Chapter 2

Studies on application of chiral $C_2$-symmetric 1,2-diamines as chiral solvating agents
2.1 Introduction

The utility of enantiomerically pure trans-1,2-diaminocyclohexane derivatives as chiral reagents and ligands in the field of asymmetric synthesis has been described in the introductory section of Chapter 1. We have made efforts to explore the application of various chiral diamines containing enantiomerically pure trans-1,2-diaminocyclohexane moiety prepared via the method described in Chapter 1, for application as chiral solvating agents for carboxylic acids. A brief review of the available reports on these topics will be helpful for discussion.

2.1.1 Enantiomeric recognition of chiral compounds by synthetic receptors

In view of the importance of chiral organic compounds in biological and pharmaceutical chemistry,1-4 there is increasing requirement for fast and accurate methodologies for the determination of the enantiomeric composition of these chiral compounds. Among the various available methods, NMR spectroscopy has the advantages of easy performance and accessibility5 with no need for special equipment apart from the common NMR spectrometers. As enantiomers cannot be distinguished in an achiral environment, these techniques require the modification of the substrate with a chiral auxiliary, which would convert the mixture of enantiomers into a mixture of diastereomeric molecular (covalent, chiral derivatizing agent, CDA) or supramolecular (non-covalent, chiral solvating agents, CSA) complexes.6 Ideally, these diastereomeric species show chemical shift non-equivalence of some of their NMR signals, allowing the determination of the enantiomeric composition of the substrate by the direct integration of these bands.7 The advantage of using non-covalent chiral solvating agents
relies on the possibility of carrying out the experiment *in situ*, without purification steps.\textsuperscript{8,9} Besides the starting chiral materials, analytes and CSA could be easily recovered after the measurement.

The first realization of this phenomenon was reported by Pirkle,\textsuperscript{10} who observed separate $^{19}$F NMR resonances for the enantiomers of (trifluoromethyl)phenylcarbinol in optically active 1-phenylethylamine solvent. This technique has recently emerged as a facile alternative for determining enantiomeric purity and absolute configuration. A brief review of the available reports will be helpful for the discussion.

### 2.1.1.1 Chiral acyclic amine derivatives as chiral solvating agents

The enantiomeric recognition by acyclic chiral amine derivatives as chiral solvating agents has been extensively studied by the $^1$H NMR spectroscopy. Salvadori *et al.*\textsuperscript{11} reported the use of quinine 1 as a chiral solvating agent for the enantiomeric purity determination of binaphthyl derivatives 2 and alkylarylcarbinols 3 by $^1$H and $^{19}$F-NMR spectroscopy.

Later, the same group demonstrated the use of quinine 1 as a chiral solvating agent for the enantiomeric purity determination of $\beta$-hydroxyesters 4.\textsuperscript{12}
In 2003, the same group synthesized the simple carbamate derivatives of quinine 5, by derivatization of the double bond, which behaves as chiral solvating agent for acids, alcohols, amine derivatives and for very simple amino acid derivatives.  

The use of (4S,5S)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxan 6 (ADPD) and (4R,5R)-5-amino-(4'-biphenyl)-2,2-dimethyl-1,3-dioxan 7 (ABDD) as chiral solvating agents for the enantiomeric purity determination of compounds bearing an acidic proton by means of $^1$H NMR spectroscopy was demonstrated.

A three step synthesis of (S)-2-(diphenylmethyl)pyrrolidine 11 (Scheme 1) and its use as a chiral solvating agent for the enantiomeric excess determination of chiral carboxylic acids such as 3-phenylbutyric, 2-bromopropionic, mandelic, 2-phenoxypropionic, 2-phenylpropionic acids and Mosher’s acid was reported.
A fast, direct and routine method has been developed for the measurement of the enantiomeric composition of imidazolinone herbicides (nicotinic and quinolinic carboxylic acid compounds) 13 and 14 containing a free carboxylic acid group, by using (R,R)-1,2-diphenylethane-1,2-diamine 12 as a chiral solvating agent.\(^6\)

