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Chiral discrimination of α -hydroxy acids and *N*-Ts- α -amino Acids induced by tetraaza macrocyclic chiral solvating agents by using ^1H NMR spectroscopy

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Abstract

In the field of chiral recognition, reported chiral discrimination by ^1H NMR spectroscopy has mainly focused on various chiral analytes with a single chiral center, regarded as standard chiral substrates to evaluate chiral discriminating abilities of a chiral auxiliary. Among them, chiral α -hydroxy acids, α -amino acids and their derivatives are chiral organic molecules involved in a wide variety of biological processes, and also play an important role in the area of preparation of pharmaceuticals, as they are part of the synthetic process in the production of chiral drug intermediates and protein-based drugs. In this paper, several α -hydroxy acids and *N*-Ts- α -amino acids were used to evaluate the chiral discriminating abilities of tetraaza macrocyclic chiral solvating agents (TAMCSAs) **1a–1d** by ^1H NMR spectroscopy. The results indicate that α -hydroxy acids and *N*-Ts- α -amino acids were successfully discriminated in the presence of TAMCSAs **1a–1d** by ^1H NMR spectroscopy in most cases. Assignment of enantiomers of the α -hydroxy acids and *N*-Ts- α -amino acids were determined based on the change of integration of the ^1H NMR signals of the corresponding protons. Enantiomeric excesses (ee) of *N*-Ts- α -amino acids **11** with different optical compositions were calculated based on the integration of the ^1H NMR signals of the CH_3 protons (Ts group) of enantiomers of (*R*)- and (*S*)-**11** in the presence of TAMCSA **1b**. At the same time, the possible chiral discriminating behaviors have been discussed by means of Job plots of ($\pm$)-**2** with TAMCSAs **1b** and proposed theoretical models of enantiomers of **2** and **6** with TAMCSA **1a**, respectively.

Graphical abstract

Several α -Hydroxy acids and *N*-Ts- α -amino acids were effectively discriminated in the presence of tetraaza macrocyclic chiral solvating agents (TAMCSAs) **1a–1d** by ^1H NMR spectroscopy

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Electronic Supplementary Information (ESI) available: Procedure of synthesis of TAMCSA **1d**, ^1H and ^{13}C NMR and HRMS spectra. See DOI: 10.1039/x0xx00000x

Introduction

Chiral discrimination is an interesting and essential phenomenon widely existing in nature.¹ It plays a critical role in biological processes, including enzyme operation, molecular transport, protein assembly and pharmacological action.² Furthermore, with the dramatic recent growth in the applications of asymmetric synthesis, especially due to an increased demand for chiral drugs as pure enantiomers, a great deal of asymmetric products or chiral drugs must be characterized by determination of absolute configuration and analysis of optical purity, in addition to characterization by routine methods such as NMR, MS, elemental analysis and even X-ray crystal diffraction.³ For this purpose, several diagnostic techniques and methods have been used separately or in tandem,⁴ such as high performance liquid chromatography (HPLC),⁵ circular dichroism (CD),⁶ mass spectrometry (MS),⁷ nuclear magnetic resonance (NMR),⁸ UV/vis⁹ and fluorescence spectroscopy.¹⁰ Among them, NMR techniques have been more widely used to meet these demands due to several advantages, including fast, accurate and convenient application, as well as ubiquitous NMR instrumentation availability in nearly all laboratories.¹¹ Most importantly, an effective chiral auxiliary is an essential component in accomplishing this goal because not all chiral compounds have strong chiral discriminating abilities. Therefore, many chemists have been engaged in designing and synthesizing more effective and versatile chiral auxiliaries for chiral discrimination. So far, various chiral auxiliaries have been prepared for this purpose, such as chiral derivatizing agents (CDAs),¹² chiral lanthanide shift reagents (CLSR),¹³ chiral shift reagents (CSRs)¹⁴ and chiral solvating agents (CSAs).¹⁵ In our previous work, a new class of tetraaza macrocyclic chiral solvating agents (TAMCSAs) has been synthesized for chiral discrimination of dipeptide derivatives with two chiral centers by ¹H NMR spectroscopy (Figure 1).¹⁶ Our results have established that TAMCSAs **1a–1c** possess excellent chiral discriminating abilities towards dipeptide derivatives. Their success may mainly result from the most outstanding feature of TAMCSAs **1a–1d**, which is the presence of two amide, two amino and two phenolic hydroxyl groups, as multiple potential hydrogen bonding interaction sites, along with an overall *C*₂-symmetry and a well-defined reaction cavity. On the basis of these outstanding features, the chiral discriminating abilities of TAMCSAs **1a–1d** should be applicable to the determination of absolute configuration and analysis of optical purity by ¹H NMR spectroscopy for a wide range of chiral substrates and drugs. In order to verify this hypothesis, TAMCSAs **1a–1d** are used in this paper for the chiral discrimination of α-hydroxy acids and *N*-Ts-α-amino acids by ¹H NMR spectroscopy. These substrates are important organic molecules involved in a wide variety of biological processes.^{1,9a}

