to an increasing extent as a result of improvements in column lifetime and performance.

Although enantiomers cannot be distinguished in an achiral medium, since the resonances of enantiotopic nuclei are isochronous, diastereoisomers may be distinguished because the resonances (of certain diastereotopic nuclei) are anisochronous. The chemical shift nonequivalence of diastereotopic nuclei in diastereoisomers in which the stereogenic centers are covalently linked in a single molecule was first noted by Cram.[12] The determination of the enantiomeric purity using NMR therefore requires the use of a chiral auxiliary that converts the mixture of enantiomers into a diastereoisomeric mixture. As long as there is a large enough chemical shift nonequivalence to give baseline resolution of the appropriate signals, then integration gives a direct measure of diastereoisomeric composition which can be related directly to the enantiomeric composition of the original mixture.

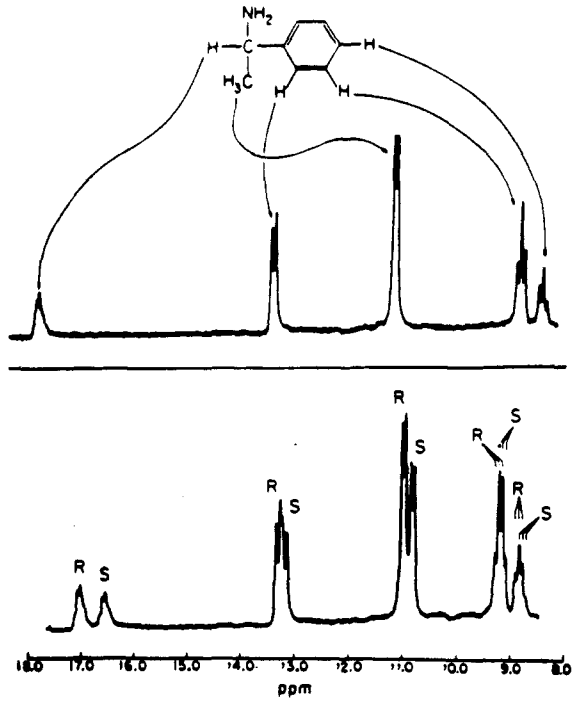
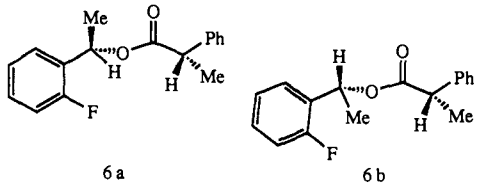


Figure 1. 100-MHz proton NMR spectra of a CCl_4 solution of $Eu(pvc)_3$ and (*S*)-α-phenylethylamine (upper) and of a mixture of (*R*)- and (*S*)-α-phenylethylamine (lower).

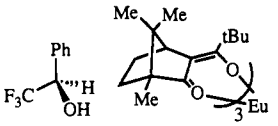
There are three types of chiral auxiliary that are used.[13] Chiral lanthanide shift reagents[14,15] and chiral solvating agents[16,17] form diastereoisomeric complexes in situ with substrate enantiomers and may be used directly. Chiral derivatizing agents[18] (CDAs) require the separate formation of discrete diastereoisomers prior to NMR analysis and care has to be taken to ensure that neither kinetic resolution nor racemization of the derivatizing agent occurs during derivatization. Indeed when Mislow and Raban first reported[19] chemical shift nonequivalence in the proton NMR spectra of diastereoisomeric 1-(methylphenyl)ethanoic acid esters of 1-(2-fluorophenyl)ethanol, they observed some racemization during the ester formation. In the diastereoisomers **6a** and **6b**, the C–Me doublet of the



6a 6b

alkoxy moiety was observed as a pair of doublets ($\Delta\delta_H$ = 0.09 ppm, CCl_4). Following Mislow's proposal,[19] Pirkle demonstrated that chiral solute enantiomers exhibit different NMR spectra when dissolved in an enantiomerically enriched chiral solvent.[20,21] With α-methylbenzylamine used as a chiral solvating agent (indeed the solvent), the ^{19}F resonances of the CF_3 group in **7** resonated as two singlets for the two diastereoisomeric complexes ($\Delta\delta_F$ = 0.04 ppm). To complete this brief historical perspective, it was Whitesides and Lewis[22] who first demonstrated the application of chiral lanthanide shift reagents in enantiomeric purity determination. By using the chiral europium complex $Eu(pvc)_3$ (**8**, pvc = 3-pivaloyl-*d*-camphor) well resolved signals for the methyl, methine, and ortho aromatic

protons of α-phenylethylamine were observed for each of which a large induced shift was observed (Figure 1).



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There have been many reviews of this subject in the past, and those cited are fairly comprehensive in their coverage up to the early 1980's at least.[13-17] This review is therefore intended to assess the major developments in the last decade, while highlighting the significant earlier work. It is not a comprehensive survey of *all* published work using NMR methods for enantiomeric purity determination—such a task is daunting indeed—but it does select those methods that are either practically useful or of interest to the NMR specialist.

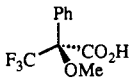
II. NMR Methods of Analysis

A. Chiral Derivatizing Agents

Derivatization of enantiomers with an enantiomerically pure compound remains the most widely used NMR technique for the assay of enantiomeric purity. In contrast to chiral lanthanide shift reagents (CLSR) and chiral solvating agents (CSA) which form diastereoisomeric complexes that are in fast exchange on the NMR time scale, derivatization yields discrete diastereoisomers for which the observed chemical shift nonequivalence $\Delta\delta$ is typically five times greater than for related complexes with a CSA. There are some intrinsic disadvantages to the CDA method. The derivatizing agent must be enantiopure: the presence of a small quantity of the enantiomeric compound will give reduced values for enantiomeric purity. The formation of the diastereoisomers must occur under conditions which exclude the possibility of racemization or of kinetic resolution due to differential reaction rates of the substrate enantiomers. The latter possibility can be minimized by using an excess of the derivatizing agent. Purification of the product diastereoisomers must only use methods (e.g. chromatography) that rigorously avoid the selective enrichment of one diastereoisomer. Crystallization is forbidden.

1. ^1H and ^{19}F NMR Analysis

A selection of the most useful CDAs for ^1H and/or ^{19}F analysis is given in Table I. Of these the most widely used is α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) (**9**). It was introduced by Mosher



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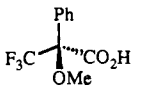
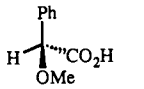
in 1969[23] and because there is no hydrogen α to the carboxy group racemization during derivatization is impossible. It is available commercially in enantiomerically pure form, either as the acid or the acid chloride, and reacts readily with primary and secondary alcohols or amines to form diastereoisomeric amides or esters that may be analyzed by ^1H or ^{19}F NMR.[24,25] In proton NMR chemical shift nonequivalence is typically 0.1 to 0.2 ppm ($CDCl_3$, 298 K) with the diastereoisomers

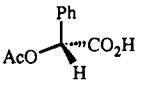
TABLE I. Common Chiral Derivatizing Agents for ^1H and ^{19}F NMR Analysis



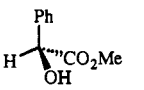
[S]-MTPA
Mosher 1969



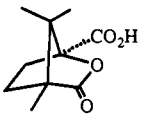
[S]-O-Methyl
Mandelic acid
Mislow 1967



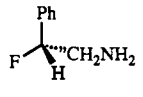
[R]-O-Acetyl
Mandelic acid
Parker 1983



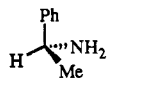
[S]-Methyl Mandelate
Parker 1981



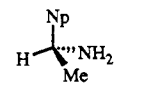
Camphanic acid
Gerlach 1973



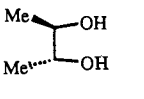
[R]-2-Fluoro-2-
Phenylethylamine
Hamman 1989



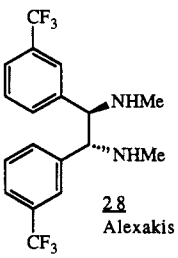
[S]-α-Phenyl-
ethylamine



[S]-α- Naphthyl-
ethylamine



[RR]- Butan-2,3-
diol



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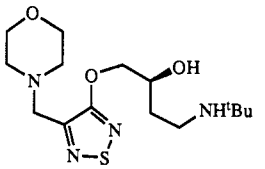
Alexakis 1989

exhibiting $\Delta\delta_F$ = 0.3 to 0.7 ppm for simple amides and esters. Although there have been isolated reports of problems with kinetic resolution leading to false values of enantiomeric purity, for example in the derivatization of timolol **10**[26] and with the enone **11**,[27] MTPA is gen-



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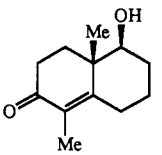

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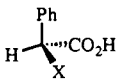
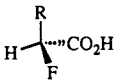
erally well behaved and reliable. It remains the method of choice for these simple chiral amines and alcohols,[28-30] and often the diastereoisomers are separable by GC or HPLC methods permitting independent verification of enantiomeric purity. Compilations of substrates analyzed by using this method have been documented.[18] The accuracy of the measured enantiomeric purity depends upon the NMR instrument used, the methods of data handling, and the size of the shift nonequivalence. The error should be no worse than ±1% even with a 90-MHz instrument. Although many simple analogues of MTPA have been examined, e.g. **12a–e**[31] and **13a–d**,[32] they suffer from racemization under the



12 : X = a] OMe
b] *t* Bu
c] CF_3
d] OH
e] Cl



13 : R= a] SPh
b] Ph
c] OPh
d] CH_2Ph

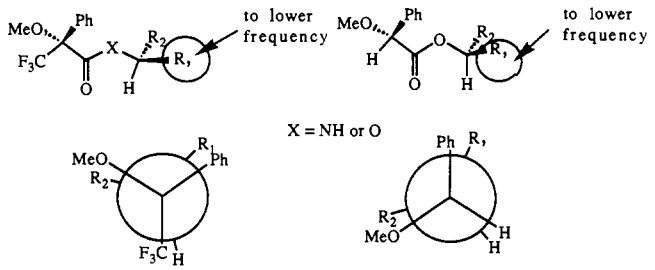
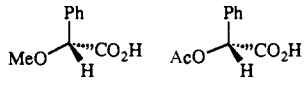


Figure 2. Conformational correlation models for (*R*)-MTPA and (*R*)-*O*-methylmandelic acid derivatives.

forcing conditions required to form ester derivatives of sterically hindered alcohols. It should be noted also that many α-fluoroacetate derivatives (e.g. **13**) are highly toxic.[32] Some success has been achieved with the isocyanate **14**.[33] Although it fails to react with hindered alcohols, it reacts with primary and secondary chiral amines in the NMR tube to yield diastereoisomeric ureas that exhibit higher chemical shift nonequivalence than the corresponding MTPA derivatives. For example with **15**, the α-methyl doublet resonated 0.38 ppm apart in the diastereoisomeric ureas, while the MTPA amide derivatives were 0.07 ppm nonequivalent under the same conditions ($CDCl_3$, 298 K).

