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Determination of Enantiomeric Composition of 2-Phenyl-2-(2-piperidyl)acetamide. A Routine Method for Evaluation of Enantiomeric Purity of Primary Amides

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Abstract: Several NMR chiral resolving agents have successfully been used to demonstrate their usefulness for the determination of the enantiomeric composition of the title compound.

It is generally accepted that any solution containing a mixture of two enantiomers will always give only one set of signals corresponding to both of them.[1] This statement holds for enantiomers that cannot associate between themselves. If there is a possibility of self-association of the enantiomers in solution, two separate sets of signals corresponding to the enantiomeric composition might occur.[2] Although it has been known for a long time that hydrogen bonds in the amides are responsible for the formation of molecular associates,[3] the first enantiomeric nonequivalence in partially resolved amides was observed relatively recently.[4] Nevertheless, in a racemic mixture again only one set of signals is obtained. We have explained this phenomenon by non-selective dimerization of the enantiomers with equal probability of formation of R-S, S-S, and R-R diastereomers through enantiomeric association and fast exchange between them, resulting in one set of signals for the racemates in solution.[5] When an enantiomer is present in a lesser amount, it will spend longer time in complex with the opposite enantiomer, thus giving two sets of signals, corresponding to the enantiomer composition. The enantiomer signal separation is proportional to the concentration and inversely proportional to the temperature and polarity of the solvent.

It is conceivable that the enantiomeric association occurs through hydrogen bonding, as well as through π-π aromatic stacking.[6] That was supported by the absence of enantiomeric discrimination in polar solvents such as DMSO. Enantiomeric discrimination can occur even in polar solvents only when a microenviroment, as in micellar media, can be formed.[7]

Discrimination of enantiomers can also be induced by lanthanide NMR shift reagents[8], and chiral solvating agents.[9] We have demonstrated that the presence of an optically pure chiral resolving agent will produce enantiomeric discrimination for all compositions of enantiomers.[6,10] The chiral resolving agent forms aggregates with the enantiomers through nonbonding interactions. The more interactions between the enantiomer and the resolving agent - multipoint interaction, the better the enantiomeric discrimination. This was demonstrated by determining the binding constants between the enantiomers and resolving agent, as well as by performing molecular mechanics calculations of the possible molecular associates.[6]

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There is a great necessity for a simple, fast and reliable method that can give an answer to the question of stereoisomeric composition not only for a product of a reaction, but also for the optimization of asymmetric synthesis.[11] Here we are offering one method that can meet these requirements. It will be demonstrated by determining the stereoisomeric composition of 2-phenyl-2-(2-piperidyl)acetamide (**1**) (Figure 1). The compound is a typical example of an organic molecule that has several stereoisomers (four), it is pharmaceutically important[12] and like many other drugs,[13] it is marketed as a mixture of stereoisomers.

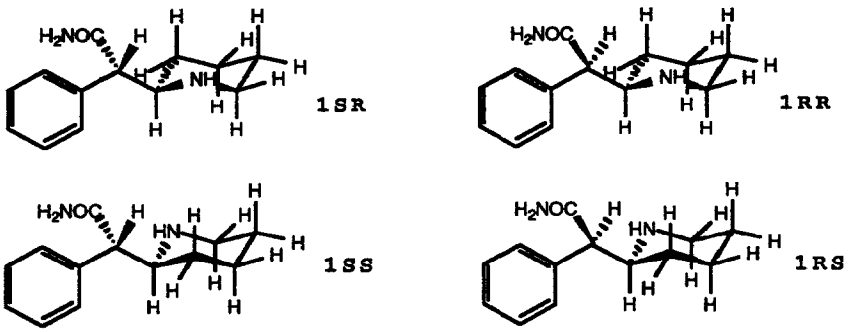

Figure 1. Four possible isomers of amide 1.

The structures of the resolving agents are presented in Figure 2. Each of them has specific characteristics that best demonstrate the capabilities of this method. They are all highly soluble in chloroform, and have an amide group that can form hydrogen bonds with the amide isomers 1. They differ in their possibility to form

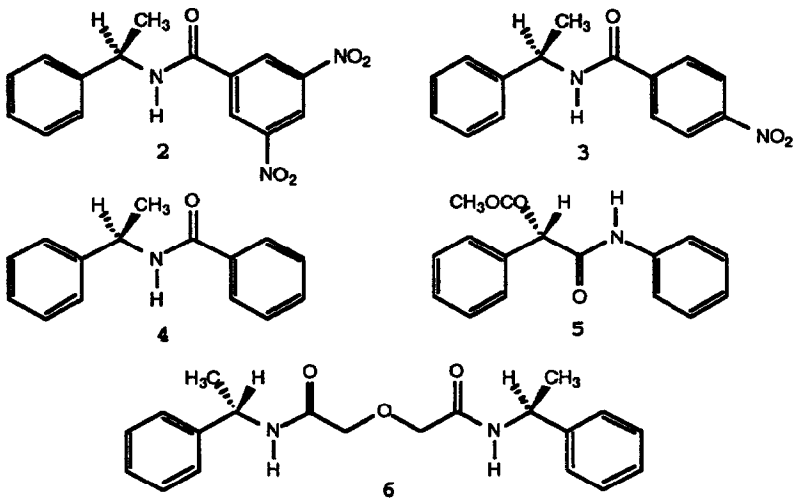

Figure 2. Chiral resolving agents for determination of enantiomeric composition of amides.

