Highly Effective Configurational Assignment Using Bisthioureas as Chiral Solvating Agents in the Presence of DABCO

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ABSTRACT: A highly effective 1H NMR method for determining the absolute configurations of various chiral α-hydroxyl acids and their derivatives has been developed with the use of bisthioureas (R)-CSA 1 and (S)-CSA 1 as chiral solvating agents in the presence of DABCO, giving distinguishable proton signals with up to 0.66 ppm chemical shift nonequivalence. Computational modeling studies were performed with Gaussian09 to reveal the chiral recognition mechanism.

Many natural products, drug molecules, and organic synthons contain chiral building blocks. Their unique biological activities and physicochemical properties are largely dependent on their stereochemistry. Thus, developing methods for the accurate assignment of absolute configuration remains an important endeavor. There are several available analytical techniques for assigning absolute configuration of an enantiomerically pure molecule, such as X-ray crystallography, circular dichroism, and NMR spectroscopy. Among them, the NMR spectroscopic methods are appealing because a stable and credible result can be obtained by a fast and easy NMR operation using only a small amount of sample. Currently, assignment of absolute configuration using NMR spectroscopy has mainly two approaches. One involves using chiral derivatizing agents (CDAs), and the other is using chiral solvating agents (CSAs). The former usually obtains well-separated NMR resonances, but tedious isolation and purification steps are usually required. In contrast, there are many advantages with the use of CSAs; for example, they are typically simple protocols to carry out; derivitization is not required; and the sample is readily recovered. However, induced chemical shift nonequivalences of the diastereomeric complexes are usually too small to easily be distinguished. Moreover, the NMR spectrum reflects the mixed signals of CSA, substrate, and the CSA−substrate complex, resulting in

Table 1. Optimization of the Discriminating Conditions for Mandelic Acid by (S)-CSA 1

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>base</th>
<th>MA</th>
<th>base</th>
<th>CSA 1</th>
<th>ΔΔδ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CDCl₃</td>
<td>DMAP</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>0.14</td>
</tr>
<tr>
<td>2</td>
<td>CDCl₃</td>
<td>triethylamine</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>0.29</td>
</tr>
<tr>
<td>3</td>
<td>CDCl₃</td>
<td>DABCO</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>0.33</td>
</tr>
<tr>
<td>4</td>
<td>C₆D₆/CDCl₃</td>
<td>DABCO</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>0.37</td>
</tr>
<tr>
<td>5</td>
<td>C₆D₆/CDCl₃</td>
<td>DABCO</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>0.35</td>
</tr>
<tr>
<td>6</td>
<td>C₆D₆/CDCl₃</td>
<td>DABCO</td>
<td>40</td>
<td>40</td>
<td>80</td>
<td>0.50</td>
</tr>
</tbody>
</table>

*(S)-CSA 1, base, and mandelic acid were mixed in the specified solvent (0.6 mL), and 1H NMR data were collected on a Bruker Avance 400 MHz spectrometer at 25 °C. Mixed solvents of C₆D₆/CDCl₃ were 50/50% (v/v). Chemical shift nonequivalences of the methine protons on the chiral centers of mandelic acid.

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In our investigation on the applicability of bishiourea CSAs for assigning the absolute configurations of chiral carboxylic acids, we first optimized the discriminating conditions for mandelic acid (MA) by (S)-CSA 1 (Table 1). Compared with triethylamine and DMAP, DABCO was the better base for discrimination of MA (Table 1, entries 1–3). In addition, using mixed solvents of C₆D₆/CDCl₃ was helpful (Table 1, entry 4). Moreover, increasing concentrations of (S)-CSA 1/MA/DABCO increased the ΔΔδ value due to the right equilibrium shift of the ternary complex formation (Table 1, entries 5–7). The best result (up to 0.50 ppm of ΔΔδ value) was obtained with 80 mM (S)-CSA 1/40 mM MA/40 mM DABCO in 50% C₆D₆/50% CDCl₃ (v/v), which gave excellent enantiodiscrimination of the two MA enantiomers (Table 1, entry 7). Then, under the optimized conditions, ¹H NMR spectra of the mixture of (R)-CSA 1/(S)-MA/DABCO and a mixture of (S)-CSA 1/(S)-MA/DABCO were recorded. By comparison of the chemical shifts of α-H signals of (S)-MA in the two mixtures, it was found that Δδ₉₈₈ (δ₉₈₈ of carboxylic acids with (R)-CSA 1 − δ₉₈₈ of carboxylic acids with (S)-CSA 1) is –0.55 ppm. Changing the carboxylic acid to (R)-MA, we repeated the process and Δδ₀₅₈ was obtained at +0.54 ppm. The results indicate that negative Δδ₀₅₈ correlates to (S)-MA and positive Δδ₀₅₈ correlates to (R)-MA.