Two flexible receptors 15 and 16 for carboxylic acids, based on 1-amino-3-fluoro-2-alcohol functional arrays and built on aminomethylpyridine platforms have been described.\(^7\) The \(C_2\)-symmetric compound 16 has been shown to be an efficient CSA due to its ability to form geometrically different diastereomeric complexes enabling the discrimination between the enantiomers of a series of carboxylic acids 17-26 in their \(^1\)H NMR spectra.
A series of compounds 29-31 have been synthesized from \((R,R)\)-1,2-diaminocyclohexane 27 (Scheme 2), which exhibited better enantiodiscriminating ability toward a variety of chiral carboxylic acids such as naproxen, ibuprofen, ketoprofen, phthalyl alanine and amino acid derivatives.\(^1\)\(^8\)

**Scheme 2**

The diastereomeric chiral auxiliaries 32a and 32b were synthesized from \((S)\)-\(\alpha\)-phenylethylamine (PEA).\(^1\)\(^9\) Compared to \((S)\)-PEA, these new chiral auxiliaries 32a and 32b have been proved to be efficient chiral NMR solvating agents for the carboxylic acids 33-36.
The compounds 37 and 38 were synthesized from natural amino acids and 1,8-naphthalic anhydride which were found to be effective chiral solvating agents for chiral α-arylalkylamines 39 and 40.20

Several chiral amino alcohols 41-43 were synthesized starting from natural amino acids, which have been shown to be efficient CSAs for the determination of enantiomeric composition of chiral carboxylic acids.21
In 2008, a family of pincer-like receptors 44-48 have been synthesized and tested as efficient CSA for different chiral carboxylic acids.\textsuperscript{22}

![Chemical structures](image)

The P(III) and P(V) organophosphorus derivatizing agents (A, B, C) prepared from $C_2$-symmetric (1R,2R)- and (1S,2S)-trans-$N,N'$-bis-[[(S)-$\alpha$-phenylethyl]-cyclohexane-1,2-diamines 49 and 50, as well as (1R,2R)- and (1S,2S)-trans-$N,N'$-bis-[[(S)-$\alpha$-phenylethyl]-4-cyclohexene-1,2-diamines 51 and 52 were used for the determination of enantiomeric composition of chiral carboxylic acids by $^{31}$P NMR (Scheme 3).\textsuperscript{23}

**Scheme 3**

![Chemical structures](image)

A bis-imidazoline compound 53 starting from isophthalaldehyde and (S,S)-1,2-diphenylethylene-1,2,-diamine was synthesized and used as a chiral solvating agent for
carboxylic acids.\textsuperscript{24} In the presence of one equivalent of this reagent, carboxylic acid racemates show \textsuperscript{1}H NMR chemical shift non-equivalences large enough for the discrimination of the enantiomers.

![Chemical structures](image)

Recently, from this laboratory the chiral methoxy Tröger’s base 55 and the corresponding $\alpha,\alpha'$-diphenyl carbinol derivative 56 have been reported to exhibit good chiral recognition ability towards carboxylic acids.\textsuperscript{25}

![Chemical structures](image)

2.1.1.2 Chiral macrocyclic amine derivatives as chiral solvating agents

Chiral macrocyclic compounds have been demonstrated to be very effective in enantiomeric recognitions by NMR spectroscopy. For instance, Fu \textit{et al}.\textsuperscript{26} synthesized the L-proline derived chiral macrocyclic dioxopolyamines 57 and 58, which exhibited
chiral recognition toward the enantiomers of racemic carboxylic acids like substituted
mandelic acids and dibenzoyltartaric acid.

\[
\begin{align*}
\text{57} & \quad \text{58} & \quad \text{59} : R = \text{CH}_2\text{COOcholesteryl} \\
\text{60} & \quad \text{61} & \quad \text{62} & \quad \text{63} & \quad \text{64}
\end{align*}
\]

The use of the chiral triazole-18-crown-6-ligands 59 and 60 with lipophilic side
arms, for the chiral recognition of the enantiomers of [1-(1-naphthyl)ethyl]ammonium
cation and [1-phenylethyl]ammonium cation has been reported.\textsuperscript{27} The (S,S) chiral host
recognizes preferentially the (R)-enantiomer of the ammonium salt over the (S) enantiomer.

