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Trianglamine as a new chiral shift reagent for secondary alcohols

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Abstract—Chiral trianglamines **1** and **2** were found to be useful as NMR chiral shift reagents for the determination of enantiomeric purity and absolute configuration of several kinds of secondary alcohols, cyanohydrins, and propargyl alcohols.

1. Introduction

The use of chiral shift reagents (chiral solvating reagents) for ^{1}H NMR spectroscopy is one of the most convenient methods to achieve quick determination of the enantiomeric excesses of chiral compounds. This method has the advantage of easy performance without using any chiral derivatization of the analyte. A wide variety of chiral shift reagents such as lanthanoide complexes,[1] crown ethers,[2] cyclodextrins,[3] porphyrins,[4] macrocycles,[5] and others[6] have been reported. Trianglamines **1** and **2**, macrocyclic amines with D_3 symmetry, can be readily synthesized through [3+3] cyclocondensation of enantiomerically pure 1,2-diaminocyclohexane with terephth aldehyde or 4,4′-diformylbiphenyl, followed by $NaBH_4$ reduction.[7] However, the chiral recognition of this type of compounds has barely been explored, while some conformational analyses and structural studies of the com pounds have been reported recently.[8] The D_3 symmetrical chiral structures of trianglamines **1** and **2** should provide a highly asymmetric environment for the chiral guest molecules through various interactions such as hydrogen bonding, π–π stacking, and CH–π interactions. Herein, we report the ^{1}H NMR study of chiral recognition of several kinds of secondary alcohols by chiral trianglamines **1** and **2**. The chiral trianglamine hosts act as an NMR chiral shift reagent for determination of absolute configuration and enantiomeric purity of these guest compounds.

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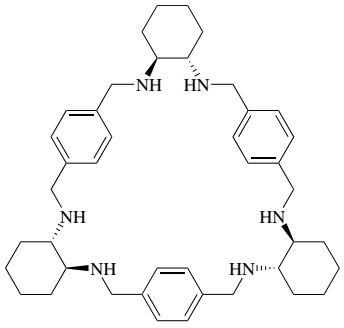
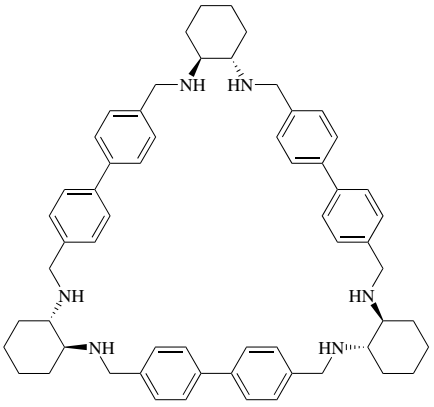
2. Results and discussion

Enantiomerically pure trianglamines, (*S,S,S,S,S,S*)-(+)-**1** and (*S,S,S,S,S,S*)-(+)-**2**, were prepared by a [3+3] condensation reaction between (*S,S*)-*trans*-1,2-diaminocyclohexane and terephthalaldehyde or 4,4′-diformylbiphenyl according to the literature method.[7]

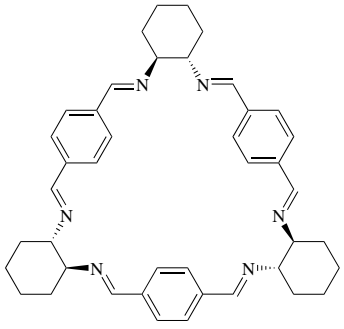
The chiral shift experiments were carried out by measuring ^{1}H NMR spectra (400 MHz) of a mixture of (+)-**1** or (+)-**2** and racemic alcohols **5**–**16** in $CDCl_3$ at room temperature. Table 1 shows the chemical shift differences ($\Delta\Delta\delta$) between the enantiomers of *rac*-alcohols **5**–**16** in the presence of 1 and 2 equiv of (+)-**1** or (+)-**2** in $CDCl_3$. For example, the methine proton signal ($C^{\alpha}H$) of 1-phenylethanol **5a** was split into two quartets with a $\Delta\Delta\delta$ value of 0.064 ppm in the presence of (+)-**1**, due to the different host–guest interactions of the two enantiomers of **5a** with (+)-**1**. The methyl proton signal was also split into two doublets ($\Delta\Delta\delta = 0.040$ ppm) in the presence of (+)-**1**. Of the chloro-substituted derivatives **5c**–**5e**, the chemical shift non-equivalence of the $C^{\alpha}H$ proton is in the order of *o*-Cl-**5c**, *m*-Cl-**5d**, and *p*-Cl-**5e**. For compounds **6** and **7**, the signals for the protons attached to the stereogenic center were split. 1-Phenyl-2-propyn-1-ol **8** showed smaller non-equivalences of both $C^{\alpha}H$ and $C{\equiv}CH$ protons, whereas 3-butyn-2-ol **10** without an aromatic ring revealed no signal splitting. However, 2-hydroxypropanenitrile **9** possessing the electronegative CN group showed baseline resolution, which means that the presence of an electronegative group attached to the stereogenic center is more important than an aromatic ring for better signal splitting. It is also interesting to note that $C^{\alpha}H$ and OCH_3 protons of methyl mandate ester **11b** can be discerned, while the