In order to understand the nature of the correlation between Δδ₀₅₈ and the absolute configuration of MA, the recognition modes were studied. The 1:1:1 stoichiometry of the complexes was assumed to be formed from CSA 1 and MA and DABCO, which were supported by Job plots (Supporting Information). The association constants of (S)-CSA 1/(S)-MA/DABCO and (R)-CSA 1/(S)-MA/DABCO were determined by a nonlinear least-squares method (Supporting Information).⁷ The relatively larger Kₛ values of (S)-CSA 1/(S)-MA/DABCO suggested that (S)-CSA 1 formed a more stable complex with (S)-MA/DABCO than (R)-CSA 1 (Table 2).

The reliability of an NMR spectroscopic method for configurational assignment heavily depends on the number and the structural variety of test substrates with easily distinguished NMR signals. The method using CDAs has been validated by a large number of examples and is the major NMR strategy for assigning absolute configurations of chiral compounds so far.⁶ In contrast, few CSAs were reported for the discrimination of α-H signals of (S)-MA in the two mixtures, it was found that Δδ₀₅₈ (δ₀₅₈ of carboxylic acids with (R)-CSA 1 − δ₀₅₈ of carboxylic acids with (S)-CSA 1) is –0.55 ppm. Changing the carboxylic acid to (R)-MA, we repeated the process and Δδ₀₅₈ was obtained at +0.54 ppm. The results indicate that negative Δδ₀₅₈ correlates to (S)-MA and positive Δδ₀₅₈ correlates to (R)-MA.

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Table 2. Association Constants for the Binding of CSA 1 with Mandelic Acid/DABCO⁴

<table>
<thead>
<tr>
<th>CSAs</th>
<th>Δδ₉₈₈ (ArNH)</th>
<th>Kₛ (M⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R)-CSA 1</td>
<td>3.11</td>
<td>226</td>
</tr>
<tr>
<td>(S)-CSA 1</td>
<td>3.04</td>
<td>356</td>
</tr>
</tbody>
</table>

¹H NMR data were collected on a Bruker Avance 400 MHz spectrometer in 50% C₆D₆/50% CDCl₃ (v/v) at 25 °C. Kₛ values were calculated by the nonlinear least-squares method.

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Figure 2. Space-filling representations and ¹H NMR spectra of complexes. Complexes: (A) (S)-CSA 1/(S)-MA/DABCO, (B) (R)-CSA 1/(S)-MA/DABCO, (C) (R)-CSA 1/(R)-MA/DABCO, (D) (S)-CSA 1/(R)-MA/DABCO. The α-Hs of (R)- and (S)-MAs are shown in green. ¹H NMR spectra of α-Hs of (R)- or (S)-MAs: (a) in complex A, (b) in complex B, (c) in complex C, (d) in complex D.
One-dimensional NOESY experiments for the mixtures of CSA 1/MA/DABCO showed strong correlation between $\alpha$-H of MA and Ar$^{-}$Hs of CSA 1 (Hc; see Supporting Information) for the mixture of ((S))-CSA 1/((S))-MA/DABCO. These results indicated that the intermolecular noncovalent bonding interactions presented in the complex structure resulted in the closeness of Hc of CSA 1 to $\alpha$-H of ((S))-MA in space.