In 2006, the use of an azamacrocyclic receptor 61 as a chiral solvating agent for
the determination of enantiomeric excess of different carboxylic acids 62-64 was
demonstrated.\textsuperscript{28}

\[
\begin{align*}
\text{62} & \quad \text{63} & \quad \text{64}
\end{align*}
\]

The use of chiral macrocyclic polyamides 65-67 derived from L/D-tartaric acid
as chiral solvating agents towards carboxylic acids has been investigated.\textsuperscript{29} All the
macrocycles exhibited ability to recognise enantiomers of racemic carboxylic acids like
mandelic acid derivatives and dibenzoyltartaric acid.
In 2007, Ma and coworkers\textsuperscript{30} synthesized a novel chiral macrocyclic compound 70 from $C_2$-symmetric aminonaphthol 68 (Scheme 4), followed by the synthesis of similar macrocyclic compounds\textsuperscript{31} 71 and 72 that shows excellent ability to discriminate the enantiomers of a broad variety of carboxylic acids such as mandelic acid derivatives and aminoacid derivatives by $^1$H NMR spectroscopy. The same group also reported these macrocyclic compounds 71 and 72 as chiral solvating agents for phosphinic, phosphonic, and phosphoric acids by $^1$H NMR and $^{31}$P NMR spectroscopy.\textsuperscript{32}

Scheme 4

NMR studies of the bifunctional macrocycles 73-76 demonstrated that, among them, the receptor ($R$)-73 functions as the best chiral solvating solvent for a wide range of chiral compounds having a carboxyl group, oxazolidinone, carbonate, lactone, alcohol, sulfoxide, sulfoximine, sulfinamide, isocyanate and epoxide functionality.\textsuperscript{33}
Tanaka et al.\textsuperscript{34} reported that the chiral macrocyclic amines 77 and 78 function as highly sensitive chiral shift reagents for several kind of secondary alcohols, cyanohydrins and propargyl alcohols.

However, these macrocycles are not useful as chiral shift reagents for carboxylic acids for multiple binding with the carboxylic acids without the introduction of both hydrogen bond acceptor and donor group in the host macrocycles.\textsuperscript{34} Another calixarene-like chiral amine macrocycle 79 containing both hydrogen bond acceptor (NH) and donor group (OH), which functions as a new chiral shift reagent for the determination of
the enantiomeric excess and absolute configuration of several kinds of carboxylic acid and amino acid derivatives has been reported.\textsuperscript{35}

During research efforts from this laboratory on the synthesis and application of chiral macrocycles\textsuperscript{36} 80-82, it was found that they are efficient chiral solvating agent for the determination of enantiomeric excess of carboxylic acids 85 and 86 by \textsuperscript{1}H NMR spectroscopy.\textsuperscript{37}
In continuation of our research efforts toward the synthesis of chiral \( N \)-alkylated \( C_2 \)-symmetric diamines containing \((R,R)\)-trans-1,2-diaminocyclohexane moiety\(^{38}\) as discussed in Chapter 1, we have examined the use of some of these derivatives as chiral solvating agents for the determination of enantiomeric excess of carboxylic acids and amino acid derivatives by \(^1\)H NMR spectroscopy. The results are discussed in the next section 2.2.
2.2 Results and Discussion

2.2.1. Application of chiral \( C_2 \)-symmetric diamines as chiral solvating agents for carboxylic acids

As discussed in the introductory section 2.1, chiral macrocyclic as well as acyclic amines are useful in chiral recognition studies. Accordingly, we have examined the application of the readily accessible chiral \( N \)-alkylated \( C_2 \)-symmetric diamines 83 and 84 (Chapter 1, Section 1.2) for the enantiomeric recognition of carboxylic acids. It was expected that the presence of the protonable chiral amine groups would lead to the formation of corresponding diastereomeric salts with the enantiomers of carboxylic acids.\(^{39}\) As a result, the methine proton (\( C^α \)H) signal of the carboxylic acids is expected to split. Accordingly, we have evaluated the chiral recognition ability of the secondary amines 83 and 84 towards the carboxylic acids 85-92 (Figure 1) by \(^1\)H-NMR spectroscopy.