Results and discussion

TAMCSA **1d** has been synthesized according to the synthetic procedure of TAMCSAs **1a–1c**.¹⁶ Meanwhile, the corresponding chiral diamine was also obtained as known chiral compound.¹⁷

Unfortunately, its crystals suitable for X-ray single-crystal diffraction analysis were not obtained. Thus, the 2D NOESY spectrum of TAMCSA **1d** was measured. The α -H of the PhCH group (C3 and C8) exhibits strong NOESY correlated signals with the CH proton of (C5 and C6). This result suggests that two protons (H3 and H5, and H6 and H8) are located on the same side of the macrocyclic framework. In accordance with the known absolute configuration (*R, R*) of phenylglycine residue (C3 and C8) and the C_2 -symmetry geometry, the stereo configurations of the newly generated chiral centers (C5 and C6) of TAMCSA **1d** are assigned as *S, S*. This is completely in line with the assignment of the absolute configuration of the same unit in TAMCSA **1a** as determined by both the NOESY spectrum and X-ray crystal diffraction analysis.

In order to further extend the study on the chiral discriminating abilities of TAMCSAs **1a–1d**, mandelic acid ($\pm$)-**2** was first used as a guest in the presence of TAMCSAs **1a** and **1d**. Their ¹H NMR spectra showed that the single peak of α -H in ($\pm$)-**2** was clearly split into two well-resolved peaks. The nonequivalent chemical shift difference (δ) of α -H in ($\pm$)-**2** was calculated to be 0.021 and 0.044 ppm. Overlaid ¹H NMR spectra of a mixture of ($\pm$)-**2** with TAMCSA **1d** (1:1), free ($\pm$)-**2** and TAMCSA **1d** are shown in Figure 2.

This preliminary result suggests that enantiomers of ($\pm$)-**2** can be clearly discriminated in the presence of TAMCSA **1d** by ¹H NMR spectroscopy. Herein, in order to obtain better baseline resolution and more clearly split ¹H NMR signals for chiral discrimination, a range of concentrations, deuterated solvents, and ratios of host and guest were tested and optimized. First, ¹H NMR spectra of ($\pm$)-**2** with **1a** were measured in different deuterated solvents, namely neat CDCl₃, CDCl₃ containing 10% CD₃COCD₃, CD₃OD and DMSO-*d*₆. The nonequivalent chemical shift of α -H in ($\pm$)-**2** was evaluated to be 0.021 ppm in neat CDCl₃. However, not all ¹H NMR signals of the protons of the enantiomers of ($\pm$)-**2** were found to be split in the presence of TAMCSA **1a** in other solvents. This result suggests that neat CDCl₃ is the most suitable solvent for chiral discrimination.

Subsequently, samples of various concentrations of ($\pm$)-**2** were prepared in the presence of TAMCSA **1a**, and their ¹H NMR spectra were recorded on a 400 MHz NMR spectrometer. The results indicate that nonequivalent chemical shifts of α -H in ($\pm$)-**2** were gradually increasing from 0.012 to 0.029 ppm with increasing concentration (Figure 3). Based on common solubilities of hosts and guests, and the general requirements for concentrations in ¹H NMR spectroscopy, a concentration of 10 mM was selected for chiral discrimination.

Finally, the ratio of host and guest was studied because it is a key factor for chiral discrimination. Samples of ($\pm$)-**2** with TAMCSA **1a** were prepared at different ratios and their ¹H NMR spectra were measured. Upon addition of TAMCSA **1a**, the nonequivalent chemical shifts of α -H in ($\pm$)-**2** were found to be gradually increasing until a maximum

(0.021 ppm) was obtained at 1:1 molar ratio of ($\pm$)-**2** versus TAMCSA **1a**. Subsequently, this trend showed a decline with continued addition of TAMCSA **1a** (Figure 4). Hence, a molar ratio of 1:1 for ($\pm$)-**2** versus TAMCSA **1a** is optimum for chiral discrimination.

