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Chiral Shift Reagent for Amino Acids Based on Resonance-Assisted Hydrogen Bonding

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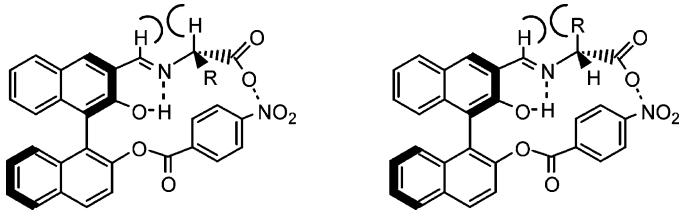
ABSTRACT



A chiral aldehyde that forms resonance-assisted hydrogen bonded imines with amino acids has been developed. This hydrogen bond not only increases the equilibrium constant for imine formation but also provides a highly downfield-shifted NMR singlet for evaluating enantiomeric excess and absolute stereochemistry of amino acids.

Over the years many interesting chiral reagents have been developed for determining enantiomeric excess of amino acids using NMR spectroscopy.[1−3] These include chiral lanthanide,[4] palladium,[5] and cobalt complexes[6] that coordinate amino acids and organic molecules[7−9] that form imines[7f] or hydrogen bonded complexes with amino acids. While some of these reagents work well for some of the amino acids or their derivatives, it has been difficult to develop a reagent that works well for a wide range of underivatized amino acids by a unified approach. Ideally, the NMR peak to be resolved should be a singlet for all amino acids and far removed from other signals. Here we show that this can be achieved with the use of resonance-assisted hydrogen

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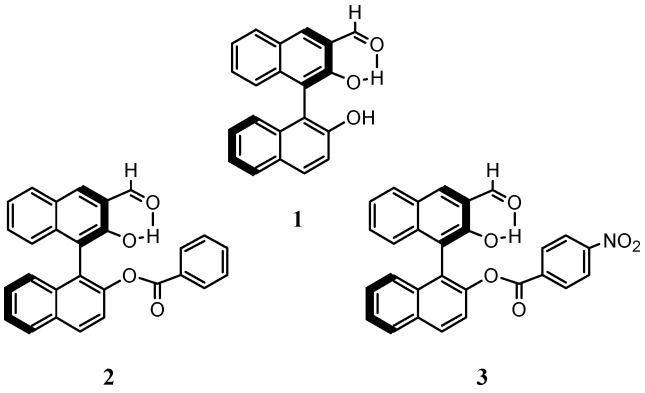
bonds (RAHBs).[10] Three organic reagents (**1**−**3**), all based on (*R*)-binol, are evaluated for determining enantiomeric excess and absolute stereochemistry of amino acids.



1 **2** **3**

In RAHB, the hydrogen bond is conjugated with the π system. It has recently been shown[10] that imines (**4**) can form rather strong intramolecular RAHBs and that the ^{1}H NMR signals of these protons are strongly downfield shifted (>13 ppm) relative to regular hydrogen bonds. DFT computation showed that in general, RAHBs are about twice as strong as regular hydrogen bonds. For example, the RAHB in **4** is about 5 kcal/mol, whereas the regular hydrogen bond in **5** is only about 2.5 kcal/mol. Such RAHBs should increase the equilibrium constant for imine formation.[11]