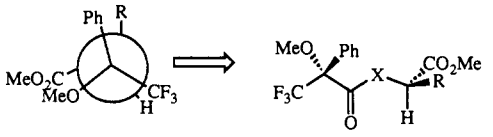
14 **15**

With improvements in synthetic methodology for forming esters (even with hindered alcohols[34]) or amides under nonracemizing conditions, derivatizing agents other than MTPA may be used. For example, in the analysis of chiral alcohols, *O*-methylmandelic acid[35-38] (**16**), and particularly *O*-acetylmandelic acid (**17**),[39] should be considered. They often lead to higher values



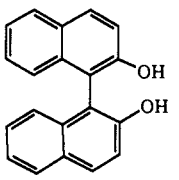
16 **17**

of Δδ for the diastereoisomeric derivatives. Useful NMR configurational correlation schemes have been devised that permit the assignment of the absolute configuration of alcohols and amines in MTPA and related mandelate derivatives.[24,36] In the MTPA model, the α-trifluoromethyl and carbonyl oxygens are eclipsed (supported by chiroptical measurements[40]) so that the preferred conformation has the carbinyl hydrogen eclipsed with the carbonyl group. Assuming an extended trans ester or amide conformation, then an extended Newman projection of the preferred conformation places one of the groups (R^1 in Figure 2) consistently close to the phenyl ring. Being close to the shielding influence of the magnetically anisotropic aromatic group, this group, R^1, resonates consistently to lower frequency (i.e. to higher field) of R^1 in the alternative diastereoisomer (where R^1 and R^2 exchange sites). Similar arguments operate with mandelate derivatives. The model extends well to MTPA derivatives of α-hydroxy esters[41] or α-amino esters.[42] In these derivatives, e.g. **18**, (shown in an extended Newman projection), it was noted that the chemical shift nonequivalence of the diastereotopic α-methoxy group was much larger ($\Delta\delta_H$ = 0.2 ppm ($CDCl_3$)) than usually ($\Delta\delta_H$ = 0.04 ppm) observed in simple MTPA amides and esters. If it is assumed that **18** is the preferred solution conformation, then the OMe group is oriented toward the anisotropic carbonyl group for the shown *RR* diastereoisomer (and therefore resonates consistently to higher frequency), whereas this is not so for the related *RS* diastereoisomer.



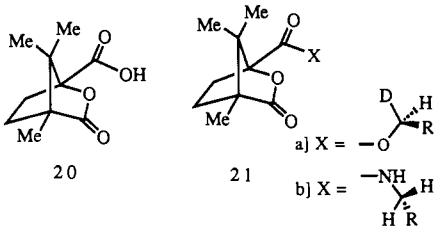
18

In many instances, the magnitude of chemical shift nonequivalence with MTPA and related derivatizing agents may be enhanced following the addition of an achiral lanthanide shift reagent, such as $Eu(fod)_3$ ["fod" is 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione]. Large induced shifts are observed the magnitude of which, in MTPA derivatives, is generally greater for the OMe singlet for the *RR* diastereoisomer than for the *RS* isomer.[43] Similarly the lanthanide-induced shift is greater for the *o*-phenyl protons in the *RR* isomer compared to the *RS* diastereoisomer. This effect has been observed in over 50 cyclic and acyclic secondary alcohols permitting reliable assignment of absolute configuration and enantiomeric purity.[44-47] The method also works well with MTPA derivatives of α- and β-amino acid esters,[48] and β- and α-hydroxy acid esters.[49] It has been further extended to compounds chiral by virtue of a "chiral axis", e.g. **19**.[50]



19

A chiral derivatizing agent which has perhaps received less attention than it merits is camphanic acid (**20**).[51] It was originally used by Gerlach[52] in ^1H NMR analysis of the enantiomeric purity of α-deuteriated primary alcohols (see section IIIF). In camphanate esters such as **21a**, the *pro-S*-hydrogen resonated consistently to higher frequency of the *pro-R*-hydrogen when $Eu(dpm)_3$ or $Eu(fod)_3$ was added. This permitted



20 **21**

the assignment of absolute configuration of chiral α-^2H primary alcohols. It has been used subsequently in the determination of the enantiomeric purity of chiral amines[39] and β-amino alcohols.[53] The methyl singlets in the camphanoyl moiety are useful ^1H NMR reporter groups, and anisochronous resonances have been observed (typically $\Delta\delta_H$ = 0.06 ppm in $CDCl_3$ or [$^2H_6$]-benzene) for a large series of substrates. In chiral agents such as camphanic acid, it is the anisotropy of the

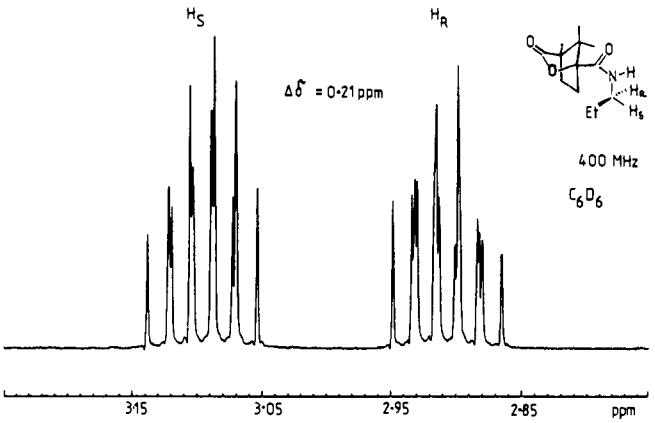


Figure 3. 400-MHz ^{1}H NMR spectrum of (1*S*,4*R*)-*N*-propylcamphanamide.

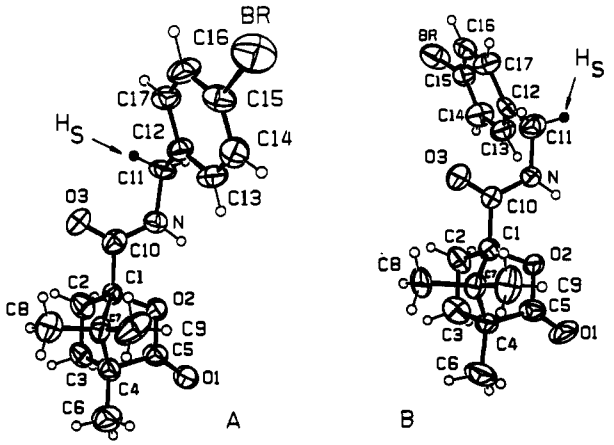


Figure 4. Molecular structures of the independent molecules observed in the unit cell for (*p*-bromobenzyl)camphanamide (showing the *pro-S*-hydrogen proximate to the amide carbonyl in molecule A).

carbonyl group that leads to differential shielding of diastereotopic groups. Confirmation of this premise has come from a detailed study of the origin of chemical shift nonequivalence in the diastereotopic methylene protons of camphanamides,[54] e.g. **21b**. It has been noted that in benzene-d_6 solution, the *pro-S*-hydrogen resonates consistently to lower frequency of the *pro-R*, with $\Delta\delta_H$ = 0.13 to 0.21 ppm (298 K, [$^2H_6$]benzene) for a number of primary amines (Figure 3). Crystallographic analysis of a *p*-bromobenzyl amide derivative revealed two conformers (Figure 4). Molecular mechanics calculations indicated that the one of lower energy (denoted A in Figure 4) corresponded to the structure in which the *pro-S*-hydrogen was closer to the anisotropic carbonyl group. In support of this $\Delta\delta_H$ increased as temperature was lowered (with the *pro-S*-hydrogen shifting to higher frequency) consistent with an increased population of this lower energy conformer so that H_S would spend more time, on average, in a magnetically deshielding environment.

There are relatively few reports of useful chiral derivatizing agents for carboxylic acids. (*R*)-α-Phenylethylamine has been used in the analysis of **22**[55] and **23**[56] (the latter aided by addition of Eu(fod)$_3$). The chiral alcohol (*S*)-methyl mandelate (**24**) is very useful as a CDA for acids.[39,57] Derivatization proceeds smoothly with chiral carboxylic acids with use of dicyclohexylcarbodimide as a coupling agent in the

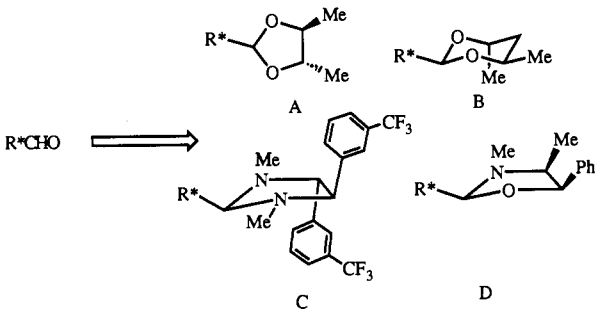
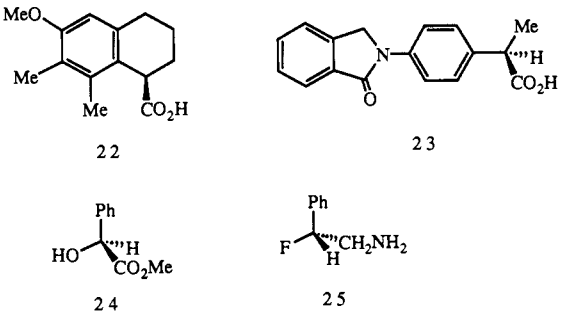


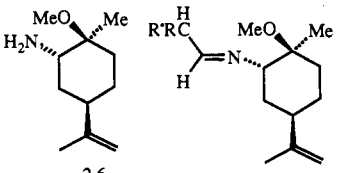
Figure 5. Derivatives of chiral aldehydes using the CDAs (A) (*R*)-butane-2,3-diol; (B) (*R*)-pentane-2,4-diol; (C) *N*,*N*′-dimethyldaryldiaminoethane; (D) (1*R*),(2*S*)-ephedrine.