Upon completion of the aforementioned optimization study, the chiral discriminating abilities of TAMCSAs **1a–1d** were evaluated by examining the enantiomeric discrimination of α -hydroxy acids ($\pm$)-**2–5** (Figure 5).

All sample combinations of ($\pm$)-**2–5** with TAMCSAs **1a–1d** were prepared, and their ^1H NMR spectra were measured, with the exception of ($\pm$)-**2**, which was only studied in the presence of TAMCSAs **1a** and **1d**. All enantiomers of ($\pm$)-**2–5** were discriminated in the presence of TAMCSAs **1a**, **1b** and **1d** by ^1H NMR spectroscopy. Their nonequivalent chemical shifts (δ , ppm) and partial ^1H NMR spectra are summarized in Table 1. However, their δ values are smaller than that reported by other research groups.^{1,18} On the other hand, enantiomers of ($\pm$)-**2–5** were not discriminated in the presence of TAMCSA **1c**. This may be because of the presence of two bromine atoms with considerable steric hindrance, which may prevent the intermolecular interaction between TAMCSA **1c** and enantiomers of ($\pm$)-**2–5**.

Subsequently, the (*R*)- or (*S*)-enantiomer of **2–5** was added into the corresponding mixture of ($\pm$)-**2–5** with TAMCSAs **1a**, **1b** and **1d**, respectively, and ^1H NMR spectra were collected. Enantiomers of ($\pm$)-**2–5** were easily assigned based on the change of integration of the ^1H NMR signals of the corresponding protons of ($\pm$)-**2–5**.

In order to acquire more evidence to evaluate the chiral discriminating abilities of TAMCSAs **1a–1d** towards various chiral substrates, *N*-Ts- α -amino acids ($\pm$)-**6–13** were used as guests (Figure 6).

All samples of ($\pm$)-**6–13** were prepared in the presence of TAMCSAs **1a–1d** in CDCl_3 and their ^1H NMR spectra were obtained. The results demonstrate that ^1H NMR signals of one, two and even more types of protons of ($\pm$)-**6–13** exhibit splitting, and the nonequivalent chemical shifts of the corresponding protons were evaluated. Among them, the δ value of the *NH* proton (Ts*NH* group) of ($\pm$)-**11** is found to provide maximum splitting (0.258 ppm) in the presence of TAMCSA **1a**. The enantiomers of ($\pm$)-**13** couldn't be discriminated in the presence of TAMCSA **1c**. Subsequently, the (*R*)- or (*S*)-enantiomer of **6–13** was added into the corresponding mixture of ($\pm$)-**6–13** with TAMCSAs **1a–1d**, respectively, and ^1H NMR spectra were measured. Enantiomers of ($\pm$)-**6–13** were clearly assigned based on the change of integration of the ^1H NMR signals of the corresponding protons of ($\pm$)-**6–13**. The δ values and partial ^1H NMR spectra of the protons with larger nonequivalent chemical shifts and less interfering signals of ($\pm$)-**6–8** and **10–13** are summarized in Table 2. The δ values and partial ^1H NMR spectra of ($\pm$)-**6–12** with **1c** and the overlapped proton signals of CH_3 group of ($\pm$)-**6–9** in the presence of TAMCSAs **1a**, **1b** and **1d** are available in the supplementary information (Table S1).

TAMCSA **1c** did not exhibit strong chiral discriminating abilities towards enantiomers of ($\pm$)-**6–13** based on their nonequivalent chemical shifts. This may be due to the same reason

responsible for the observed lack of discrimination of enantiomers of ($\pm$)-**2-5** in the presence of TAMCSA **1c**.

Now that TAMCSAs **1a**, **1b** and **1d** have been established to demonstrate strong chiral discriminating abilities towards *N*-Ts- α -amino acids by ^1H NMR spectroscopy, their practical applicability was tested in determining enantiomeric excess (ee). Samples containing (*R*)-**11** with 90, 80, 65, 45, 25, 0, -25, -45, -65, -80 and -90 % were prepared in the presence of TAMCSA **1b**, and their ^1H NMR spectra were measured. Enantiomeric excesses of all samples were calculated based on the integration of the ^1H NMR signals of the CH_3 protons (Ts group) of enantiomers of (*R*)- and (*S*)-**11**. The overlaid partial ^1H NMR spectra and linear correlation between the theoretical (x) and observed $ee\%$ (y) are shown in Figure 7.