π-π aromatic stacking interactions in chloroform solutions, as well as by the acidity of the amide hydrogen. Chiral resolving agent **2** has an electron deficient aromatic ring (dinitrobenzoyl) and can form at least a three point interaction with stereoisomers **1** (at least two hydrogen bonds if the nitro groups are excluded, and one π-π aromatic stacking). The probability for π–π aromatic stacking in chloroform solution decreases from **2** to **6**. Because **2-5** have only two signals in the aliphatic part of the ^{1}H NMR spectra there is a broad NMR window where the stereoisomer signals can easily be observed. Chloroform solutions were exclusively used, although a small effect can be observed in methanol, but not in dimethyl sulfoxide.

The chloroform mixture of two enantiomers, **1RR** and **1SS**, shows only one set of signals regardless of their molar ratio. By adding any of the chiral resolving agents **2-6** separation of signals occurs (Figure 3). If

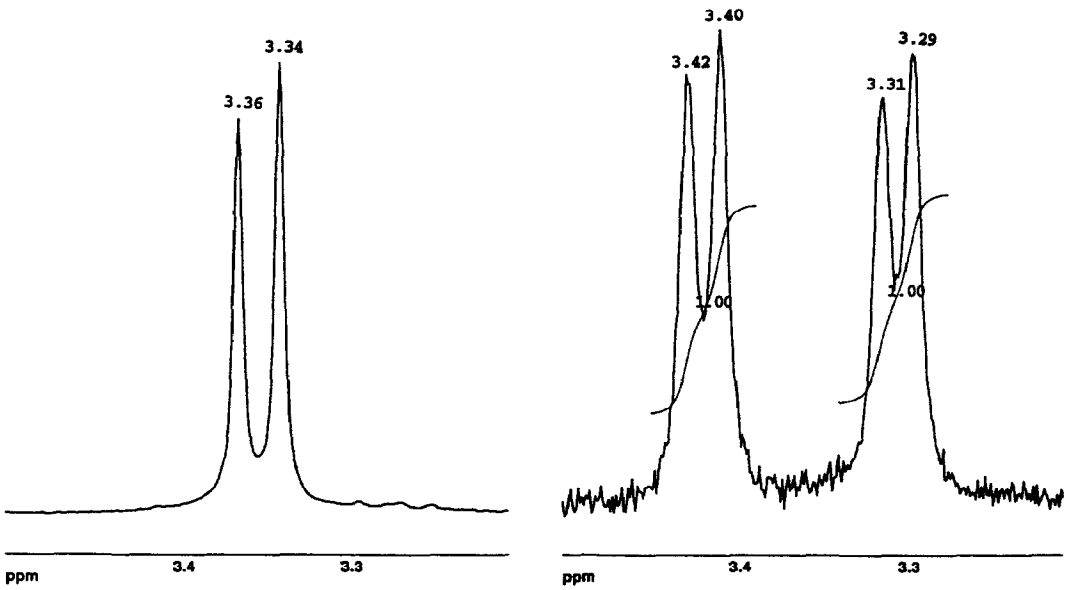

Figure 3. ^{1}H NMR signals of α-amide proton for racemate **1RR:1SS** without (**A**) and with (**B**) amide **3** as resolving agent.

the ^{1}H NMR spectrum of all possible isomers is recorded only two sets of signals are observed corresponding to the two enantiomeric pairs **1SS:1RR** and **1RS:1SR**. By adding the chiral resolving agents the signals for all possible stereoisomers are separated and their integral ratio corresponds to the isomer ratio in the mixture (Figure 4). We have determined the enantiomeric composition of a large number of aliphatic and aromatic amides in this way. In all our studies enantiomeric discrimination was observed with the chiral resolving agents **2-5**, although not to the same degree. The best resolution was observed with **2** (Table 1). Even chiral resolving agent **3**, which does not produce as high of a signal separation as amide **2**, shows satisfactory separation of the stereoisomer signals, so that their integrals can be obtained without fear of overlapping. Resolving agents **4-6** produce very small differences in the enantiomeric signals and can be successfully used only for qualitative estimation of