4 **5**

Chiral aldehydes **1**−**3** can form intramolecular resonance-assisted hydrogen bonded imines with amines and amino acids. The ^{1}H NMR signal of the RAHB protons in the imines formed from **1** and racemic alanine were strongly downfield shifted (>13 ppm) as expected. However, the signals for the RAHB protons in the dieastereomeric mixture were not resolved. Molecular mechanics computation[12] revealed that **3** should be a better design than **1**. Indeed, two baseline-resolved peaks can be observed for the RAHB protons in the imines formed from **3** and racemic alanine (Figure 1a). Even the methyl peaks of alanine in the diastereomeric complex are split and baseline resolved (Figure 1b). To see if epimerization takes place under our experimental conditions, we added a 1:2 mixture of D- and L-alanine to **3**. This ratio does not change appreciably even after 24 h (<10%), indicating that epimerization is slow. In a typical experiment, known mixtures of D- and L-alanine (10 mM) were added to **3** (20 mM) dissolved in DMSO-d_6 and allowed to react for 5 min at 25 °C before taking the spectrum. The RAHB signals remain sharp even with 1% water in DMSO-d_6. The imine-forming reactions take place rapidly with a half-life of about 10 s, assisted by the RAHBs.

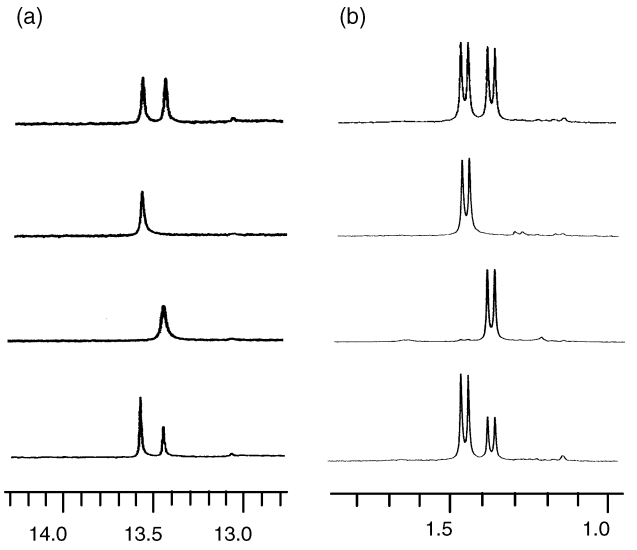


Figure 1. ^{1}H NMR spectra (DMSO-d_6) for the imines formed with **3** and alanine in the regions of (a) RAHB protons and (b) CH_3 protons. From top, **3** + 0.5 equiv of D-/L-ala; 3 + 0.5 equiv of L-ala; 3 + 0.5 equiv of D-ala; 3 + 0.4 equiv of L-ala + 0.2 equiv of D-ala.

Reagent **1** is a known compound,[13] and reagents **2** and **3** were prepared[14] by following the procedure for making the corresponding pivaloyl ester.[12] In designing the reagent, we reasoned that there should be at least two points of reasonably strong interactions between the aldehyde and the amino acid. The first interaction is the hydrogen bonded imine, and the second is the electrostatic interaction between the carboxylate oxygen of the amino acid and the nitro group nitrogen of the reagent (Figure 2, **6** and **7**). Molecular mechanics computation showed that the global minimum structures of **6** and **7** have the carboxylate groups in van der Waals contact with the nitro groups (Figure 2). Computation further reveals that the RAHB is shorter for the imine formed with L-alanine (**6**: N···H 1.700 Å) compared to that formed with D-alanine (**7**: N···H 1.706 Å). Since the shorter H-bond should be stronger, the ^{1}H NMR chemical shift of the shorter H-bond should shift further downfield. In agreement with this interpretation, the signal for the RAHB proton in the imine formed with L-alanine is more downfield shifted (Figure 1). The longer H-bond in **7** compared to that in **6** may be caused by the steric interaction between the alanine methyl group and the imine hydrogen in **7**. As shown below, this could be the basis for determining the absolute stereochemistry of α-amino acids that have a hydrogen at the α-position.

