DIRECT ^{1}H NMR ASSAY OF THE ENANTIOMERIC COMPOSITION OF AMINES AND β-AMINO
ALCOHOLS USING O-ACETYL MANDELIC ACID AS A CHIRAL SOLVATING AGENT

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Abstract – The chiral solvating agent (R)-O-Acetyl Mandelic Acid (ROAM)
is an effective agent for the direct ^{1}H NMR assay of the enantiomeric
composition of amines and amino-alcohols.

The continued interest in asymmetric synthesis and the more stringent demands,
within the pharmaceutical industry, for licensing drugs of known enantiomeric
composition has stimulated the need for accurate methods for the determination of
enantiomeric purity. Non-chiroptical methods rely upon the formation of
diastereoisomeric derivatives or complexes for analysis by multinuclear NMR or
chromatography. The NMR methods either involve use of a chiral derivatising
agent,[1] chiral shift reagent,[2] or chiral solvating agent[3] in order that chemical
shift non-equivalence may be observed in the diastereoisomeric species. Although
substantial developments have been made in these methods, further improvements are
still needed for *in situ* NMR methods for determining the enantiomeric composition
of amines and β-amino alcohols. The latter group of compounds are important α and
β-adrenoreceptor blockers for which a precise knowledge of enantiomeric purity is
critical. The preparatory drug 'Propranalol',4 for example, is a β-amino alcohol
in which the S enantiomer acts as a 'β-blocker' while the R isomer may function as
a contraceptive. There have been some preliminary reports discussing the potential
of using the NMR properties of diastereoisomeric salts for assaying acids[4] and
amines.[5] We herein report the use of (R)-O-acetyl mandelic acid (R)-OAM as a
convenient chiral solvating agent. It forms soluble diastereisomeric salts with a
wide range of amines and amino-alcohols, permitting a direct measure of their
enantiomeric composition.

In a typical experiment, the amine or amino-alcohol (0.05 mmol.) and (S) or
(R)OAM(0.06 mmol.) are dissolved in CDCl$_3$ or C$_6$D$_6$ and their ^{1}H NMR spectrum
recorded. In these non-polar solvents, proton transfer is essentially complete
and in the resultant diastereoisomeric salts ^{1}H NMR chemical shift non-equivalence
is observed for one or more of the solvate resonances proximate to the nitrogen.
The compounds investigated, 1-10, are shown above and the NMR data are collated in
Table 1. Using mixtures of 1-3 and 7-10 of pre-determined enantiomeric
composition, an excellent agreement (±1%) between known composition and NMR
determined values was obtained. A typical set of ^{1}H NMR spectra are shown in
Figure 1 for salts of 3 and (R)-OAM, observing the α C-H proton of 3. The chemical
shift difference between anisochronous resonances is sufficient to permit direct
integration, and the method is intrinsically sensitive. Using a commercially
available sample of S-(-)α-methylbenzylamine (Aldrich 11, 556-8), it was possible
to measure the percentage of the residual (R) enantiomer as 2% (Δδ(CDCl$_3$)298 K =
0.182 ppm, using (S)-OAM). Therefore the sample was 96% enantiomerically pure.
The detection limit of this method is set by the signal to noise limit of the
FTNMR spectrometer used.

The spectra were typically observed in benzene-d$_6$, although in certain cases
addition of pyridine-d$_5$ ensured that the salts remained in solution. For a given
solute, the magnitude of the shift non-equivalence was always greater than that
observed using (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) or
R-mandelic acid as a solvating agent.[5] Moreover, these other agents tend to form

Table 1. Chemical Shift Non-Equivalence for the ($\underline{S}$)-OAM Salts of
Racemic Chiral Amines and β-Amino Alcohols, $\underline{1}$-$\underline{10}$[a]

Compound	Resonance Observed	Δδ (ppm)	Solvent
$\underline{1}$	CH_3	0.063	C_6D_6
	CH	0.075	C_6D_6
$\underline{2}$	CH_3	0.058	C_6D_6
	CH	0.061	
$\underline{3}$	CH_3	0.102	C_6D_6
	CH	0.142	C_6D_6
$\underline{4}$[b,d]	CH	0.017	$C_5D_5N/C_6D_6(1:1)$
$\underline{5}$[c]	CH_2	0.017	C_5D_5N
$\underline{6}$[d]	CH	0.018	C_6D_6
$\underline{7}$[b]	NCH_3	0.060	$CDCl_3$
$\underline{8}$	NCH_3	0.040	C_6D_6
$\underline{9}$	CH_3	0.053	
	CH	0.020	$C_6D_6/C_5D_5N(2:1)$
$\underline{10}$	CH_3	0.021	$C_6D_6/C_5D_5N(2:1)$

[a] Spectra were recorded at 298 K and 250 MHz.
[b] Using ($\underline{R}$)-OAM.
[c] Simplified by simultaneous irradiation of the adjacent CH.
[d] Simplified by simultaneous irradiation of adjacent CH_2.