![Structural formulas of receptor amines and carboxylic acids](image)

**Figure 1.** Structures of the receptor amines 83-84 and carboxylic acids 85-92
Initially, the $^1$H NMR experiments were carried out by incrementally adding solution of racemic mandelic acid 85 in CDCl$_3$ (2.5 mM) to a solution of chiral amine 83 in CDCl$_3$ (2.5 mM). Immediately after each addition, the $^1$H NMR spectrum was acquired in a 400 MHz spectrometer at 25 °C. Due to the difference in the interaction of the enantiomers of carboxylic acids with chiral amines, the methine proton (C$^\alpha$H) of mandelic acid 85, 2,3-diphenylsuccinic acids 86 and N-Ts-phenylglycine 89 were split into two singlets. The splitting values between methine proton (C$^\alpha$H) signals corresponding to each enantiomer of acid 85 ($\Delta\Delta\delta$), after addition of the receptor 83 with different molar ratio, are summarized in Table 1.

**Table 1. Measurement of the chemical shift non-equivalence ($\Delta\Delta\delta$) of the mandelic acid 85 in the presence of chiral amine receptor (1R,2R,1'R,1''R)-83 by $^1$H NMR spectroscopy (400 MHz) in CDCl$_3$ with different amine:acid molar ratio$^a$**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine 83:Acid 85</th>
<th>$\Delta\Delta\delta$ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1: 1.6</td>
<td>13.2</td>
</tr>
<tr>
<td>2</td>
<td>1: 1.8</td>
<td>13.6</td>
</tr>
<tr>
<td>3</td>
<td>1:1.9</td>
<td>15.2</td>
</tr>
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<td>4</td>
<td>1:2.0</td>
<td>16.4</td>
</tr>
<tr>
<td>5</td>
<td>1:2.5</td>
<td>17.2</td>
</tr>
<tr>
<td>6</td>
<td>1:2.8</td>
<td>17.8</td>
</tr>
<tr>
<td>7</td>
<td>1:3.0</td>
<td>18.0</td>
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<tr>
<td>8</td>
<td>1:3.5</td>
<td>17.2</td>
</tr>
<tr>
<td>9</td>
<td>1:4.0</td>
<td>16.8</td>
</tr>
<tr>
<td>10$^b$</td>
<td>1:3.0</td>
<td>16.0</td>
</tr>
</tbody>
</table>

$^a$Typical conditions: concentration of the acid and the receptor was 2.5 mM in 0.5 mL of CDCl$_3$, and the spectra were recorded at 25 °C.

$^b$Sample in the NMR tube was subjected to ultra sonication for 30 min. and the spectrum was recorded at 25 °C.
When the receptor amine 83 to mandelic acid 85 molar ratio is 1:3, maximum non-equivalence (18.0 Hz) of the C^αH proton of the acid was observed at 2.5 mM of total molar concentration (Table 1, entry 7). When the same sample was subjected to ultra sonication for 30 min, ΔΔδ decreases from 18.0 Hz to 16.0 Hz (Table 1, entry 10). We have observed that increase or decrease in the molar ratio between amine 83 and mandelic acid 85 from 1:3, the non-equivalences of the C^αH proton of the acid 85 decreases (Table 1).

According to the theory of chemical equilibrium, upon increasing the concentration of reactants, mole fraction decreases for a combination reaction. So, it can be predicted that at a larger concentration of reactants, the fractional population of free acid will be smaller and the chemical shift non-equivalence (ΔΔδ) would be larger. Accordingly, in the presence of receptor 83, the chemical shift non-equivalences (ΔΔδ) of the strong acid 85 increases from 18.0 Hz to 53.6 Hz, as the total molar concentration increases from 2.5 mM to 100 mM (Table 2).