presence of the acyl transfer catalyst, 4-(dimethylamino)pyridine. The mandelate methine proton res-



onates at 6.05 ppm in typical esters, and a shift nonequivalence of up to 0.2 ppm is commonly observed. This agent has also been used in the determination of the enantiomeric purity and absolute configuration of chiral α-deuteriated primary carboxylic acids.[58,39,59] By using ^{19}F NMR the chiral amine **25** shows promise: $\Delta\delta_F$ ($CDCl_3$, 298 K) varied from 0.1 to 0.6 ppm in amides derived from carboxylic acids such as 2-methylbutanoic acid and 2-fluorophenylacetic acid.[60]

There are even fewer reports of chiral derivatizing agents for carbonyl compounds. Usually the aldehyde or ketone is further reduced to the corresponding alcohol which is then derivatized with MTPA. However the use of the diterpene derived chiral amine **26** has been reported[61] in assaying chiral aldehydes. In the imine **27**, the C*H*=N proton resonated 0.17 ppm ($CDCl_3$) apart in the two diastereoisomers. More recently,



the approach has been to form chiral 1,3-dioxolanes under acid catalysis with enantiomerically pure diols[62] such as (*R*)-butane-2,3-diol or (*R*)-pentane-2,4-diol.[63-65] Similarly chiral oxazolidines[66] have been derived from (1*R*,2*S*)-ephedrine, and imidazolidines prepared from enantiomerically pure 1,2-diaryldiamines.[67,68] These related structures are compared in Figure 5 and have been analyzed by ^{1}H (and ^{19}F) NMR. The imidazolidines perform best giving reasonable $\Delta\delta_F$ values for a wide range of chiral aldehydes. Although the size of the shift nonequivalence observed is modest (Figure 6), the singlets are well resolved even at 56 MHz. Excess diamine may be used during derivatization in order to

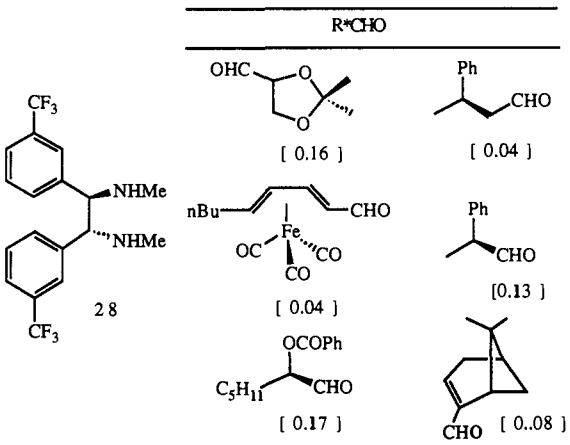


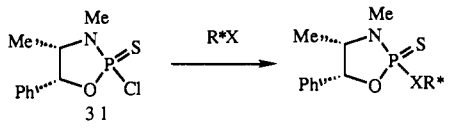
Figure 6. Magnitude of ^{19}F NMR nonequivalence ($\Delta\delta_F$) for derived chiral imidazolidines (C_6D_6, 298 K) from shown aldehydes and the CDA **28**.

ensure quantitative reaction and avoid kinetic resolution. This step is chemoselective: ketones fail to react under the mild derivatization conditions (Et_2O, 4 Å sieves).

2. ^{31}P NMR Analysis

Phosphorus-31 is a very attractive nucleus to use for NMR chiral analysis. The chemical shift dispersion is large and spectra are usually simple when broad-band proton decoupling is used. Several chiral phosphoryl or thiophosphoryl chlorides have been examined as chiral derivatizing agents for alcohols and amines (Table II). The chlorodioxaphospholane (**29**) reacts with chiral primary and secondary alcohols (in the presence of base) to give diastereoisomeric phosphates for which $\Delta\delta_P$ was small, typically 0 to 0.13 ppm ($CDCl_3$).[69] The binaphthyl CDA **30** is more useful perhaps, giving larger $\Delta\delta_P$ values, and reacts smoothly with a variety of chiral alcohols in the presence of 1-methylimidazole to give the diastereoisomeric phosphates.[70] In these reagents, as in the chiral diamine derived CDA **32**,[71] the phosphorus atom is not chiral so that inversion or retention of configuration at phosphorus during derivatization of an enantiopure alcohol yields a single diastereoisomer. The reduced electrophilicity of the phosphorus atom in **32**, associated with the presence of two P–N bonds, renders this a less useful agent because forcing conditions are required (NaH, THF, reflux). However larger $\Delta\delta_P$ values were obtained: the phosphates derived from butan-2-ol gave $\Delta\delta_P$ values of 0.006 ppm for **29**, but 0.454 ppm for **32** (Z = 0) and 0.20 ppm for the diastereoisomers derived from **31**, (see Table II). The latter CDA, derived easily from (1*R*,2*S*)-ephedrine[72] reacts readily with chiral amines (THF, Et_3N, 24 h, 65 °C) but requires formation of the alkoxide (BuLi, Et_2O) in order to form derivatives of chiral alcohols. The thio analogue gives larger $\Delta\delta_P$ values, and a representative set of chiral amines and alcohols which have been assayed by using it is listed (Figure 7).

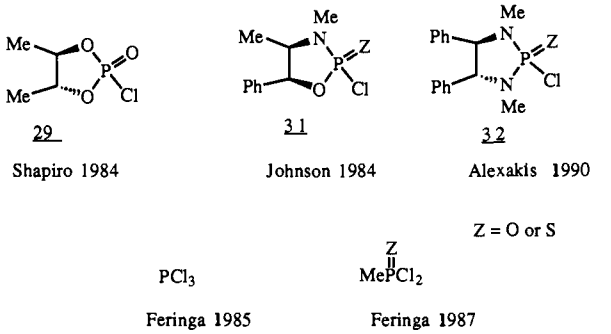
The chiral phosphorus(III) CDA **33** is much more reactive than the phosphorus(V) based CDA's **29–32** and forms diastereoisomeric derivatives with chiral primary, secondary, *and* tertiary alcohols (C_6D_6, 20 °C). Further reaction with sulfur yields the thiophosphates (which are more stable to air and moisture) which are also amenable to ^{31}P NMR analysis. Representative

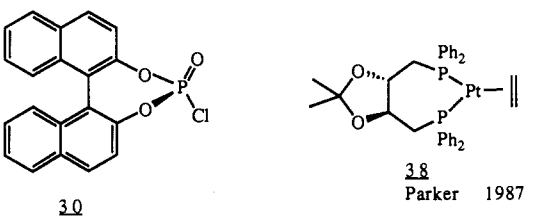


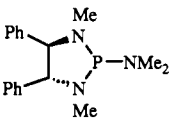
R*X	$\Delta\delta_P$ [ppm, $CDCl_3$]
α-phenylethylamine	0.175
sec-butylamine	0.628
1,3-dimethylbutylamine	0.843
1-methyl-2-phenoxy-ethylamine	0.347
α-phenylethanol	0.111
2-octanol	0.307
2-methyl-2-butanol	0.167
4- methyl-2-pentanol	0.301

Figure 7. ^{31}P NMR shift nonequivalence of derivatives of chiral amines and alcohols using the CDA **31**.

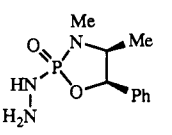
TABLE II. Derivatizing Agents Used in ^{31}P NMR Analysis







$\Delta\delta_P$ values are given for a broad range of chiral alcohols (Figure 8). Attempts to extend this principle of ^{31}P analysis with phosphoridates to the analysis of chiral ketones have met with only partial success. By using the chiral hydrazine **34**, condensation with both sterically demanding or α,β-unsaturated ketones was not satisfactory, and successful use of the method was restricted to some chiral monosubstituted cyclohexanones.[73]



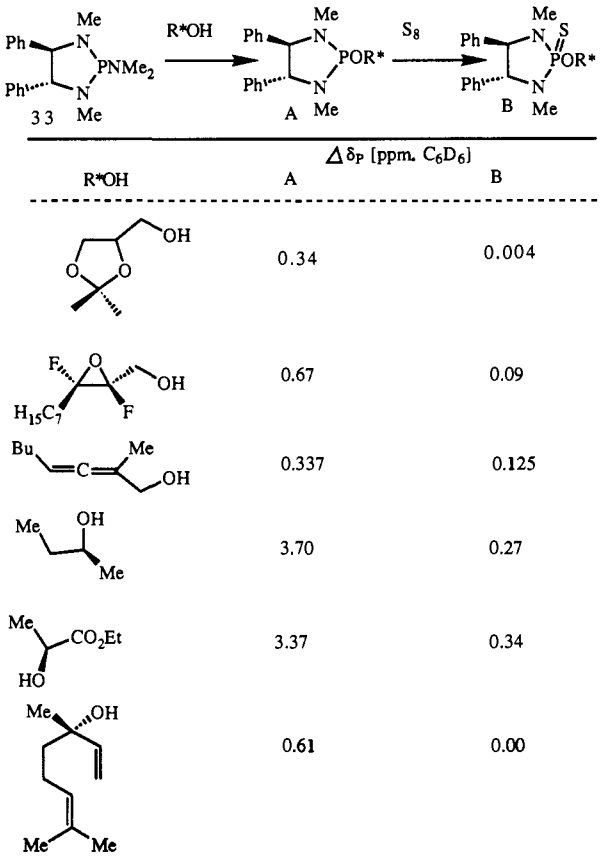


Figure 8. ^{31}P NMR shift nonequivalence of chiral derivatives formed from the C_2 symmetric CDA **33**.

