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

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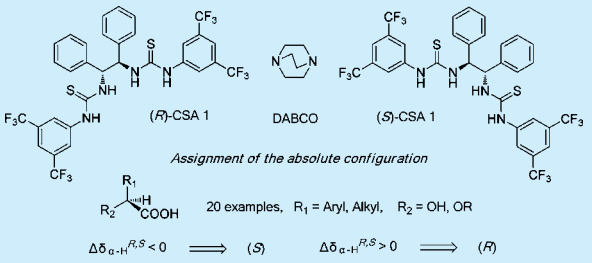
Supporting Information

ABSTRACT: A highly effective ^{1}H 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.[1] There are several available analytical techniques for assigning absolute configuration of an enantiomerically pure molecule, such as X-ray crystallography,[2] circular dichroism,[3] and NMR spectroscopy.[1a−d,4] 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.[1a,4a] 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

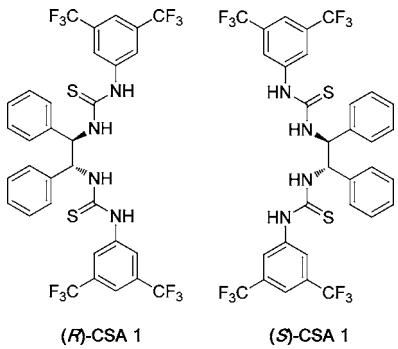


Figure 1. Structures of bisthiourea CSAs.

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

			C (mM)			
entry	solvent[b]	base	MA	base	CSA 1	$\Delta\Delta\delta^c$ (ppm)
1	$CDCl_3$	DMAP	20	20	20	0.14
2	$CDCl_3$	triethylamine	20	20	20	0.29
3	$CDCl_3$	DABCO	20	20	20	0.33
4	$C_6D_6/CDCl_3$	DABCO	20	20	20	0.37
5	$C_6D_6/CDCl_3$	DABCO	20	40	20	0.35
6	$C_6D_6/CDCl_3$	DABCO	40	40	40	0.39
7	$C_6D_6/CDCl_3$	DABCO	40	40	80	0.50

[a](*S*)-CSA 1, base, and mandelic acid were mixed in the specfied solvent (0.6 mL), and ^{1}H NMR data were collected on a Bruker Avance 400 MHz spectrometer at 25 °C. [b]Mixed solvents of $C_6D_6/CDCl_3$ were 50/50% (v/v). [c]Chemical shift nonequivalences of the methine protons on the chiral centers of mandelic acid.

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Table 2. Association Constants for the Binding of CSA 1 with Mandelic Acid/DABCO[a]

CSAs	$\Delta\delta_{max}$ (ArNH)	K_a[b] (M^{-1})
(*R*)-CSA 1	3.11	226
(*S*)-CSA 1	3.04	356

[a]^{1}H NMR data were collected on a Bruker Avance 400 MHz spectrometer in 50% C_6D_6/50% $CDCl_3$ (v/v) at 25 °C. [b]K_a values were calculated by the nonlinear least-squares method.

the difficulty of establishing a correlation between the stereochemistry of the substrate and NMR signals. Although, there is a so-called "mix and shake" method,[5] which is a combination of the above two approaches, it is often difficult to obtain clean and sharp spectra because of the presence of an excessive amount of derivatization reagent and additive.

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.[4a] In contrast, few CSAs were reported for configurational assignments, and the number and structural variety of test substrates are limited with small chemical shift nonequivalences.[6] Thus, use of CSAs for determining absolute configuration with both broad substrate scope and large induced chemical shift nonequivalences remains challenging.

In this paper, we present the use of (*R*)/(*S*)-bisthiourea as CSAs (Figure 1) for accurately assigning the absolute configurations of various α-hydroxyl carboxylic acids and their derivatives by ^{1}H NMR in the presence of DABCO. The proton signals were easily distinguished, and up to 0.66 ppm of ^{1}H chemical shift nonequivalence ($\Delta\Delta\delta$) was obtained.

In our investigation on the applicability of bisthiourea 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 C_6D_6/$CDCl_3$ was helpful (Table 1, entry 4). Moreover, increasing concentrations of (*S*)-CSA 1/MA/DABCO increased the $\Delta\Delta\delta$ 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 $\Delta\Delta\delta$ value) was obtained with 80 mM (*S*)-CSA 1/40 mM MA/40 mM DABCO in 50% C_6D_6/50% $CDCl_3$ (v/v), which gave excellent enantiodifferentiation of the two MA enantiomers (Table 1, entry 7). Then, under the optimized conditions, ^{1}H 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 $\Delta\delta_{\alpha\text{-H}}^{R,S}$ ($\delta_{\alpha\text{-H}}$ of carboxylic acids with (*R*)-CSA 1 − $\delta_{\alpha\text{-H}}$ of carboxylic acids with (*S*)-CSA 1) is −0.55 ppm. Changing the carboxylic acid to (*R*)-MA, we repeated the process and $\Delta\delta_{\alpha\text{-H}}^{R,S}$ was obtained at +0.54 ppm. The results indicate that negative $\Delta\delta_{\alpha\text{-H}}^{R,S}$ correlates to (*S*)-MA and positive $\Delta\delta_{\alpha\text{-H}}^{R,S}$ correlates to (*R*)-MA.