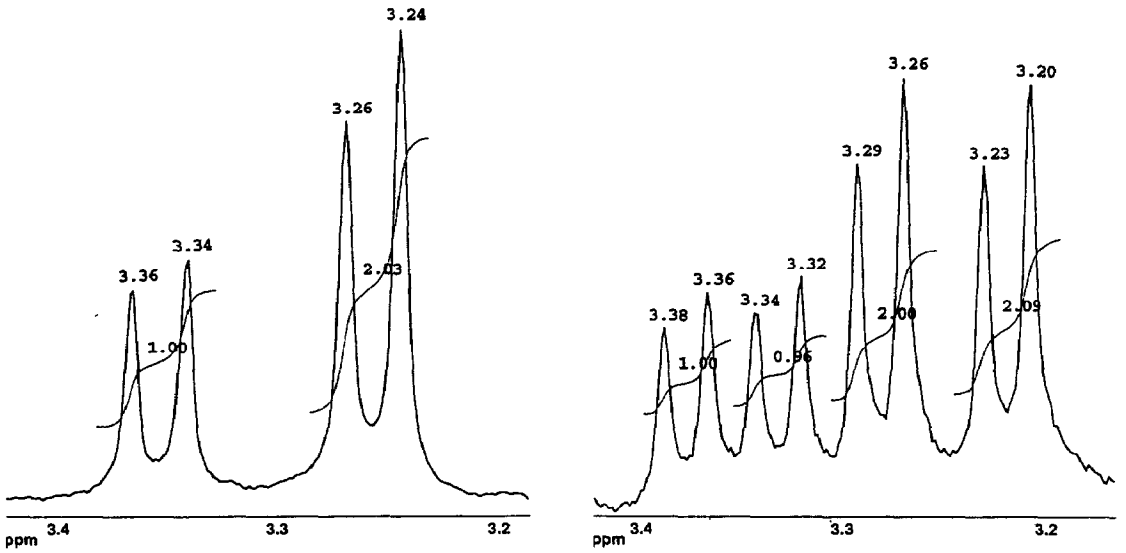

Figure 4. ^{1}H NMR signals of α-amide proton for stereoisomer mixture of **1RR:1SS:1RS:1SR**=1:1:2:2 without (**A**) and with (**B**) resolving agent **3**.

Table 1. Discrimination of α-amide enantiomeric protons **1RR** and **1SS** (0.01M) in the presence of different chiral resolving agents (0.1 mol/L).

Resolving agent	**2**	**3**	**4**	**5**	**6**
Δd/(Hz)	37.2	21.3	7.8	6.9	7.2

enantiomeric purity of the studied amides. All chiral resolving agents **2-6** can be used for determination of the enantiomeric purity on a variety of aliphatic and aromatic amides[14] due to formation of diastereomeric molecular associates between enantiomers and resolving agents through amide hydrogen bonding. Chiral resolving agents **4-6** fail to determine the enantiomeric composition of compounds that do not make strong molecular associates with the amide group, such as aromatic esters and alcohols. That is not the case with electron deficient chiral resolving agents, such as **2** and **3**, which are useful for determination of the enantiomeric composition of aromatic alcohols and esters as well.[6b] This finding is in agreement with the assumption that multipoint interactions between resolving agents and stereoisomers must be present for enantiomeric discrimination. Thus, resolving agent **2** is superior over the others and can be used for determination of stereoisomeric composition of amides and other electron rich aromatic compounds.

The chiral resolving agents can be recovered from the NMR solution. For example, 72-85% of resolving agent **2** was recovered from the NMR solution after determination of stereoisomers of **1** by evaporating the chloroform, followed by crystallization from chloroform-petroleum ether.

Experimental Procedure

Stereoisomers of amide **1** were synthesized as racemic mixture of **1RR:1SS** and **1RS:1SR** from 2-phenyl-2-(2-piperidyl)acetonitrile following the procedure described by Panizzon.[15] The preparation of the chiral resolving agents **2**[6b] and **3-6**[5] was reported previously. All NMR spectra were recorded on a Varian Gemini 300 instrument with a hydrogen probe operating at 300 MHz. For the determination of the enantiomeric composition 1-3 mg samples were used.

Conclusion

The determination of the enantiomeric composition of amide **1** with optically pure amides **2-4** as chiral resolving agents has been demonstrated. The method is extremely simple and reliable. It is best to prepare a 0.1 mol/L stock deutero chloroform solution of any of the resolving agents, and use it for the preparation of NMR samples instead $CDCl_3$. It can be used for the determination of enantiomeric composition of as little as 1 mg of material and enantiomer compositions of up to 97:3 can be detected. We suggest it as the method of choice for the routine determination of the enantiomeric composition of aliphatic and aromatic primary amides. All resolving agents employed can be obtained in large amount (even on a kilogram scale!) and in a single step from commercially available reactants.

Acknowledgment

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