The use of an *achiral* derivatizing agent for the ^{31}P NMR analysis of chiral alcohols and thiols has been defined.[74] It relies upon a principle—first expounded by Horeau[75]—that recognizes the intrinsic chirality differences between enantiomerically pure and (partly) racemic substances. The *coupling* of two enantiomers with an achiral reagent, X, results in the diastereoisomers (*R*)-X-(*R*) and (*S*)-X-(*S*) and an achiral pair of diastereoisomers (*R*)-X-(*S*) and (*S*)-X-(*R*). Thus for example PCl_3 reacts with butan-2-ol to yield four stereoisomers, the relative amounts of which permit a calculation of enantiomeric purity: racemic material gives three singlets in its ^{31}P NMR spectrum. Two resonances for two distinct "meso" compounds and one for the enantiomeric pair, (Figure 9), with chemical shifts of δ_P ($CDCl_3$) = 5.60, 4.78, and 5.25 ppm, respectively. The method is especially useful for chiral compounds with complex ^1H or ^{13}C spectra, and the derivatization conditions ($CDCl_3$, pyridine, 20 °C) tolerate large variations in alcohol structure (α-hydroxy esters and amides allylic/benzylic alcohols). Improvements to this method has been made.[76-78] Larger chemical shift nonequivalence ($\Delta\delta_P \approx 1$ ppm, $CDCl_3$) is observed by using $MePOCl_2$ and $MePSCl_2$ as the achiral coupling agent for chiral alcohols and thiols. When derivatization of a chiral alcohol occurs with a phosphorothioic acid a different situation arises. Reaction of menthol with $(PhO)_2P(S)SH$ in $CDCl_3$ gives diastereoisomeric *O,O*-dialkylphosphorodithioates. The phosphorus atom in the diastereoisomeric derivatives **35** and **36** is stereogenic but achirotopic so that only one

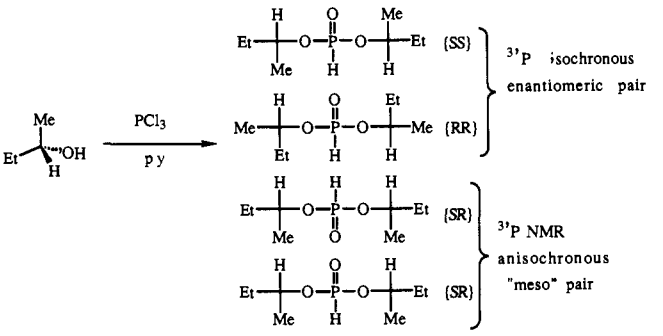
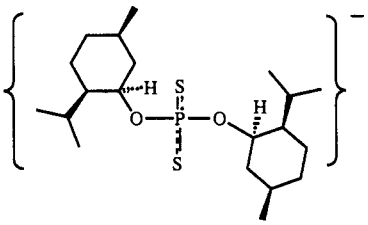
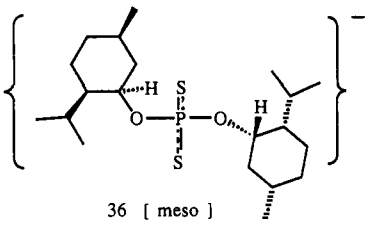


Figure 9. Stereoisomers formed by reaction of PCl_3 with butan-2-ol for ^{31}P NMR analysis of enantiomeric purity.

meso isomer can result. The observed nonequivalence $\Delta\delta_P$ was 0.5 ppm ($CDCl_3$) for the two diastereoisomers.[77]

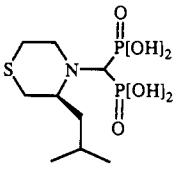


35 racemate [RR shown]



36 [meso]

For polycrystalline samples, the use of ^{31}P solid-state magic-angle spinning NMR offers an intriguing alternative. Enantiomers and racemates generally crystallize in different point groups, so crystallization of a mixture of 2 enantiomers gives some racemic crystallite the amount of which is governed by the quantity of the enantiomer representing the minor constituent. Observable differences for the isotropic chemical shifts of the racemate and pure enantiomer were first noted by using ^{13}C MAS NMR with (*RR*)- and (*RS*)-tartaric acid.[79] ^{31}P NMR is much more suitable as the elements of ^{31}P chemical shift tensors and hence the isotropic ^{31}P chemical shifts are particularly sensitive to crystal effects and to changes in electronic environments. Thus, the enantiomeric purity of an enriched sample of (−)-**37** was measured as 91.6% ee (Figure 10).



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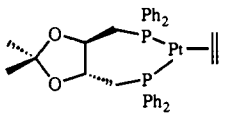
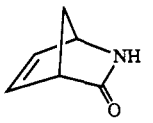
An organometallic CDA has been devised for the ^{31}P NMR analysis of the enantiomeric purity of chiral 2-electron donors such as alkenes, alkynes, and allenes. By using the C_2-symmetric biphosphine, DIOP, the zerovalent platinum and palladium ethene complexes, **38**, were studied.[81,82] Displacement of ethene with alkynes, allenes, and electron-poor or strained alkenes



38

(e.g. enones or norbornenes) proceeds readily in situ (THF or C_6D_6) and the resultant diastereoisomeric complexes give good ^{31}P NMR chemical shift differences. Spectral analysis is slightly complicated when a non-C_2-symmetric 2 electron donor is used, since binding of the *si* or *re* face may give rise to constitutionally isomeric species. A selection of substrates examined is given in Table III. Chiral norbornenes and related alkenes bind selectively via the less-hindered exo face and certain enones e.g. carvone (**40**) also bind with high face selectivity, in the case of **40** via the less-hindered *si–si* face of the endocyclic double bond. The enantiomeric purity of (−)-2-azabicyclo[2.2.1]hept-5-enone (**39**)[83] for example (Figure 11) was measured as



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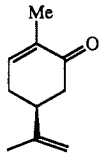
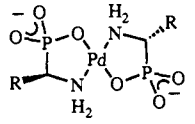


40

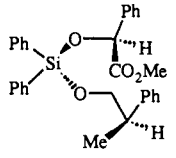
98.6 (±0.2)% ee.[84] A related palladium complexation method has been defined for the analysis of α-aminophosphonic acids. Complexation of *two* ligands with $PdCl_4^-$ in D_2O leads to formation of a single meso diastereoisomer e.g. **41** and of an enantiomeric pair (*RR*/*SS*), the relative proportions of which give the enantiomeric purity. Complexes were typically 0.1 ppm anisochronous (pD 8.5, 298 K).[85]



41 [RS]

3. NMR Analysis with Other Nuclei

The use of ^{29}Si NMR in the analysis of the enantiomeric purity of chiral alcohols has been reported. Successive reaction of diphenyldichlorosilane with an enantiomerically pure alcohol (menthol, quinine, or methyl mandelate) followed by the alcohol to be determined (pyridine, 4.5 h, 60 °C) yields diastereoisomeric silyl acetals with modest chemical shift nonequivalence ($\Delta\delta_{Si}$ = 0.053 ppm ($CDCl_3$, 298 K), for **42**[86]).



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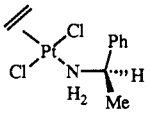

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This ^{29}Si NMR method—in principle—ought to be amenable to analysis involving direct reaction of *two* equivalents of a chiral alcohol with the achiral derivatizing agent R_2SiCl_2 to give "racemic" and "meso" diastereoisomers analogous to those defined in ^{31}P NMR analysis with $MePOCl_2$.[76,78] This has yet to be described. Platinum-195 is not the most attractive nucleus for study in the context of chiral analysis. Its lack of sensitivity and line broadening at high field strengths (chemical shift anisotropy) render it of academic in-

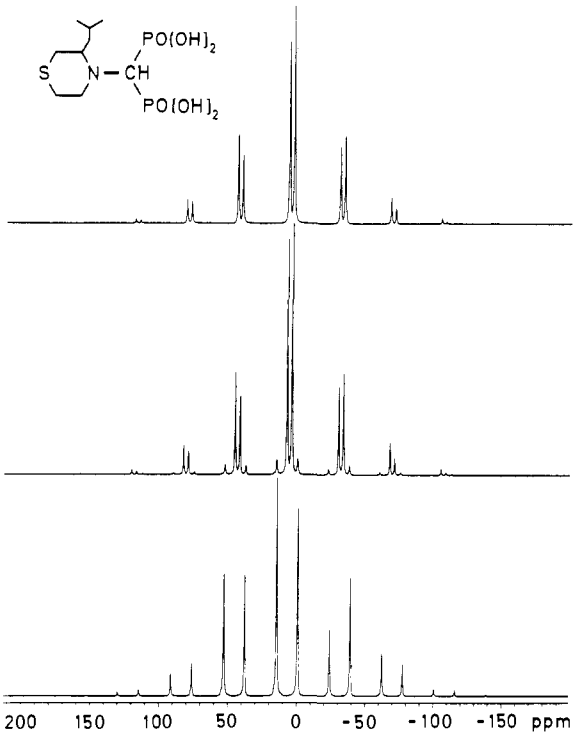
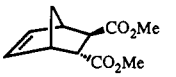
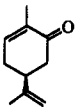
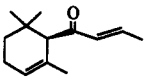
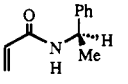
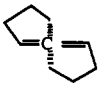
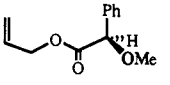
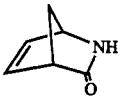


Figure 10. ^{31}P CP-MAS NMR spectrum of (−)-**37** (upper), (+)-**37** (center), and racemic **37** (lower). One hundred-twenty transients for each sample, ν = 4.6 kHz.

TABLE III. Chiral Alkenes and Allenes Examined Using DIOP-Pt-ethene (38)

entry	substrate	$\Delta\delta_P$ (298 K, benzene-d_6) P[a]	P[b]
1		0.3	0.7
2		1.3	0.9
3		0.85 [0.16]	0.5 [0.06]
4		0.5 [0.3]	0.9 [1.2]
5		0.3	0.7
6		0.9	0.2
7		0.97	0.78

[a] P arbitrarily assigned as resonating to higher frequency. Diastereoisomeric species were anisogamous, e.g. for entry 4, J_{PtP_a} = 3246 and 3060 for the two isomers. [b] With entries 3 and 4 constitutionally isomeric species were also observed through binding of the *si* and *re* faces of the chiral alkene.