1

2

3

'propranalol'
4

'salbutamol'
5
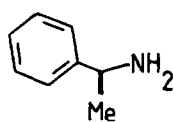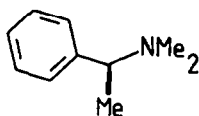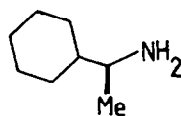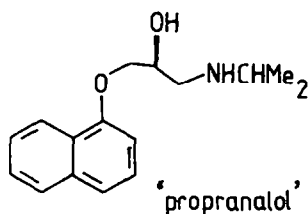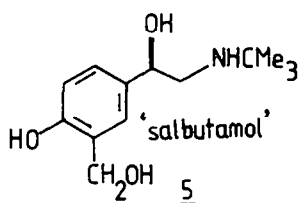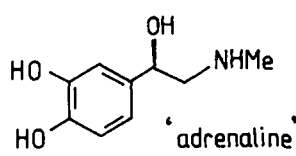
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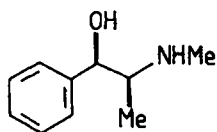
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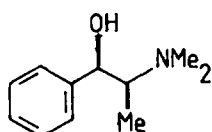
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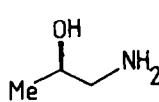
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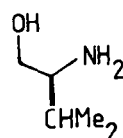
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diastereoisomeric salts, which are often
soluble only in polar solvents (methanol,
dimethylsulphoxide) in which the ion-pairs
are solvent separated and $\Delta\delta$ tends to zero.

By observing the sense of chemical
shift non-equivalence for a range of known
enantiomeric compositions, the absolute
configuration of the solute may be
correlated with chemical shift. This
information may then be used to assign the
absolute configuration of the solute,
within a related series of compounds. The
sense of the shift non-equivalence is the
same, for example, for 1, 2 and 3 and for
7 and 8. Such observations concur with
similar findings in other diastereo-
isomeric salt systems,[5] although the
related series should be cautiously
defined.

The magnitude of the observed non-
equivalence, $\Delta\delta$, is a complex function of
solvating agent and solute structure,
solvent, temperature and in certain cases
solute enantiomeric composition. The
solvating agent (R)-OAM incorporates
anisotropic phenyl and carbonyl function-
ality which are desirable elements for
optimizing chemical shift non-
equivalence.[3,6] The temperature variation
of $\Delta\delta$ has been examined more closely for
(R)-OAM and compound 1 in CDCl$_3$, and is
illustrated in Figure 2. There are two
factors contributing to the observed
temperature dependence. As the temperature
is lowered, there will be a preferential
population of specific lower energy con-
formations. With compound 1, as tempera-
ture decreases the methyl group doublet due
to [(S)-1]$^+$[R-OAM]$^-$ shifts to lower
frequency relative to all other resonances
indicating that, on average, this group
spends more time in a magnetically shielded
environment. The relative shift of the
methyl doublet in [(R)-1]$^+$[R-OAM]$^-$ remains
approximately constant, however. Such
behaviour, which has been defined previously
in related systems,[6] accounts for the linear
dependence of $\Delta\delta$ with temperature in the
range 248-288 K. Above 288 K, $\Delta\delta$ tends to a
limit, representing the intrinsic shift
non-equivalence of the two diastereoisomeric
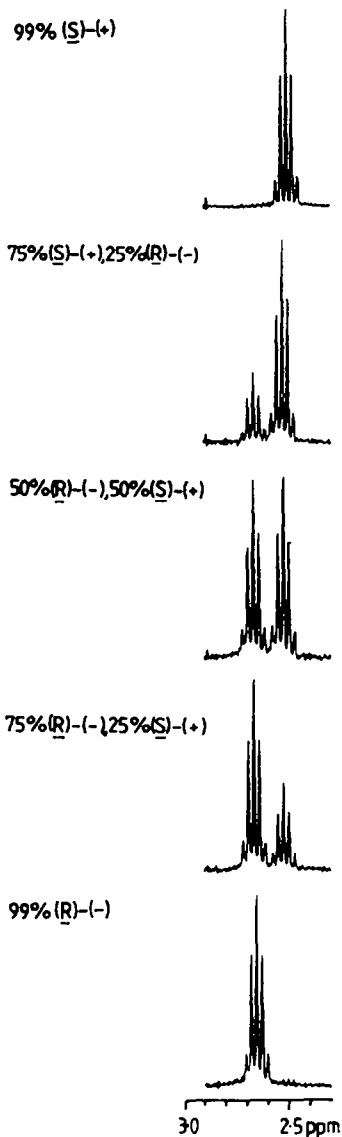complexes. Although lowering the temperature

99% (S)-(+)

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

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

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

99% (R)-(-)