In order to further investigate the chiral discriminating behaviour, Job plots of ($\pm$)-**2** were carried out in the presence of TAMCSA **1b**. A maximum value ($X^* \delta = 0.007$ ppm) of α -H in ($\pm$)-**2** was observed at a molar fraction of $X = 0.5$, which suggests that a diastereoisomer complex with 1:1 stoichiometry is established between ($\pm$)-**2** and TAMCSA **1b** (Figure 8).

To better understand the chiral discriminating behaviour between TAMCSAs and α -hydroxy acid, ($\pm$)-**2** and TAMCSA **1a** were selected as typical species. Theoretical calculations were performed by means of hybrid density functional theory (B3LYP)¹⁹ with the standard basis sets of 3-21G of the Gaussian 03 program.²⁰ The proposed models suggest that a pair of diastereoisomer complex of ($\pm$)-**2** and TAMCSA **1a** is formed with 1:1 stoichiometry. The proposed structures exhibit the formation of intermolecular hydrogen bonds of (*R*)-**2** with TAMCSA **1a** (PhOH...O(H)CH, 1.65 Å; PhOH...O=C-OH, 2.32 Å; NH...O=C-OH, 2.47 Å), and (*S*)-**2** with TAMCSA **1a** (PhOH...O(H)CH, 1.63 Å). Obviously, hydrogen bonds between hydrogen atom of phenolic hydroxyl group (TAMCSA **1a**) and oxygen atom of hydroxyl group of two enantiomers of ($\pm$)-**2** are a major force for the formation of complexes of (*R*)-**2** and (*S*)-**2** with TAMCSA **1a**. The individual structures of (*R*)-**2** and (*S*)-**2** with TAMCSA **1a** are shown in Figure 9.

In this study, the TAMCSAs **1a-1d** give much better chiral discrimination for *N*-Ts- α -amino acids than for α -hydroxy acids. The theoretical studies of complexes of them may be a more interesting issue. For this purpose, theoretical calculations of enantiomers of **6** and TAMCSA **1a** were performed by using the aforementioned method. Formation of Hydrogen bonds and their distances are shown in Figure 10.

As shown in Figure 10, the complex of (*R*)-**6** with TAMCSA **1a** was formed through three hydrogen bonds ($\text{CH}_3\text{CHC}(\text{OH})=\text{O}\dots\text{HN}$, 2.02 Å; $\text{C}=\text{O}\dots\text{HNSO}_2$, 1.66 Å; $\text{O}=\text{S}=\text{O}\dots\text{HOPh}$, 1.62 Å). However, the complex of (*S*)-**6** with TAMCSA **1a** was formed by only one hydrogen bond, which distance ($\text{SO}_2\text{NH}\dots\text{O}=\text{CNH}$) is 1.74 Å. Obviously, (*R*)-**6** formed a much tighter complex with TAMCSA **1a** than (*S*)-**6**.

Meanwhile, the calculated chemical shifts and nonequivalent chemical shifts of the CH_3 protons (Ts) with well split signals of (*R*)-**6** and (*S*)-**6** were given in the presence of TAMCSA **1a** (Table 3). The calculated chemical shift of the CH_3 protons of (*S*)-**6** moved

downfield with a smaller δ value. These results show that the trends of the calculated chemical shifts of the CH_3 protons of (*R*)-**6** and (*S*)-**6** are consistent with that of the observed chemical shifts of the corresponding CH_3 protons of (*R*)-**6** and (*S*)-**6**.

In addition, to further investigate the interaction of enantiomers of ($\pm$)-**6** with TAMCSA **1a**, the NOESY spectrum of was recorded in the presence of TAMCSA **1a** (Figure 11). The intramolecular NOEs of corresponding protons of enantiomers of ($\pm$)-**6** or TAMCSA **1a** were clearly found. However, the intermolecular NOEs between the split protons (CH_3 and PhCH_3 groups) of ($\pm$)-**6** with aromatic protons of TAMCSA **1a** could be partly observed by their weak cross signals. The result indicated that there may be large distance between the split protons of ($\pm$)-**6** and aromatic protons of TAMCSA **1a**.