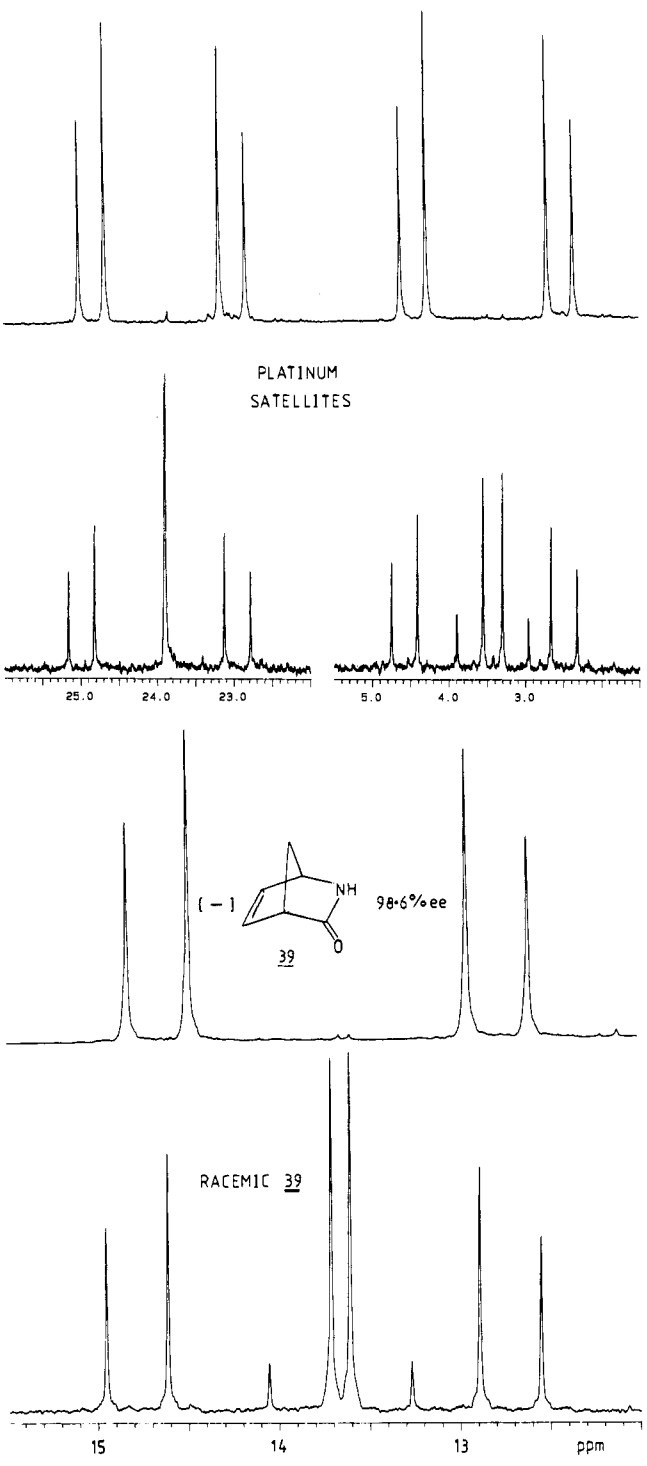
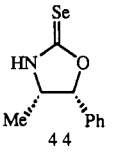


Figure 11. ^{31}P NMR spectrum of the DIOP-Pt complex of **39** (C_6D_6 298 K). The anisogamy of the complexes is seen in the appearance of the platinum satellites.

terest only. Nevertheless the bound ethene in the chiral platinum amine complex **43** may be displaced by chiral allylic ethers and alcohols to give four diastereoisomeric complexes (each constitutional isomer exists as a pair of diastereoisomers). Shift nonequivalence was reasonably large ($\Delta\delta_{Pt}(Me_2CO\text{-}d_6$, 298 K) = 22 ppm)[87] and chiral trisubstituted allenes may also be analyzed by this method.[88] At least 50 mg of complex is required in order to get reasonable signal/noise ratios within tolerable times of acquisition.

In contrast, selenium-77 is a relatively sensitive NMR nucleus (2.98 compared to ^{13}C), possesses a large chemical shift range (~3400 ppm) and is particularly sensitive to electronic environment. The selenocarbonyl group itself displays a chemical shift range of 2600 ppm; accordingly, the use of ^{77}Se NMR has been described for the assay of the enantiomeric purity of compounds bearing some *remote* chiral centers.[89] Reaction of racemic 5-methylheptanoic acid with the enantiomerically pure selone **44** (DCC-DMAP, CH_2Cl_2, 0°, 1 h) yielded



44

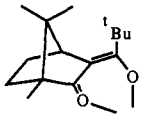
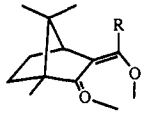
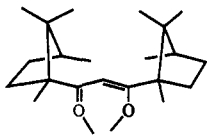
the corresponding diastereoisomeric *N*-acyl selones in which $\Delta\delta_{Se}$ ($CDCl_3$, 293 K) = 0.1 ppm. Finally ^2H and ^3H NMR have been used often in the determination of the enantiomeric purity of compounds chiral by virtue of isotopic substitution. Such examples are discussed in more detail in section III.F.

B. Chiral Lanthanide Shift Reagents

Addition of a lanthanide shift reagent to an organic compound may result in shifts of resonances to higher (or lower) frequency, the size of which is determined primarily by the distance of the given type of proton from the donor group. The six-coordinate lanthanide complex forms a weak addition complex with a large variety of organic compounds that is in fast exchange with the unbound organic substrate on the NMR time scale. The induced shifts are caused by a large difference in the magnetic susceptibility tensors for the seven-coordinate complex and the McConnell equation ($\Delta\delta = k(1 - 3\cos^2\theta)r^{-3}$) qualitatively defines the relationship between the induced shift $\Delta\delta$, r is the distance from the metal center and θ is the number of degrees that the nucleus lies away from the axial axis of symmetry. Lanthanide-shift reagents are in general *less* useful at high fields. Under the fast exchange conditions that typically prevail, line broadening is proportional to B_0^2, and for substrates that show large induced shifts (e.g. alcohols) it is preferable to acquire spectra on a 100-MHz ^1H instrument, rather than a 500-MHz instrument where line broadening will be 25 times more severe.

Following the early work of Whitesides with the camphor-based chiral shift reagent $Eu(pvc)_2$[22] (**8**), several other chiral shift reagents were introduced (Table IV), many of which are available commercially. The dicamphoyl reagent $Eu(dcm)_3$ exhibits the best differential shift dispersion, and $Eu(hfc)_3$ gave particularly large $\Delta\delta$ values for its diastereoisomeric complexes with chiral substrates in ^{13}C rather than in ^1H NMR. The praseodymium complex $Pr(hfc)_3$ performs better than $Eu(hfc)_3$ in ^1H NMR giving largest $\Delta\delta$ values at lowest concentrations of added shift reagents,[93,94] while $Yb(hfc)_3$ has been shown to be superior to $Pr(hfc)_3$ in the analysis of a series of chiral sulfoxides.[95] The praseodymium shift reagents offer the possible advantage (e.g. in analysis of diastereotopic methyl groups) that induced shifts are to *lower* frequency, rather than to higher frequency as noted for the europium and ytterbium complexes. This phenomenon has been used to good effect in the determination of the enantiomeric purity of carboxylates. By using the achiral shift

TABLE IV. Common Chiral Lanthanide Shift Reagents

structure of L in LnL_3	lanthanon	abbreviation[a]	ref
	Eu	Eu[pvc]$_3$	22
	R = CF_3: Eu	Eu[tfc]$_3$	90
	R = CF_3: Pr	Pr[tfc]$_3$	90
	R = CF_3: Yb	Yb[tfc]$_3$	90
	R = C_3F_7: Eu	Eu[hfc]$_3$	91
	R = C_3F_7: Pr	Pr[hfc]$_3$	91
	R = C_3F_7: Yb	Yb[hfc]$_3$	91
	Eu	Eu[dcm]$_3$	92

[a] pvc = pivaloyl-*d*-camphorato; tfc = trifluorohydroxymethylene-*d*-camphorato; hfc = heptafluorohydroxymethylene-*d*-camphorato; dcm = dicamphoyl-*d*-methanato.

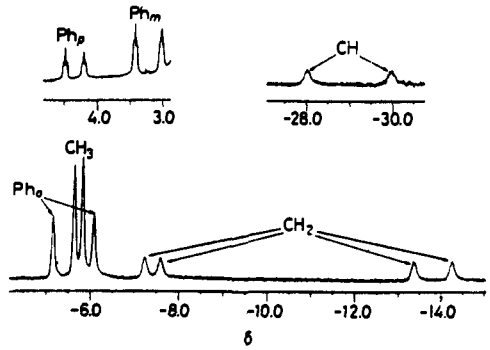
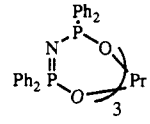


Figure 12. ^{1}H NMR spectrum of the two diastereoisomeric complexes obtained from Pr(tpip)$_3$ (**45**) and 2-phenylbutyrate (CD_2Cl_2, 293 K).

reagent tris(tetraphenylimidodiphosphinato)praseodymium (III), Pr(tpip)$_3$[96,97] (**45**), the adducts formed with



45

potassium salts of chiral carboxylic acids are in *slow* exchange on the NMR time scale and form dinuclear complexes.[98] Thus a racemic 2-phenylbutyric acid gives rise to diastereoisomeric complexes (*SS*/*RR* and *RS*) which are clearly distinguished in ^{1}H NMR (CD_2Cl_2 or $2H_6$) (Figure 12) and are shifted to lower frequency.

Several early reviews have compiled details of the application of chiral lanthanide shift reagents.[14,99] Most applications involve ^{1}H NMR analysis, but ^{13}C, ^{19}F, and ^{31}P are commonly used. It remains a mystery why Eu(tfc)$_3$ and Eu(hfc)$_3$ are used almost exclusively,[100-103] when Pr(hfc)$_3$ and Yb(hfc)$_3$ offer distinct advantages. It is of course imperative to *dry* the shift reagent prior to use (as hydrolysis leads to formation of Eu_2O_3 and severe line broadening), although sublimation (200 °C, 0.05 mmHg) is preferred. Provided that care is taken in data acquisition and manipulation (aided for example by the use of Gaussian line narrowing methods and base line correction routines), accurate values of enantiomeric purity may be obtained.[104] In the range 40 to 60% ee, the best claimed deviation is ±2%,[105] although a note of caution is required for ee values ≥90%, where the error in measurement is reported to be of the order of 10%.[106] Polar substrates such as chiral 1,2- and 1,3-diols are amenable to analysis in acetonitrile-d_3 as NMR solvent. For example, the nonequivalence of the enantiotopic C-2 hydroxy resonances in 3-chloropropane-1,2-diol have been observed by using CLSRs.[107] Chiral carboxylic acids are usually not amenable to direct analysis in this manner. They may either be converted into their corresponding tertiary amides (amides are good σ-donors for europium or ytterbium),[110] or may be examined directly in aqueous solution.[108,109] The methyl resonances of several α-hydroxycarboxylates have been resolved in the presence of $EuCl_3$ (or $PrCl_3$) and 3 equiv of enantiopure citramalate or malate.[108]

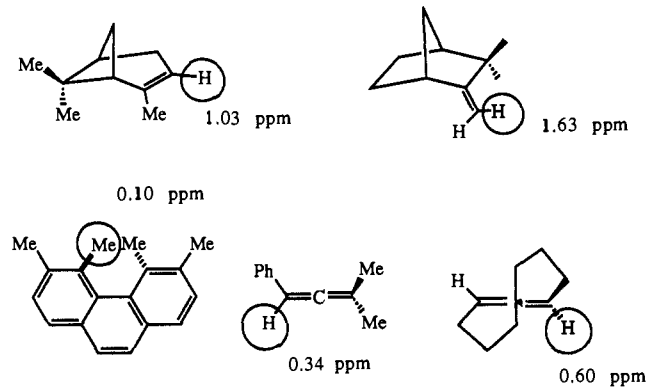
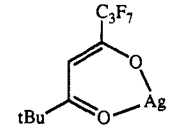


Figure 13. ^{1}H NMR chemical shift nonequivalence ($\Delta\delta_H$, ppm, $CDCl_3$) observed with use of Yb(hfc)$_3$/Ag(fod) and substrates shown.