3·0   2·5 ppm

Fig. 1. ^{1}H NMR spectra (298 K,
C$_6$D$_6$) for diastereoisomeric
complexes of 3 with (R)-OAM,
observing the CH proton in 3 as
a function of enantiomeric
composition.

restricts the solvent choice, it is a useful method for those systems where Δδ may be very small at room temperature. In the case of 1 with (R)-OAM, Δδ was also sensitive to the enantiomeric composition of the solute (Table 2). Indeed there is a linear dependence between Δδ and enantiomeric composition, which is mirrored in the behaviour of the [1/(S)-OAM] system. Such behaviour has been reported previously[4] and is consistent with a minimal degree of ion-pair aggregation in the concentration range studied (0.002 to 0.1 M). It may be attributed to an inequality of the dissociation constants for the two diastereoisomeric complexes. Although this effect was only observed with 1 as a solute (and may be associated with systems showing the non-linear temperature dependence observed in Figure 2) Δδ may be maximised by the choice of R or S-OAM as the solvating agent.

In conclusion, the commercially available solvating agents (R)-OAM and (S)-OAM are convenient, accurate and effective solvating agents for the _in situ_ NMR determination of the enantiomeric purity of chiral amino-alcohols and amines. They are to be preferred over mandelic acid or MTPA, and will augment the use of chiral shift or derivatising agents for these analyses.

Table 2. Variation of Chemical Shift Non-Equivalence with Enantiomeric Composition and Solvent for the OAM Salts of 1

Enantiomeric Composition of 1%	Solvent (298 K)	Δδ (ppm)
75 R, 25 S[a]	C_6D_6	0.130
	$CDCl_3$	0.140
50 R, 50 R[a]	C_6D_6	0.097
	$CDCl_3$	0.096
25 R, 75 S[a]	C_6D_6	0.066
	$CDCl_3$	0.054
75 R, 25 S[b]	$CDCl_3$	0.050
50 R, 50 S[b]	$CDCl_3$	0.094
25 R, 75 S[b]	$CDCl_3$	0.140

[a] Using (R)-OAM

[b] Using (S)-OAM

EXPERIMENTAL

Proton NMR spectra were recorded on a Bruker AC-250 (250.13 MHz) spectrometer. The temperature was maintained at ±1°C using the Bruker temperature unit, previously calibrated using 100% methanol. The limit of detection for the assay of enantiomeric purity using this method was determined to be < 1%.
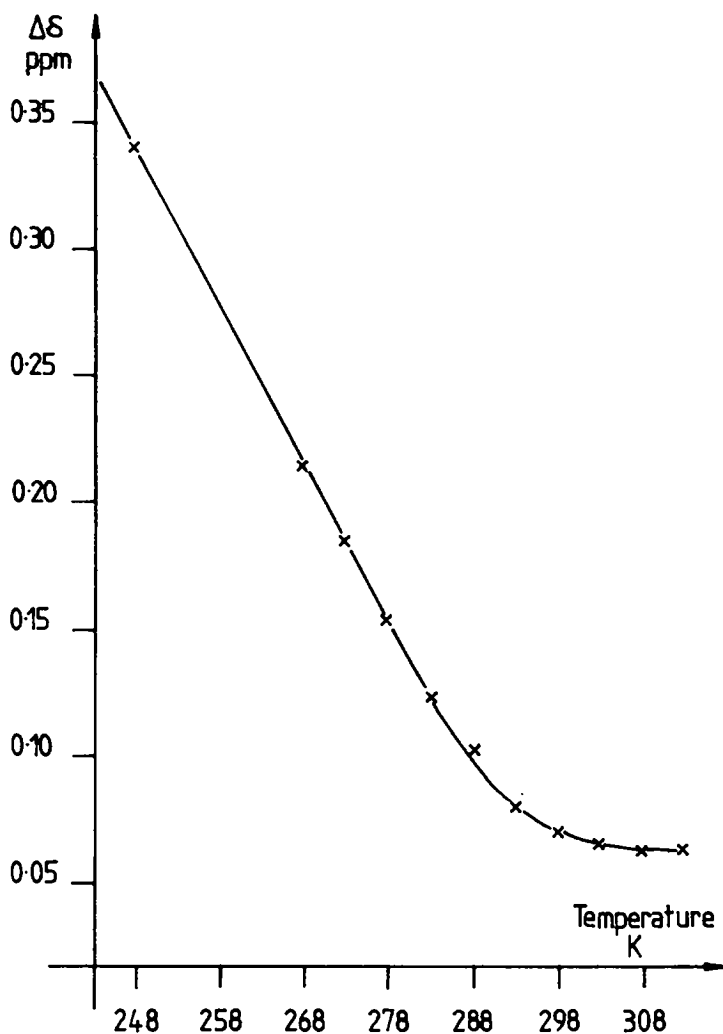
Fig. 2. Temperature Variation of Δδ for (R)-OAM and (±)1 (250 MHz,CDCl₃).

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