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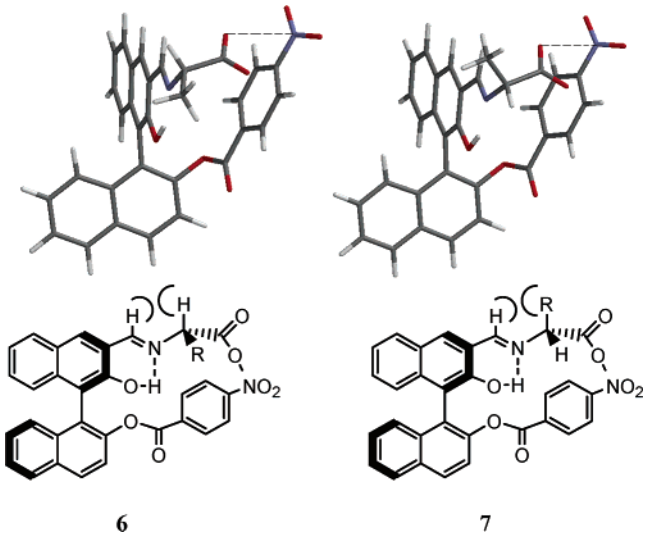

Figure 2. Computed structures of **6** and **7**. N···O distances in **6** and **7** (dashed lines) are 3.24 and 3.28 Å, respectively.

To test the general applicability of **3**, we used the above method to test the effectiveness of the reagent for determining the enantiomeric excess of amino acids and phenethylamine. Table 1 lists the NMR signals due to RAHBs formed from the reactions of **3** with 10 different amino acids and with phenethylamine. As with alanine, it is L-amino acids that form the shorter and stronger RAHB and the more downfield-shifted RAHB proton. For phenethylamine, computation shows favorable $\pi-\pi$ interaction between the phenyl group of the amine and the nitrophenyl group of the reagent. Thus, the phenyl group of the amine in the imine complex occupies the same general location as the carboxylate groups in the imine complexes formed with the amino acids. Computation shows that the RHAB is shorter in the imine formed between **3** and (*S*)-phenethylamine than in the imine formed with (*R*)-phenethylamine. Here as with amino acids, the steric interaction between the methyl group of (*R*)-phenethylamine and the imine hydrogen appears to weaken and lengthen the H-bond. In agreement with the computational data, the ^{1}H NMR signal of the RAHB proton in the imine formed with (*S*)-phenethylamine is more downfield shifted (Table 1). This consistent relationship between the relative chemical shift and the chirality at the α-position should be useful for assigning the absolute stereochemistry of α-amino acids and amines that have a hydrogen at the α-position.

Table 1. ^{1}H NMR Chemical Shifts for RAHB Protons of the Imines in DMSO-d_6 (Last Entry in $CDCl_3$)

	chemical shifts (δ, ppm)		
imines	L form	D form	Δ δ
1 + alanine	13.09	13.09	0.0
2 + alanine	13.41	13.35	0.06
3 + alanine	13.57	13.44	0.13
3 + valine	13.76	13.56	0.20
3 + phenylalanine	13.40	13.26	0.14
3 + tyrosine	13.47	13.35	0.12
3 + tryptophan	13.64	13.50	0.14
3 + threonine	13.74	13.66	0.08
3 + methionine	13.43	13.26	0.17
3 + serine	13.69	13.61	0.08
3 + asparagines	13.45	13.35	0.10
3 + phenylglycine	13.37	13.28	0.09
3 + alanine ester	13.31	13.25	0.06
3 + phenethylamine	13.64	13.57	0.07
3 + alanine ester	12.94	12.83	0.11

In conclusion, we have developed a chiral aldehyde (**3**) that forms a strong RAHB upon imine formation with amino acids. This hydrogen bond not only increases the rate and equilibrium constant for imine formation but also provides a highly downfield-shifted NMR singlet for evaluating the enantiomeric excess of amino acids. The ^{1}H NMR signals of the RAHB protons in the diastereomeric imine complexes are well resolved for a wide variety of amino acids. This reagent (**3**) is useful for determining the enantiomeric excess and also the absolute stereochemistry of amino acids.

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Supporting Information Available: Experimental procedures, including synthesis and characterization of **2** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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