A useful ^{1}H NMR method for the analysis of chiral alkenes, arenes, and allenes has been devised.[111-118] It uses a mixture of Yb(hfc)$_3$ and the achiral silver shift reagent Ag(fod) (**46**) following an initial report[111] that



46

used Eu(tfc)$_3$ and silver trifluoroacetate for chiral alkene analysis. A mixed complex forms in solution and the chiral hydrocarbons interact weakly with the silver ion and induced shifts are observed. Chemical shift nonequivalence for diastereotopic nuclei was typically $\Delta\delta_H$($CDCl_3$, 298 K) = 0.3 to 1.00 ppm for chiral alkenes, 0.3 ppm for chiral allenes (Figure 13).

C. Chiral Solvating Agents

Chiral solvating agents form diastereoisomeric solvation complexes with solute enantiomers via rapidly reversible equilibria in competition with the bulk solvent. Chemical shift anisochrony has two possible causes in this method. The first is the relative position of magnetically anisotropic groups (e.g. phenyl, carbonyl) in the low energy solution conformers with respect to other substituents in the diastereoisomeric complexes. In addition, the relative size of the diastereoisomeric complexation constants K_R and K_S may be important:

$$R_{CSA} + R^* \overset{K_R}{\rightleftharpoons} [R_{CSA}{\cdot}R^*]$$

$$R_{CSA} + S^* \overset{K_S}{\rightleftharpoons} [R_{CSA}{\cdot}S^*]$$

Exchange between chiral and achiral solvates is rapid on the NMR time scale and the observed resonance signals derived from each enantiomer δ_R(obs) and δ_S(obs) represent population weighted averages of the chemical shifts for the discrete chiral and achiral solvates δ_R, δ_S, and δ_{ach}, respectively. Given that ϕ_R and ϕ_S are the fractional populations of achiral solvates, so that $K_R = (1 - \phi_R)/\phi_R$, then

$$\delta_R(\text{obs}) = \phi_R\delta_{ach} + (1 - \phi_R)\delta_R$$

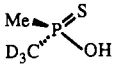
$$\delta_S(\text{obs}) = \phi_S\delta_{ach} + (1 - \phi_S)\delta_S$$

hence

$$\Delta\delta = \phi_R(\delta_{ach} + K_R\delta_R) - \phi_S(\delta_{ach} + K_S\delta_S)$$

The advantages of the method are that it is quick and simple to perform, with no problems of kinetic resolution or sample racemization, provided that the complexes remain in solution. Even the enantiomeric purity of the CSA is not critical: if it is less than 100% then only the size of the chemical shift nonequivalence is reduced. Only for a racemic CSA is $\Delta\delta$ zero. The main drawback of the method is that $\Delta\delta$ values tend to be small, but with high-field NMR instrumentation widely available this is not critical. In addition only a limited range of cosolvents may be used. Nonpolar solvents ($CDCl_3$, CCl_4, C_6D_6) tend to maximize the observed anisochrony between the diastereoisomeric complexes while more polar solvents preferentially solvate the solute and $\Delta\delta$ falls to zero. There have been two fairly comprehensive reviews compiling the applications of CSAs in enantiomeric purity determination.[16,17]

It was Pirkle who first observed distinct ^{19}F NMR resonances for the enantiomers of 2,2,2-trifluoro-1-phenylethanol in the presence of (*R*)-α-phenylethylamine.[20] By using (*R*)-2-naphthylethylamine, the size of the shift nonequivalence increased. These amines have also been used in the analysis of chiral carboxylic acids forming diastereoisomeric salts[119-127] through complete proton transfer. In ^1H NMR, shift nonequivalences are generally small ($\Delta\delta_H$ ($CDCl_3$) ≤ 0.05 ppm, 298 K), although the methyl doublets of the chiral thiophosphinic acid (47) were 0.07 ppm anisochronous



47

in the presence of (*R*)-α-naphthylethylamine.[126] Few other chiral amines have been examined as CSAs in this context, although quinine has been reported as a CSA in the analysis of certain alkylarylcarbinols and some binaphthyl derivatives.[128] Recently, 1,2-diphenyldiaminoethane has been found to be an excellent CSA for the direct analysis of chiral carboxylic acids. In the analysis of 2-arylpropanoic acids (such as the drugs "ibuprofen" and "ketoprofen"), the methine multiplets were up to 0.17 ppm anisochronous (298 K, $CDCl_3$), and the methyl doublets in 2-halopropionic acids were

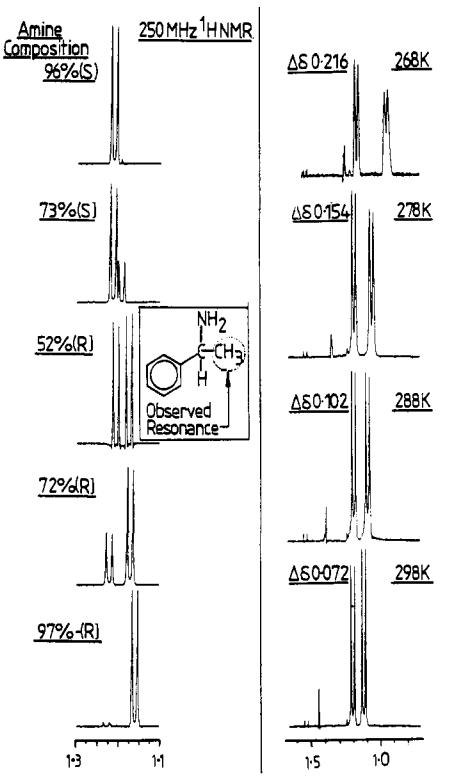
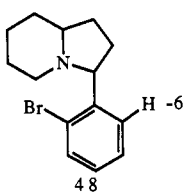


Figure 14. Variation of $\Delta\delta_H(CDCl_3)$ for the methyl doublets of 2-phenylethylamine diastereoisomeric salts with (*R*)-*O*-acetylmandelic acid.

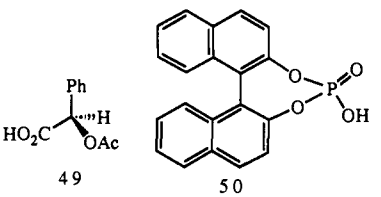
greater than 0.3 ppm nonequivalent under the same conditions.[84]

The reciprocal experiment—analysis of chiral amines and amino alcohols using an enantiopure carboxylic acid CSA—has been more thoroughly investigated.[123,124,129-133] The chiral derivatizing agent MTPA (Table V) has been examined, although its use is rather restricted by the tendency of its salts to precipitate in $CDCl_3$ and C_6D_6. Pyridine-d_5 offers an alternative in these solutions.[129] With the chiral tertiary amine 48,



48

the effect of temperature, concentration, and CSA/solute ratio on $\Delta\delta_H$ has been studied. For example, lowering the temperature from 18 °C to −30 °C increases $\Delta\delta_H$ from 0.096 to 0.174 ppm for the H-6 proton, while high concentrations (≥0.3 M) lead to ion-pair aggregation and a diminution in $\Delta\delta_H$. As expected, $\Delta\delta_H$ reaches a maximum value at 1:1 stoichiometry, when salt formation is complete. The enantiopure acids **49** ((*R*)-*O*-acetylmandelic acid)[132] and **50**[131] gives larger $\Delta\delta_H$ gen-

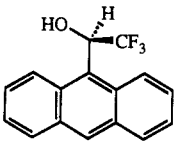


49 50

erally and tolerate a wider range of functionality in the amine substrate while retaining solubility. In the case

of the diastereoisomeric salts formed by (*R*)-*O*-acetylmandelic acid and α-phenylethylamine, $\Delta\delta_H$ for the C–Me doublet varies with both temperature and enantiomeric composition, (Figure 14). The dissociation equilibrium constants for salt formation of the two diastereoisomers must be nonequivalent, so that as the enantiomeric composition of the solute changes $\Delta\delta_H$ varies also.[124,132] This behavior is precisely mirrored using (*S*)-*O*-acetylmandelic acid. The methyl doublet due to the (*S*)-α-phenylethylamine/(*R*)-*O*-acetylmandelic acid complex shifts to lower frequency (relative to all other resonances) as the temperature is lowered, consistent with it spending more time on average in a low-energy conformation that places it proximate to an anisotropic group. The linearity of a [$\ln\Delta\delta_H$] versus $1/T$(T in Kelvin) plot over the range 318–268 K supports this idea of a preferred conformer being increasingly populated as the temperature is lowered.