However, the mixture of ((R))-CSA 1/((S))-MA/DABCO gave weaker NOESY signals between $\alpha$-H of ((S))-MA and Ar$^{-}$Hs of CSA 1 (Hc and Hf; see Supporting Information), indicating that the $\alpha$-H was farther from Hc and closer to Hf in the complex of ((R))-CSA 1/((S))-MA/DABCO, compared with the $\alpha$-H in the complex of ((S))-CSA 1/((S))-MA/DABCO. The mixture of ((R))-CSA 1/((R))-MA/DABCO gave similar 1D NOESY signals as the mixture of ((S))-CSA 1/((S))-MA/DABCO and the mixture of ((S))-CSA 1/((R))-MA/DABCO gave 1D NOESY signals similar to those of the mixture of ((R))-CSA 1/((S))-MA/DABCO.

Based on the above results and the model in our previous study,8 we proposed two kinds of ternary complexes of CSA 1/MA/DABCO formed via multiple intermolecular hydrogen-bonding interactions (Figure 2).9 One kind is formed from ((S))-CSA 1/((S))-MA/DABCO (Figure 2A) or ((R))-CSA 1/((R))-MA/DABCO (Figure 2C). The other is formed from ((R))-CSA 1/((S))-MA/DABCO (Figure 2B) or ((S))-CSA 1/((R))-MA/DABCO (Figure 2D). In all complexes, $\alpha$-Hs of MAs are located in the deshielding range of the aromatic system of CSA 1 (shielding...
range, above/below the ring plane and inside the ring; deshielding range, on the periphery of the ring plane). Compared with the $\alpha$-H of (S)-MA in complex B, the $\alpha$-H of (S)-MA experiences more deshielding in complex A due to a closer distance so that the $^1$H NMR signal of $\alpha$-H of (S)-MA should be more downfield. Therefore, the $\Delta \delta_{\alpha-H}^{R,S}$ is negative. For (R)-MA, the stronger deshielding effect in complex C compared to that in complex D results in a positive $\Delta \delta_{\alpha-H}^{R,S}$ value. 

Mastering the nature of correlation, we can judge the absolute configurations of carboxylic acids according to the positive or negative sign of $\Delta \delta_{\alpha-H}^{R,S}$.

In order to confirm the validity of this correlation, assignments of a series of $\alpha$-hydroxyl acids and their derivatives with known absolute configurations were carried out using the above method (Table 3). The assigned configurations were consistent with the actual configurations for all investigated molecules. Furthermore, an acid with unknown absolute configuration was correctly assigned by this correlation (Table 3, entry 20), which was confirmed by comparing the chiral HPLC data of its deprotected derivative with that of natural product danshensu (Supporting Information). How-chiral HPLC data of its deprotected derivative with that of e

assignments of a series of $\alpha$-hydroxyl acids and their derivatives. Therefore, it can be used as a general tool for assignments of various $\alpha$-hydroxyl acids and their derivatives in the presence of DABCO. The negative $\Delta \delta_{\alpha-H}^{R,S}$ correlates to (S)-acids, and positive $\Delta \delta_{\alpha-H}^{R,S}$ correlates to (R)-acids. The method is simple to operate and widely valid for broad substrate scope. In addition, the obtained spectra are easy to interpret because of large enough $^1$H NMR chemical shift nonequivalences and no interference from bisthiourea CSAs and DABCO. Therefore, it can be used as a general tool for configurational assignments of $\alpha$-hydroxyl acids and their derivatives.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, NMR spectroscopy data, and results of computational modeling. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) Computational modeling studies were performed with Gaussian09, using a molecular mechanics method initially and then a DFT method at the B3LYP/6-31+g(d,p) level. All geometry optimizations were carried out in the gas phase. Frisch, M. J.; et al. Gaussian 09, revision A1; Gaussian Inc.: Wallingford, CT, 2009 (see Supporting Information for full reference).