In order to understand the nature of the correlation between $\Delta\delta_{\alpha\text{-H}}^{R,S}$ 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 K_a 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).

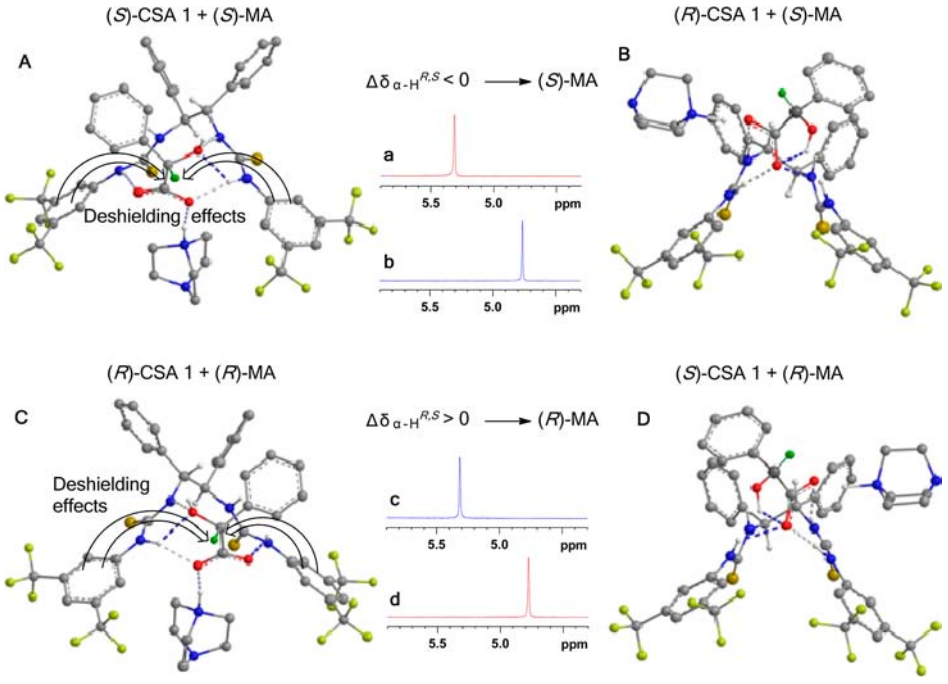

Figure 2. Space-filling representations and ^{1}H NMR spectra of complexes. Complexes: (A) (*S*)-CSA 1/(*S*)-MA/DABCO, (B) (*R*)-CSA 1/(*S*)-MA/DABCO, (C) (*R*)-CSA 1/(*R*)-MA/DABCO, (D) (*S*)-CSA 1/(*R*)-MA/DABCO. The α-Hs of (*R*)- and (*S*)-MAs are shown in green. ^{1}H NMR spectra of α-Hs of (*R*)- or (*S*)-MAs: (a) in complex A, (b) in complex B, (c) in complex C, (d) in complex D.

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Table 3. Measurements of $\Delta\delta_{\alpha\text{-H}}{}^{R,S}$ of Chiral Carboxylic Acids in the Presence of (*R*)-CSA 1 or (*S*)-CSA 1[a]