The most commonly used CSA is 1-(9-anthryl)-2,2,2-trifluoroethanol (**51**),[133–140] which has been used to determined the enantiomeric purity of a very broad range of compounds, including lactones,[138,141] ethers,[142] oxaziridines,[136] and sulfinate esters.[135] It is a hydro-



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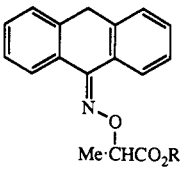
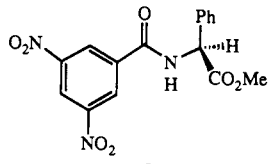


52

gen-bond donor, and a solvation model has been proposed[17] involving a secondary interaction between the methine hydrogen of **51** and the less basic of the two "basic sites" in a given solute. By using this model, the absolute configuration of a series of dibasic solutes may be predicted with some confidence,[17] from the "sense" of the observed shift. Although hydrogen-bonding interactions are the most common primary diastereoselective interactions found in CSA–solute complexes, other interactions also contribute. π-stacking (π-acid–π-base)[143] is the likely major source of complexation involved in the binding of hexahelicene to the CSA **52**.[144] It also plays a significant role in the use of the π-acidic CSAs **53**[145] and **54**[146] each containing 3,5-dinitroaryl groups. The latter CSA was used to deter-



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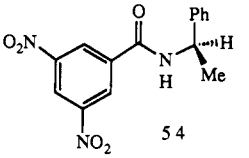
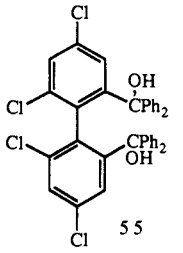


54

mine the enantiomeric purity of a series of chiral methyl sulfoxides, and $\Delta\delta_H$ was typically 0.015 ppm ($CDCl_3$, 298 K) for the diastereotopic methyl singlets in the complexes. Larger chemical shift nonequivalence in sulfoxide analysis has been observed by using the more esoteric CSA **55**.[146] For both alkyl and aryl methyl sulfoxides $\Delta\delta_H$ ($CDCl_3$, 298 K) ≥ 0.05 ppm, and **55** may also be used to assay the enantiomeric purity of chiral amines. By using the related diol **56**, the enantiomeric purity of chiral amine oxides has been determined.[147,148] The *N*-methyl groups in **57** were up to 0.05 ppm ($CDCl_3$, 295 K) nonequivalent.



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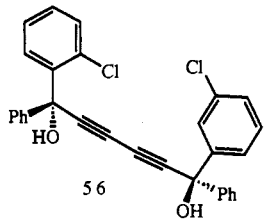

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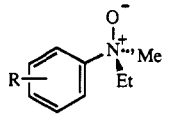


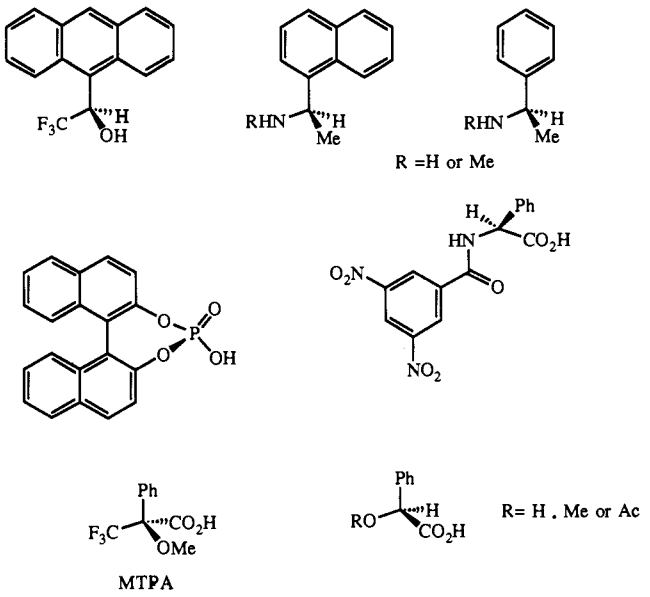
57 R= H or Me

D. Experimental Considerations

It is important to choose the conditions under which the enantiomeric purity determination is made with some care, in order to maximize the observed nonequivalence, minimize linebroadening, and achieve sufficient signal/noise and digital resolution that accurate integrals may be obtained. The choice of solvent is important. When CDAs and CSAs are used, deuterochloroform is used most often, although benzene-d_6 often leads to enhanced values of $\Delta\delta$ through specific solvation effects or the enhanced population of a different low-energy conformer. Deuterotoluene is preferred if a low-temperature is needed. Indeed lowering the temperature often leads to an increase in the observed nonequivalence, although with lanthanide shift reagents this can lead to increased line-broadening and poorer resolution. For analysis with CSAs and CDAs, increasing the field strength not only improves sensitivity so that smaller samples may be analyzed but also obviously leads to enhanced resolution of the diastereotopic resonances. This is not necessarily the case with lanthanide shift reagents. Although improved resolution is gained through the resonances being separated further apart ($\Delta\nu$ in Hz), exchange broadening is *considerably* worse as it varies with $(\Delta\nu)^2$, i.e. with the square of the applied field. A further point with CLSRs is that spectra should be acquired immediately after adding the lanthanide reagent as time-dependent precipitation or formation of different diastereoisomeric lanthanide complexes (e.g. dimers) may occur. The choice of the lanthanide complex itself is important. Ytterbium complexes give larger induced shifts than the europium analogues and praseodymium reagents shift the ^1H NMR resonances to lower frequency which may be advantageous in the analysis of diastereotopic methyl groups.

The choice of the NMR nucleus observed is also important. If the compound has a complex ^1H NMR spectrum, then ^{19}F or ^{31}P analysis should be considered—particularly with CDAs which usually contain only one or two different F or P atoms. If ^{31}P and particularly ^{13}C analysis is used, a suitable pulse delay should be included to ensure that nuclei are fully relaxed. In spectral acqusition good lineshapes should be sought—through careful shimming—and digital resolution should be sufficient (e.g. minimum of 16 K data points in ^1H NMR) so that each peak is defined by an adequate number of data points. Peak intensities

TABLE V. Common Chiral Solvating Agents

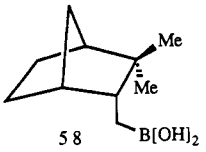


should be measured with care on spectra that have been "base line corrected" if appropriate and to which a small amount of line-broadening has been introduced (e.g. 0.7 Hz in ^{1}H NMR) prior to Fourier transformation of the FID. A useful internal reference in the analysis of diastereotopic methyl groups in ^{1}H NMR spectra of highly enantiomerically pure samples is to use the ^{13}C satellite peaks ((1/180) + (1/180) of the intensity of the central peak). When older continuous wave instrumentation is used, it may be more accurate to trace the major resonances carefully and "cut and weight"!

III. Examples of Enantiomeric Purity Determination

A. Alcohols, Thiols, and Diols

Alcohols are analyzed most often via conversion into their MTPA ester derivative[23-25,28-31] via reaction of the acid chloride of MTPA with the chiral alcohol in the presence of base. The CDAs *O*-methylmandelic[35,36] and *O*-acetylmandelic acid[39] (both available commercially) often give improved shift nonequivalence in ^{1}H NMR analysis (particularly the latter) and the esters may be formed under nonracemizing conditions with use of dicyclohexylcarbodiimide as a coupling agent, in the presence of the acyl-transfer catalyst dimethylaminopyridine. Alcohols are amenable to analysis using CSA but generally only small $\Delta\delta$ values are obtained, and in CLSR analysis, line broadening can prove troublesome.[99,100] A highly convenient method of analysis is to use a ^{31}P NMR method through formation of diastereoisomeric phosphate ester derivatives using either a chiral phosphorus derivatizing agent[67-72] or an achiral dichlorophosphorus derivative e.g. PCl_3 or $MePSCl_2$.[76-78] These methods also work well with thiols. Diols may be analyzed with CLSR,[104] particularly when acetonitrile-d_3 is used as solvent,[106] and a ^{13}C NMR method has been devised using the boronic acid, CDA, **58**.[149] Admixture of **58** with the chiral diol at 20 °C gave diastereoisomeric cyclic boronate esters for which ^{13}C shift nonequivalence was observed ($\Delta\delta_C$ (C_6D_6) ≈ 0.08 ppm typically). No data were given for ^{11}B analyses—although this is feasible in principle.



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B. Amines, Amino Alcohols, and Amino Acids

There are many examples of ^{1}H and ^{19}F NMR analysis using MTPA as a CDA for analyzing amines[23-25] and β-amino alcohols and α-amino acids.[150,151] Camphanoyl chloride is a useful alternative CDA for these substrates.[39,52,53] The isocyanate analogue of MTPA,[33] **14**, for example reacts with chiral amines in the NMR tube and gives larger values of $\Delta\delta$ in both ^{1}H and ^{19}F analysis. Amines and amino alcohols (but not α-amino acids) are particularly amenable to analysis with CSAs. By using either mandelic acid,[130] *O*-acetylmandelic acid[132] or the binaphthylphosphonic acid (**50**),[131] diastereoisomeric salts are formed on mixing in equimolar ratio in $CDCl_3$, C_6D_6, or pyridine-d_5. Although the observed shift nonequivalence is less than that obtained with a CDA, the method is quicker to use and the sample may be easily recovered. The CDAs based on mandelic acid derivatives are certainly cheaper than (9-anthryl)trifluoroethanol, which, although still used for such analyses[139,140] of chiral amines, often gives inferior shift nonequivalence.

C. Aldehydes and Ketones

Cyclic and acyclic ketones may be analyzed by ^{13}C NMR following derivatization with (*RR*)-butane-2,3-diol or the dithiol analogue.[152] This CDA has also been used for ^{1}H NMR analysis to determine the enantiomeric purity of chiral aldehydes,[62] and related methods have developed based on the formation of other chiral 1,3-dioxolanes,[63] oxazolidines,[66] or imidazolidines.[67] The latter method involving the use of a chiral bis(trifluoroaryl) diamine, (**28**) is selective for aldehydes in the presence of ketones and permits ^{19}F NMR analysis. In general, there are relatively few methods for determining the enantiomeric purity of chiral carbonyl compounds as it is often easier to reduce the compound to the corresponding alcohol and analyze the alcohol.