**Table 2. Concentration variation of ¹H NMR chemical shift non-equivalence (ΔΔδ) of acid 85 in the presence of receptor amine 83 with amine:acid molar ratio of 1:3**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Total molar conc. (mM)</th>
<th>ΔΔδ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>20.4</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>37.6</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>41.2</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>53.6</td>
</tr>
</tbody>
</table>
Table 3. Measurement of the chemical shift non-equivalences ($\Delta\Delta\delta$) of the racemic acids 85-92 in the presence of chiral amine receptor ($1R,2R,1'R,1''R$)-83 by $^1$H NMR spectroscopy (400 MHz) in CDCl$_3$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Proton</th>
<th>Amine:Acid</th>
<th>$\Delta\Delta\delta$ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>COOH</td>
<td>$\alpha$-H</td>
<td>1:3</td>
<td>53.6</td>
</tr>
<tr>
<td>2</td>
<td>HOOC</td>
<td>$\alpha$-H</td>
<td>1:1</td>
<td>69.0</td>
</tr>
<tr>
<td>3</td>
<td>COOH</td>
<td>$\alpha$-H</td>
<td>1:1-1:3</td>
<td>0.0</td>
</tr>
<tr>
<td>4</td>
<td>NHTs COOH</td>
<td>$\alpha$-H</td>
<td>CH$_3$(Ts)</td>
<td>0.0</td>
</tr>
<tr>
<td>5</td>
<td>NHTs Ph CO$_2$H</td>
<td>$\alpha$-H</td>
<td>CH$_3$(Ts)</td>
<td>1:3</td>
</tr>
<tr>
<td>6</td>
<td>NHTs Ph COOH</td>
<td>$\alpha$-H</td>
<td>CH$_3$(Ts)</td>
<td>1:1-1:3</td>
</tr>
<tr>
<td>7</td>
<td>COOH</td>
<td>$\alpha$-H</td>
<td>1:1-1:3</td>
<td>0.0</td>
</tr>
<tr>
<td>8</td>
<td>COOH</td>
<td>$\alpha$-H</td>
<td>1:1-1:3</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Typical conditions: concentration of the acid and the receptor amine 83 was 100 mM in 0.5 mL of CDCl$_3$ and the spectra were recorded at 25 ºC*
Then, we examined the chiral recognition ability of chiral amine (1\(R\),2\(R\),1'\(R\),1''\(R\))-83 towards different racemic carboxylic acids 85-92 at 100 mM concentration. The maximum chemical shift non-equivalence (\(\Delta\Delta\delta\)) observed at different amine:acid molar ratio is summarized in Table 3. In the presence of receptor amine 83, the chemical shift non-equivalences of at least one of the protons of acids 85, 86 and 89 are large enough to give base line resolution on a 400 MHz NMR spectrometer at 25 °C.

When the receptor amine 83 to mandelic acid 85 ratio was 1:3, maximum non-equivalence of the C\(^\alpha\)H proton (53.6 Hz) was obtained (Table 3, entry 1). A partial \(^1\)H NMR spectrum of the racemic mandelic acid 85 in the presence of chiral amine receptor 83 is shown in Figure 2. In the case of 2,3-diphenylsuccinic acid 86, the maximum non-equivalence of the C\(^\alpha\)H proton (69.0 Hz) was observed at amine to acid molar ratio of 1:1 (Table 3, entry 2).

When the amine 83 to N-Ts-phenylglycine 89 ratio was 1:3, excellent non-equivalence of the C\(^\alpha\)H proton (118.0 Hz) was obtained (Table 3, entry 5). In this case, the NH proton also shows good non-equivalence (68.7 Hz), whereas the CH\(_3\) (Ts) proton shows poor non-equivalence might be due to the presence of CH\(_3\) group far away from the chiral centre. A partial \(^1\)H NMR spectrum of the racemic N-Ts-phenylglycine 89 in the presence of chiral amine receptor (1\(R\),2\(R\),1'\(R\),1''\(R\))-83 is shown in Figure 3.