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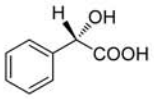
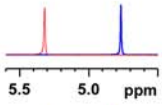
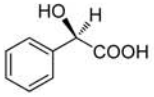
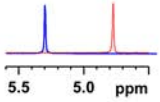
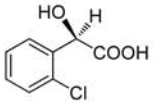
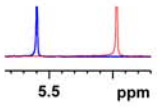
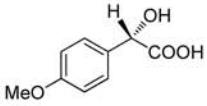
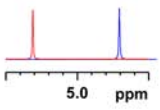
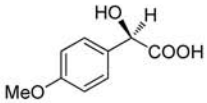
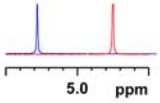
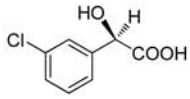
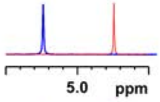
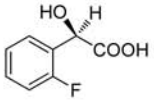
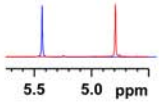
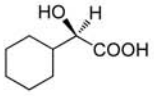
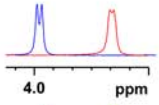
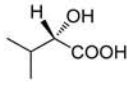
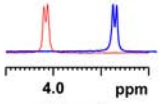
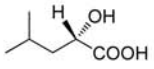
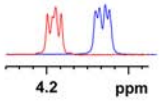
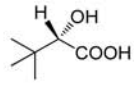
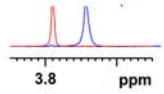
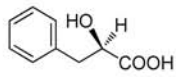
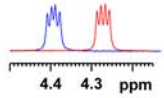
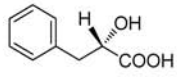
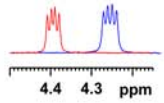
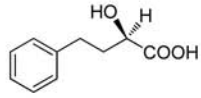
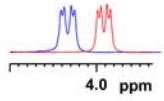
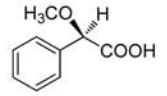
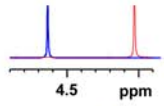
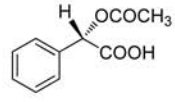
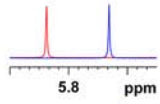
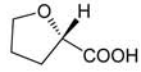
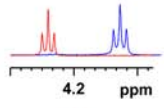
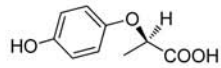
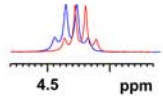
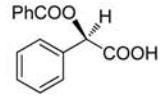
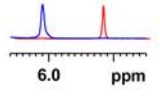
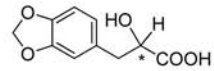
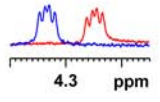
1			-0.55 (*S*)
2			+0.54 (*R*)
3			+0.63 (*R*)
4			-0.56 (*S*)
5			+0.54 (*R*)
6			+0.51 (*R*)
7			+0.66 (*R*)
8			+0.13 (*R*)
9			-0.13 (*S*)
10			-0.10 (*S*)

entry	carboxylic acid	contrasting spectra[b]	$\Delta\delta_{\alpha\text{-H}}{}^{R,S}$ (ppm)[c]
11			-0.08 (*S*)
12			+0.13 (*R*)
13			-0.13 (*S*)
14			+0.09 (*R*)
15			+0.54 (*R*)
16			-0.22 (*S*)
17			-0.21 (*S*)
18			+0.02 (*R*)
19			+0.17 (*R*)
20			+0.09 (*R*)[d]
21			+0.30 (*R*) *incorrect*

[a]All samples were prepared by mixing 2:1:1 of CSA 1, DABCO, and carboxylic acids in NMR tubes (entry 20 is 25 mM, and the others are 40 mM in 50% C_6D_6/50% $CDCl_3$ (v/v)). [b]Red spectra were obtained with (*S*)-CSA 1, and blue spectra were obtained with (*R*)-CSA 1 by ^{1}H NMR (400 MHz) at 25 °C. [c]Assigned configurations are labeled in parentheses. [d]Assigned configuration was confirmed by chiral HPLC analysis (comparing its derivative with natural product danshensu).

One-dimensional NOESY experiments for the mixtures of CSA 1/MA/DABCO showed strong correlation between α-H of MA and Ar−Hs of CSA 1 (H_c; 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 H_c of CSA 1 to α-H of (*S*)-MA in space. However, the mixture of (*R*)-CSA 1/(*S*)-MA/DABCO gave weaker NOESY signals between α-H of (*S*)-MA and Ar−Hs of CSA 1 (H_c and H_f; see Supporting Information), indicating that the α-H was farther from H_c and closer to H_f in the complex of (*R*)-CSA 1/(*S*)-MA/DABCO, compared with the α-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, α-Hs of MAs are located in the deshielding range of the aromatic system of CSA 1 (shielding

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range, above/below the ring plane and inside the ring; deshielding range, on the periphery of the ring plane). Compared with the α-H of (*S*)-MA in complex B, the α-H of (*S*)-MA experiences more deshielding in complex A due to a closer distance so that the ^{1}H NMR signal of α-H of (*S*)-MA should be more downfield. Therefore, the $\Delta\delta_{\alpha\text{-H}}{}^{R,S}$ is negative. For (*R*)-MA, the stronger deshielding effect in complex C compared to that in complex D results in a positive $\Delta\delta_{\alpha\text{-H}}{}^{R,S}$ value. Mastering the nature of correlation, we can judge the absolute configurations of carboxylic acids according to the positive or negative sign of $\Delta\delta_{\alpha\text{-H}}{}^{R,S}$.

In order to confirm the validity of this correlation, assignments of a series of α-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). However, for α-nitrogen-substituted carboxylic acids, such as an amino acid derivative, our method was not applicable (Table 3, entry 21).

In summary, chiral bisthioureas derived from 1,2-diphenylethane-1,2-diamine as CSAs have been shown to be quite efficient for ^{1}H NMR assignments of the absolute configurations of various α-hydroxyl acids and their derivatives in the presence of DABCO. The negative $\Delta\delta_{\alpha\text{-H}}{}^{R,S}$ correlates to (*S*)-acids, and positive $\Delta\delta_{\alpha\text{-H}}{}^{R,S}$ 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 α-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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