Conclusions

In summary, enantiomers of α -hydroxy acids and *N*-Ts- α -amino acids were successfully discriminated in the presence of TAMCSAs **1a**, **1b** and **1d** by ^1H NMR spectroscopy. TAMCSA **1c** did not exhibit strong chiral discriminating abilities towards the guests employed. This may be because of the presence of the two sterically demanding bromine atoms, which may prevent or weaken the intermolecular interaction between TAMCSA **1c** and the guests. Enantiomeric excesses (ee) of **11** with different optical compositions were calculated based on the integration of ^1H NMR signals of CH_3 protons (Ts group) of enantiomers (*R*)-**11** and (*S*)-**11** in the presence of TAMCSA **1b**. The results indicate that TAMCSA **1a**, **1b** and **1d**, are capable of discriminating enantiomers of α -hydroxy acids ($\pm$)-**2–5** and *N*-Ts- α -amino acids ($\pm$)-**6–13** by ^1H NMR spectroscopy, establishing them as effective and versatile solvating agents. The results further demonstrate that the outstanding features of TAMCSAs **1a**, **1b** and **1d**, namely, a combination of two amide, two amino and two phenolic hydroxyl residues as multiple potential intermolecular interaction sites, along with an overall C_2 -symmetry and a 12-membered cavity as part of the framework, are helpful to improve inherent abilities of chiral discrimination by ^1H NMR spectroscopy.

Supplementary Material

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Acknowledgments

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Figure 1.
Structures of TAMCSAs **1a–1d**.

Figure 2. Overlaid ¹H NMR spectra (400 MHz) of TAMCSA **1d**, free (±)-**2**, and mixture of (±)-**2** with TAMCSA **1d**, H:G = 1:1.

Figure 3. Overlaid ¹H NMR spectra and nonequivalent chemical shifts of concentration variation of (±)-2 in the presence of TAMCSA 1a. The molar ratio of TAMCSA 1a: (±)-2 is 1:1 in all cases.

Figure 4. Overlaid ^1H NMR spectra and nonequivalent chemical shifts of α -H of (±)-**2** with various molar ratios in the presence of TAMCSA **1a**. The concentration of (±)-**2** is 10 mM in CDCl_3 in all cases.

Figure 5.
Structures of α -hydroxy acids ($\pm$)-2–5.

Figure 6.
Structures of *N*-Ts- α -amino acids ($\pm$)-**6–13**.

Figure 7.

(a) Determination of enantiomeric excesses of **11** with different optical purities ($ee\% = R\% - S\%$) in the presence of TAMCSA **1b** (1.0 equiv). (b) Linear correlation between the observed (Y) and theoretical $ee\%$ values (X) of **11** in the presence of 1.0 equiv of TAMCSA **1b**.

Figure 8.

Job plots for the complexation of TAMCSA **1b** with (*R*)- and (*S*)-**2**, respectively. The δ is standing for chemical shift change of α -H of (*R*)- and (*S*)-**2** in the presence of TAMCSA **1b**, and X is standing for the mole fraction of ($\pm$)-**2**, $X = [(\pm)\text{-}\mathbf{2}] / [(\pm)\text{-}\mathbf{2}] + [\text{TAMCSA } \mathbf{1b}]$.

Figure 9.
Proposed bonding models for the interactions between TAMCSA **1a** with enantiomers of (*R*)-**2** (a) and (*S*)-**2** (b).

(a)

Figure 10. Proposed bonding models for the interactions between TAMCSA **1a** with enantiomers of (*R*)-**6** (a) and (*S*)-**6** (b).

Figure 11.
NOESY spectrum of (±)-**6** with TAMCSA **1a** in CDCl₃.

Scheme 1.

Synthesis of TAMCSA 1d. Conditions: (i) Zn powder/MsOH, dried THF, -18°C .