In the case of racemic carboxylic acids 87, 88, 90, 91 and 92 the splitting of the corresponding C\(^\alpha\)H proton was not observed. Presumably, the presence of bulky groups
attached to the CαH proton centre may disturb the interaction between the chiral amine 83 and the racemic carboxylic acids.

**Figure 2.** Partial 1H NMR spectrum of racemic mandelic acid 85 in the presence of chiral amine receptor 83

![NMR spectrum](image)

**Figure 3.** Partial 1H NMR spectra showing CαH and NH signals for the racemic N-Ts-phenylglycine 89 (100 mM, CDCl3, 400 MHz, 25 °C) (a) in the absence and (b) in the presence of 0.33 equiv. of (1R,2R,1'R,1''R)-83

![NMR spectra](image)

Then, we examined the chiral recognition ability of chiral amine 84 towards different racemic carboxylic acids 85-92 at 100 mM concentration. Maximum chemical shift non-equivalence (ΔΔδ) observed at different amine:acid molar ratio is summarized in Table 4. When the receptor amine 84 to mandelic acid 85 ratio was 1:2.3, maximum non-equivalence of the CαH proton (48.0 Hz) was obtained (Table 4, entry 1). In the
case of 2,3-diphenylsuccinic acid 86, maximum non-equivalence of the C\textsuperscript{α}H proton (55.2 Hz) was obtained at amine:acid molar ratio of 1:2 (Table 4, entry 2).

Table 4. Measurement of the chemical shift non-equivalences (ΔΔδ) of the racemic acids 85-92 in the presence of chiral receptor amine (1\textit{R},2\textit{R},1'\textit{R},1''\textit{R})-84 by \textsuperscript{1}H NMR spectroscopy (400 MHz) in CDCl\textsubscript{3}\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Proton</th>
<th>Amine:Acid</th>
<th>ΔΔδ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>COOH</td>
<td>α-H</td>
<td>1:2.3</td>
<td>48.0</td>
</tr>
<tr>
<td>2</td>
<td>HOOC</td>
<td>α-H</td>
<td>1:2</td>
<td>55.2</td>
</tr>
<tr>
<td>3</td>
<td>COOH</td>
<td>α-H</td>
<td>1:1-1:3</td>
<td>0.0</td>
</tr>
<tr>
<td>4</td>
<td>COOH</td>
<td>α-H</td>
<td>CH\textsubscript{3}(Ts)</td>
<td>0.0</td>
</tr>
<tr>
<td>5</td>
<td>COOH</td>
<td>α-H</td>
<td>CH\textsubscript{3}(Ts)</td>
<td>1:3</td>
</tr>
<tr>
<td>6</td>
<td>COOH</td>
<td>α-H</td>
<td>CH\textsubscript{3}(Ts)</td>
<td>1:1-1:3</td>
</tr>
<tr>
<td>7</td>
<td>COOH</td>
<td>α-H</td>
<td>1:1-1:3</td>
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<tr>
<td>8</td>
<td>COOH</td>
<td>α-H</td>
<td>1:1-1:3</td>
<td>0.0</td>
</tr>
</tbody>
</table>
aTypical conditions: concentration of the acid and the receptor amine 84 was 100 mM in 0.5 mL of CDCl₃ and the spectra were recorded at 25 °C.

A partial ¹H NMR spectrum of the racemic 2,3-diphenylsuccinic acid 86 in the presence of chiral amine (1R,2R,1′R,1″R)-84 is shown in Figure 4.

Figure 4. Partial ¹H-NMR spectrum of racemic 2,3-diphenylsuccinic acid 86 in the presence of chiral amine (1R,2R,1′R,1″R)-84

When the receptor amine 84 to N-Ts-phenylglycine 89 ratio was 1:3, maximum non-equivalence of the CαH proton (28.6 Hz) was observed (Table 4, entry 5), which shows less splitting compared to that observed by using chiral amine 86 (Table 3, entry 5).