D. Carboxylic Acids and Acid Derivatives

In contrast to the plethora of methods for NMR analysis of chiral amines and alcohols, there are relatively few reports of good, reliable analyses for carboxylic acids. Chiral derivatizing agents based on α-phenylethylamine or α-naphthylethylamine[55,56] have been reported, but sometimes require the addition of an achiral shift reagent in order to give observable shift differences in ^{1}H NMR. More useful is (*S*)-methyl mandelate which is commercially available and for which the mandelate methine proton (resonating in a clear spectral window at ca. 6 ppm) in the diastereoisomeric ester derivatives is typically ≥ 0.1 ppm anisochronous.[39,152] There are a few reports[119-127] of the use of chiral amines as CSAs in carboxylic acid analysis. Most use α-phenylethylamine, although improved $\Delta\delta_H$ values are found with the monomethylated amine analogue and with certain chiral diamines and amide

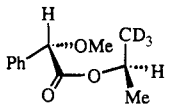
derivatives of (2S)-proline.[153] Chiral lanthanide shift reagents work poorly for carboxylic acids, but the derived *N,N*-dimethylamides are effective σ-donors to the lanthanon center and give good shift nonequivalence ($\Delta\delta_H \geq 0.1$ ppm, CCl_4, 298 K) on addition of a low molar percent of CLSR. The recent observation of large shift nonequivalence in dinuclear dicarboxyato complexes following addition of chiral carboxylates to the achiral complex $Pr(tpip)_3$ (**45**)[98] is a significant step forward. Carboxylic acid esters and lactones are much more amenable to analysis with CSLR,[13,14,127,155] and γ and δ lactones in particular are sensitive to investigation with 1-(9-anthryl)-2,2,2-trifluoroethanol.[17,141]

E. Alkenes, Alkynes, Allenes, and Arenes

It is particularly important to develop NMR methods for these compounds as chiroptical data are rather sparse and sometimes misleading.[3] A CLSR method using $Yb(hfc)_3$ in the presence of Ag(fod) has worked well for certain 1,3-disubstituted allenes,[117,118] chiral phenanthrenes,[113] and a number of simple alkenes e.g. limonene, and α-pinene.[113] Other efforts have used organometallic CDAs using either ^{31}P NMR with a chiral biphosphine complex of platinum(0) containing a displaceable ethene ligand, **38**,[81,82] or involve ^{195}Pt NMR and a chiral amine analog of Zeise's salt, **43**.[87,88] The insensitivity and chemical shift anisotropy of ^{195}Pt NMR render this a method for aficianados only. The ^{31}P NMR method is particularly suitable for chiral norbornenes, alkynes, enones and other η^2-donors with a relatively low-lying LUMO.

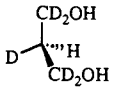
F. Compounds Chiral by Virtue of Isotopic Substitution

Compounds which owe their chirality to isotopic substitution are not amenable to chromatographic (GC and HPLC) methods of analysis. The analysis of such compounds is of particular interest to those involved in determining the stereochemical course of microbiological and enzymatic conversions. Classical approaches using chiroptical methods are difficult, owing to the weak circular dichroism spectra and the small optical rotations (even at shorter wavelength) involved. Although α-deuteriated benzylic alcohols may be assayed by using chiral shift reagents,[156] the method is not generally applicable and CDAs have proved much more useful. Following the early observations of Mislow,[157] who noted that the methyl doublets in **59** were 0.08



59

ppm ($CDCl_3$, 293 K) nonequivalent, Gerlach introduced (−)-(1*S*,4*R*)-camphanoyl chloride as a useful CDA for determining the enantiomeric purity of chiral α-deuteriated primary alcohols.[51,52] ^1H NMR analysis of the derived camphanate esters in the presence of $Eu(fod)_3$ gave well-separated resonances for the diastereotopic protons. In all cases examined the *pro-S*-hydrogen resonated to higher frequency of the *pro-R* permitting the assignment of absolute configuration. This postulation has been vindicated in many subsequent analyses.[158-161] The method extends to the analysis of α-deuteriated primary amines, both in the presence of added shift reagent,[162] e.g. for the analysis of (2*S*)-[2-^2H]glycine, and in its absence provided that benzene-d_6 is used as the NMR solvent.[39] For example in the analysis of [2,3-$^2H_2$]ethylamine, the spectrum of the derived camphanamide (C_6D_6, 298 K) reveals the *pro-R*- and *pro-S*-hydrogens to be 0.15 ppm anisochronous. Integration of the ^1H or ^2H NMR spectrum (Figure 15) gives a direct measure of enantiomeric composition.[39,58,59] α-Deuteriated alcohols may also be analyzed conveniently by analysis of the diastereoisomeric esters of (*S*)-acetylmandelic acid, formed by coupling with dicyclohexylcarbodiimide in the presence of 4-(dimethylamino)pyridine.[3]19 For a series of chiral α-deuteriated alcohols, $\Delta\delta_{H_S/H_R}$ was between 0.09 and 0.12 ppm, with the *pro-R*-hydrogen resonating consistently to lower frequency of the *pro-S*. Again a combined $^1H/^2H$ NMR analysis permits enantiomeric composition and absolute configuration to be accurately measured. This method has been applied to the determination of the enantiomeric purity of **60**, derived from (*R*)-[1-



60

$^{13}C_1$,2-$^2H_1$]malonate.[163] Reaction of enantiomerically enriched **60** with *O*-acetylmandelic acid gives the four esters **61–64**, with **61** and **62** derived from (*R*)-malonate. The diastereoisomeric sets (**61** + **62**) and (**63** + **64**) are distinguished by ^2H decoupling with simultaneous single-frequency ^{13}C decoupling of C_1 (the upper carbon). Irradiation of C_1 leaves H_A of **61** and H_B of **63** as doublets, but collapses H_B of **62** and H_A of **64** to singlets. The intensity ratio of these singlets gives the ratio of *R* to *S* malonate in the original mixture.

For the determination of the enantiomeric composition (and absolute configuration) of α-deuteriated

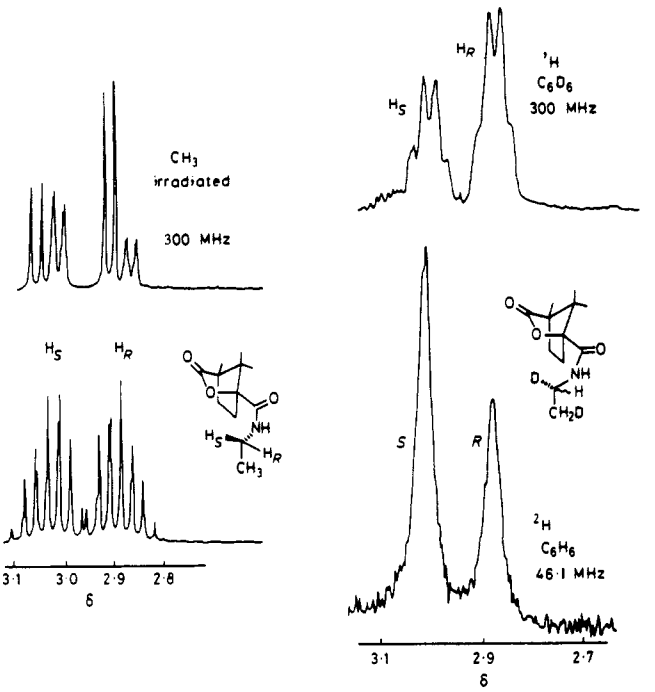
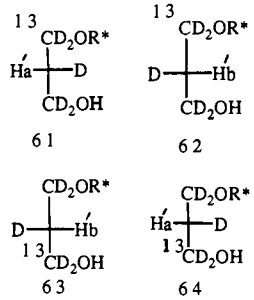
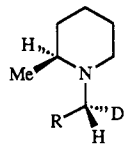


Figure 15. ^1H and ^2H NMR spectra of camphanamides (300 MHz, C_6D_6).[39]



61 62 63 64

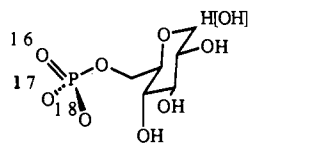
primary carboxylic acids, (*S*)-methyl mandelate is the preferred CDA.[39] In the mandelate esters, the *pro-S*-hydrogen resonates consistently about 0.1 ppm to lower frequency of the *pro-R* (C_6D_6) permitting ^1H and ^2H NMR analysis.[59,164] The ultimate application of NMR methods involves the analysis of chiral methyl groups (CHDT-X) using ^3H NMR spectroscopy.[165,166] In the molecule **65**, the geminal methylene protons of the CH_2D group are diastereotopic ($\Delta\delta$ = 0.014 ppm, CD_2Cl_2), allowing therefore analysis of the stereogenic methyl groups in **66** by tritium NMR analysis. The



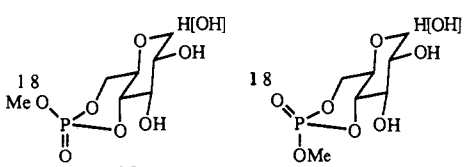
65 R= H

66 R = ^{3}H

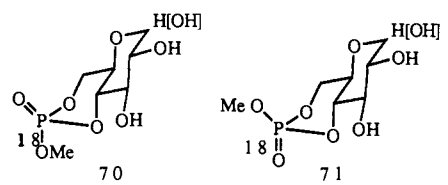
tritiun NMR method has permitted the assay of the enantiomeric purity of chiral acetic acid, $CHDTCO_2H$, which was converted into **66** by a Schmidt reaction (to the chiral methylamine) followed by ditosylation and S_N2 displacement of the NTs_2 leaving group by the enantiopure piperidine. This obviates the need for the more lengthy enzymatic methods devised by Cornforth and Arigoni which although more sensitive than the ^3H NMR method are certainly less accurate.[167,168] A ^3H NMR method of analysis has also been reported in distinguishing the diastereotopic methylene groups of a cephalosporin C derived form "chiral methyl valine".[169] The availability of the three stable isotopes of oxygen ^{16}O, ^{17}O, and ^{18}O has permitted the synthesis



67



68 69



70 71

of chiral phosphate esters.[170-174] These have been analyzed by ^{31}P NMR spectroscopy[170,173] as diastereoisomeric cyclic phosphate triesters, e.g. derived from D-glucose [(*S*)-^{16}O,^{17}O,^{18}O]phosphate and adenosine 5'-[(*S*)-^{16}O,^{17}O,^{18}O]phosphate. The critical factors in permitting the ^{31}P NMR analysis of these esters were that when ^{17}O is directly bound to phosphorus, the ^{31}P resonance is broadened so as to be unobserved and secondly that the size of the ^{18}O isotope effect is dependent on the nature of the P–O bond order: the isotope shift being greater the higher the bond order. Thus reaction of **67** (cyclization, esterification) yielded the cyclic esters **68–71** that may be distinguished by ^{31}P NMR. The axial triesters **68** and **71** are distinguished by the isotope shift (**71** contains P=^{18}O). The equatorial triesters **69** and **70** are similarly distinguished permitting an analysis of chiral phosphate absolute configuration and enantiomeric purity from the ^{31}P NMR spectrum.

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