Table 1

Nonequivalent chemical shifts (δ , ppm) and partial ^1H NMR spectra of ($\pm$)-**2-5** in the presence of TAMCSAs **1a**, **1b** and **1d** in CDCl_3 at room temperature.^a

TAMCSA/Guest	Proton/ δ	Spectra	TAMCSA/Guest	Proton/ δ	Spectra
1a /($\pm$)- 2	α -H 0.021		1a /($\pm$)- 4	α -H 0.032	
1b /($\pm$)- 2	α -H 0.016		1b /($\pm$)- 4	α -H 0.021	
1d /($\pm$)- 2	α -H 0.044		1d /($\pm$)- 4	α -H 0.056	
1a /($\pm$)- 3	α -H 0.013		1a /($\pm$)- 5	OCH_3 0.035	

TAMCSA/Guest	Proton/ δ	Spectra	TAMCSA/Guest	Proton/ δ	Spectra
1b/(+)-3	α -H 0.013		1b/(+)-5	OCH ₃ 0.025
1d/(+)-3	α -H 0.034		1d/(+)-5	OCH ₃ 0.027

^aNonequivalent chemical shifts (δ , ppm) of (±)-**2-5** (10×10^{-3} M) in the presence of TAMCSAs **1a**, **1b** and **1d**, respectively, H:G = 1:1.

Table 2

Nonequivalent chemical shifts (δ , ppm) and partial ^1H NMR spectra of the more representative protons of ($\pm$)-**6-8** and **10-13** in the presence of TAMCSAs **1a**, **1b** and **1d** in CDCl_3 at room temperature.^a

TAMCSA/Guest	Proton/ δ	Spectra	TAMCSA/Guest	Proton/ δ	Spectra
1a /($\pm$)- 6	PhCH_3 0.087		1a /($\pm$)- 8	PhCH_3 0.157
	TsNH 0.188			TsNH 0.093
1b /($\pm$)- 6	PhCH_3 0.068			CH_3 0.105

TAMCSA/Guest	Proton/ δ	Spectra	TAMCSA/Guest	Proton/ δ	Spectra
	TsNH 0.225			PhCH ₃ 0.144
1d /(±)- 6	PhCH ₃ 0.056			TsNH 0.098
1a /(±)- 7	CH ₃ 0.075		1b /(±)- 8	CH ₃ 0.077

TAMCSA/Guest	Proton/ δ	Spectra	TAMCSA/Guest	Proton/ δ	Spectra
	PhCH_3 0.198			PhCH_3 0.098	
	TsNH 0.138			TsNH 0.151	
1b/(±)-7	CH_3 0.060		1d/(±)-8	CH_3 0.083	
	PhCH_3 0.139			PhCH_3 0.108	

TAMCSA/Guest	Proton/ δ	Spectra	TAMCSA/Guest	Proton/ δ	Spectra
	α -H 0.105			TsNH ^b 0.113
	TsNH 0.125		1a/(±)-10	PhCH ₃ 0.104
1d/(±)-7	CH ₃ 0.059			TsNH 0.222
1b/(±)-10	PhCH ₃ 0.104		1d/(±)-11	PhCH ₃ 0.072

TAMCSA/Guest	Proton/ δ	Spectra	TAMCSA/Guest	Proton/ δ	Spectra
	α -H 0.052
1d/(±)-10	PhCH ₃ 0.098		1a/(±)-12	PhCH ₃ 0.180
1a/(±)-11	PhCH ₃ 0.110			TsNH 0.101

TAMCSA/Guest	Proton/ δ	Spectra	TAMCSA/Guest	Proton/ δ	Spectra
	α -H 0.058		1b/(±)-12	PhCH_3 0.122
	TsNH 0.258		1d/(±)-12	PhCH_3 0.131
1b/(±)-11	PhCH_3 0.082		1a/(±)-13	α -H 0.068
	α -H 0.038		1b/(±)-13	α -H 0.068

TAMCSA/Guest	Proton/ δ	Spectra	TAMCSA/Guest	Proton/ δ	Spectra
	Ts:NH 0.189		1d/(±)-13	α -H 0.061

^aNonequivalent chemical shifts and ¹H NMR spectra of (±)-**6-13** (10×10^{-3} M) in the presence of TAMCSAs **1a-1d**, respectively, H:G = 1:1.

^bNonequivalent chemical shifts and ¹H NMR spectra of the NH protons of the Ts:NH group of (±)-**8** (10×10^{-3} M) by adding (S)-**8** to the mixture of (±)-**8** and TAMCSA **1d**.

Table 3

Calculated and observed chemical shifts (δ , ppm) and non-equivalent chemical shifts ($\delta_{(SR)}-6$, ppm) for the protons (CH_3) of the $PhCH_3$ group of (*R*)-**6** and (*S*)-**6** in the presence of TAMCSA **1a**.

	$\delta_{(R)}-6$	$\delta_{(S)}-6$	$\delta_{(SR)}-6$
Calcd values	2.410	2.565	0.155
Obsd values	2.258	2.345	0.087