For racemic carboxylic acids 87, 88, 90, 91 and 92, the splitting of the corresponding CαH proton was not observed (Table 4), might be due to the presence of bulky groups attached to the CαH proton centre which may disturb the interaction between chiral amine 84 and the racemic carboxylic acids as observed in the case of the amine 83 (Table 3).

Some interesting observations have been made during these studies. First of all, the signals from the acids move upfield (Δδ<0), suggesting a deprotonation of carboxylic group. Only, the NH proton from N-Ts-phenylglycine 89 resonates at lower field upon addition of the receptor, which can be interpreted as formation of a stronger intramolecular hydrogen bond with the carboxylate anion thus formed. Concomitantly,
signals from the receptor move downfield, which clearly indicates the proton transfer from the acid to the receptor, leading to the corresponding diastereomeric salts. These salts are expected to form intimate ionic pairs in CDCl₃.

The stoichiometry of the complex formed between the amine 83 and mandelic acid 85 was evaluated by carrying out the Job’s titration between the amine 83 and both (R)- and (S)-mandelic acids in different ratios. The product ($\Delta \delta X$) of the difference in chemical shift ($\Delta \delta$) and the mole fraction of the acid (X) was plotted against the mole fraction of the acid to obtain the Job’s plot (Table 5, Figure 5). A maximum was observed when the mole fraction of the (R) or (S)-mandelic acid was 0.75, indicating that the amine 83 forms a 1:3 complex with (R) or (S)-mandelic acid 85. From the plot (Figure 5), it is evident that the chemical shift changes of the (S)-mandelic acid is greater when compared to the (R)-mandelic acid.

**Table 5. Job’s plot of the chiral amine 83 with (R) and (S)-mandelic acids 85**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mole fraction of the acid 85 (X)</th>
<th>(S)-Mandelic acid 85</th>
<th>(R)-Mandelic acid 85</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\Delta \delta$</td>
<td>$\Delta \delta X$</td>
<td>$\Delta \delta$</td>
</tr>
<tr>
<td>1</td>
<td>0.1</td>
<td>0.310</td>
<td>0.031</td>
</tr>
<tr>
<td>2</td>
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<td>0.062</td>
</tr>
<tr>
<td>3</td>
<td>0.3</td>
<td>0.312</td>
<td>0.094</td>
</tr>
<tr>
<td>4</td>
<td>0.4</td>
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<td>0.126</td>
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<tr>
<td>5</td>
<td>0.5</td>
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<td>0.162</td>
</tr>
<tr>
<td>6</td>
<td>0.6</td>
<td>0.436</td>
<td>0.262</td>
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<td>7</td>
<td>0.65</td>
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<td>0.7</td>
<td>0.472</td>
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</tr>
<tr>
<td>9</td>
<td>0.75</td>
<td>0.425</td>
<td>0.319</td>
</tr>
<tr>
<td>10</td>
<td>0.8</td>
<td>0.377</td>
<td>0.301</td>
</tr>
<tr>
<td>11</td>
<td>0.9</td>
<td>0.207</td>
<td>0.186</td>
</tr>
</tbody>
</table>

*aThe change in the chemical shift ($\Delta \delta$) of the acid 85 in the presence of amine 83 was calculated with
reference to the methine (CαH) proton signal of the acid at 5.257 δ ppm in the absence of 83.

\[
\Delta\delta = \text{change in the chemical shift of the CαH proton signal of (R)- and (S)- mandelic acid 85}
\]

**Figure 5.** Job’s plot of chiral receptor amine 83 with (R) and (S)-mandelic acids 85 [X = mole fraction of the acid; Δδ = change in the chemical shift of the CαH proton signal of (R)- and (S)- mandelic acid 85]

Finally, we have examined the practical applicability of this method for the measurement of enantiomeric excess of carboxylic acids. With this objective, samples containing different proportions of both the enantiomers of mandelic acid 85 (100 mM in 5 mL CDCl₃) were prepared and analyzed with ¹H NMR method using the receptor amine 83 (100 mM in 5 mL CDCl₃) with amine:acid molar ratio of 1:3. Integration of the corresponding CαH ¹H NMR signals shows an excellent linear correlation of the observed % ee values with that of expected % ee values based on HPLC method (Figure 6).⁴₀
Figure 6. Selected region of the $^1$H NMR (400 MHz) spectra of mandelic acid 85 (100 mM) with various enantiomeric purities in the presence of (1$R$,2$R$,1'$R$,1"$R$)-83 (100 mM) in CDCl$_3$ at 25 °C. The % ee values were obtained from the integration of the C$\alpha$H signals. The % ee values obtained by HPLC analysis are given in parentheses.

From these results, it is evident that the readily accessible chiral $C_2$-symmetric diamines 83 and 84 are useful chiral solvating agents for the carboxylic acids 85, 86 and N-Ts-phenylglycine derivative 89.
2.3 Conclusions

The use of the readily accessible chiral $C_2$-symmetric acyclic diamines 83 and 84 containing $trans$-1,2-diaminocyclohexane moiety as chiral solvating agents (CSAs) for the determination of enantiomeric excess of representative carboxylic acids 85, 86 and an amino acid derivative 89 is illustrated. The enantiomeric composition of different carboxylic acids estimated herein by the $^1$H NMR method, based on the integration of the corresponding methine proton (C$^α$H) signals are in excellent correlation with that determined using HPLC method. The data are in accordance with the formation of multimolecular diastereomeric complexes in solution, which render good splitting of the NMR signals for the enantiomers of representative carboxylic acids 85 and 86 as well as for $N$-Ts-phenylglycine 89 (up to $\Delta\Delta\delta = 0.295$ ppm, 118.0 Hz). The high symmetry and simple $^1$H NMR spectrum of these chiral amines reduce the possibility of large overlapping with signals of the substrates. The easy accessibility of the chiral amine receptors 83 and 84 from commercially available 1,2-diaminocyclohexane should make this methodology very attractive for practical application as chiral solvating agents (CSAs) for carboxylic acids.
2.4 Experimental Section

2.4.1 General Information

Several information given in the section 1.4 are also applicable for the experiments outlined in this section. The racemic 2,3-diphenylsuccinic acid 86 was synthesized following a reported procedure.\textsuperscript{41} The N-Ts-amino acid derivatives 88-90 were synthesized following a reported procedure.\textsuperscript{42} The racemic mandelic acid 85 supplied by Sigma-Aldrich, USA and the (S)-(+) mandelic acid supplied by E-Merck (Germany) were used. Ultrasonication was carried out in a Sonorex washing bath (BANDELIN electronic, type RK31H, 120W, 35 kHz).

2.4.2 \textsuperscript{1}H-NMR shift experiments

\textsuperscript{1}H NMR shift experiments were performed on a 400 MHz NMR spectrometer at 25 °C by mixing the chiral amines 83 or 84 with the acids 85-92 in varying ratios in CDCl\textsubscript{3}, until maximum splitting of the signals were observed.

2.4.3 Evaluation of stoichiometry of the complex formed between the amine 83 and (R)- or (S)-mandelic acid 85 by Job’s method

The stoichiometry of the complex formed between 83 and 85 was determined according to Job’s method of continuous variations. Equimolar amounts of 83 (25 mM) and (R) or (S)-85 (25 mM) were prepared in CDCl\textsubscript{3} (5 mL). These solutions were distributed among ten NMR tubes in such a way that the mole fractions of 85 in the resulting solutions increased from 0.1 to 0.9. The complexation induced shifts of the methine (C\textsuperscript{\alpha}H) signal (\(\Delta\delta\)) were multiplied by the mole fraction of the acid 85 (X) (Table 5, Section 2.2.1) and plotted against X to obtain the Job’s plot (Figure 5, Section 2.2.1).
2.5 References


References