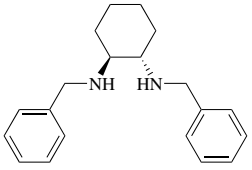
(*S*,*S*,*S*,*S*,*S*,*S*)-(+)-**1**



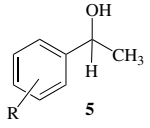
(*S*,*S*,*S*,*S*,*S*,*S*)-(+)-**2**



(*S*,*S*,*S*,*S*,*S*,*S*)-(+)-**3**



(*S*,*S*)-(+)-**4**



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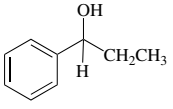
a: R = H
b: R = *p*-CH_3
c: R = *o*-Cl
d: R = *m*-Cl
e: R = *p*-Cl



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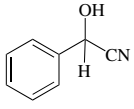

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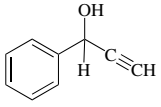

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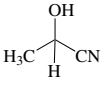

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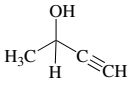

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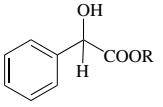
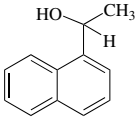


11 a: R = H
b: R = Me



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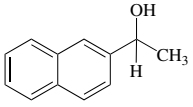

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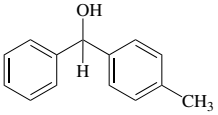

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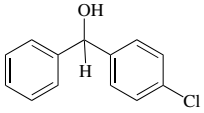

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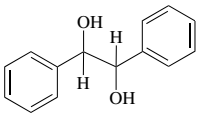

16

signals of mandelic acid **11a** show no changes with the addition of (+)-**1**. In α- and β-1-naphthyl-1-ethanols **12** and **13**, both $C^{\alpha}H$ and CH_3 proton signals were also resolved successfully. The diphenylmethanol derivatives **14** and **15** and 1,2-diphenylethan-1,2-diol **16** showed smaller non-equivalences of the signal than that observed in 1-phenylethanol derivatives **5a**–**5d**. From Table 1, (+)-**1** exhibits a better discriminating ability than (+)-**2**, except for compounds **7** and **16**. The NH groups of (+)-**1** and (+)-**2** are important for the chiral recognition, since the imine compound (+)-**3** does not show any signal splitting in the NMR. Acyclic compound (+)-**4** also does not work as a chiral shift reagent for these compounds.

Upon gradual addition of (+)-**1**, the ^{1}H NMR signal of the $C^{\alpha}H$ proton of **7** moved upfield and the chemical shift difference between the two enantiomers increased gradually until the molar ratio is 1:1. Therefore, the mole ratio of 1:1 is the best for the chiral recognition, giving a maximum difference of 0.040 ppm (Fig. 1).

Table 1. Chemical shift difference ($\Delta\Delta\delta$) between enantiomers of *rac*-alcohols **5**–**16** in the presence of (+)-**1** or (+)-**2** in $CDCl_3$

Alcohol	Signal	(+)-**1**		(+)-**2**	
		Ratio	$\Delta\Delta\delta$ (ppm)	Ratio	$\Delta\Delta\delta$ (ppm)
5a	$C^{\alpha}H$	1:1	0.064	2:1	0.011
	CH_3	1:1	0.040	2:1	0.016
5b	$C^{\alpha}H$	2:1	0.061	2:1	0.010
5c	$C^{\alpha}H$	2:1	0.078	1:1	0.012
	CH_3	2:1	0.027	1:1	0.016
5d	$C^{\alpha}H$	1:1	0.047	2:1	0.007
	CH_3	1:1	0.014	2:1	0
5e	$C^{\alpha}H$	1:1	0.044	2:1	0.005
	CH_3	1:1	0.026	2:1	0
6	$C^{\alpha}H$	2:1	0.047	1:1	0.012
7	$C^{\alpha}H$	1:1	0.040	2:1	0.064
8	$C^{\alpha}H$	1:1	0.014	1:1	0.006
	$C{\equiv}CH$	1:1	0.014	1:1	0.006
9	$C^{\alpha}H$	1:1	0.099	1:1	0.035
	CH_3	1:1	0.016	1:1	0.008
10	$C^{\alpha}H$	1:1	0	1:1	0
	$C{\equiv}CH$	1:1	0	1:1	0
11a	$C^{\alpha}H$	1:1	0	1:1	0
	OCH_3	1:1	0	1:1	0
11b	$C^{\alpha}H$	1:1	0.006	1:1	0
	OCH_3	1:1	0.005	1:1	0.002
12	$C^{\alpha}H$	1:1	0.059	1:1	0.009
	CH_3	1:1	0.016	1:1	0
13	$C^{\alpha}H$	1:1	0.032	1:1	0
	CH_3	1:1	0.017	1:1	0
14	$C^{\alpha}H$	1:1	0.010	1:1	0
	CH_3	1:1	0.013	1:1	0
15	$C^{\alpha}H$	2:1	0.012	2:1	0
16	$C^{\alpha}H$	2:1	0.016	2:1	0.020

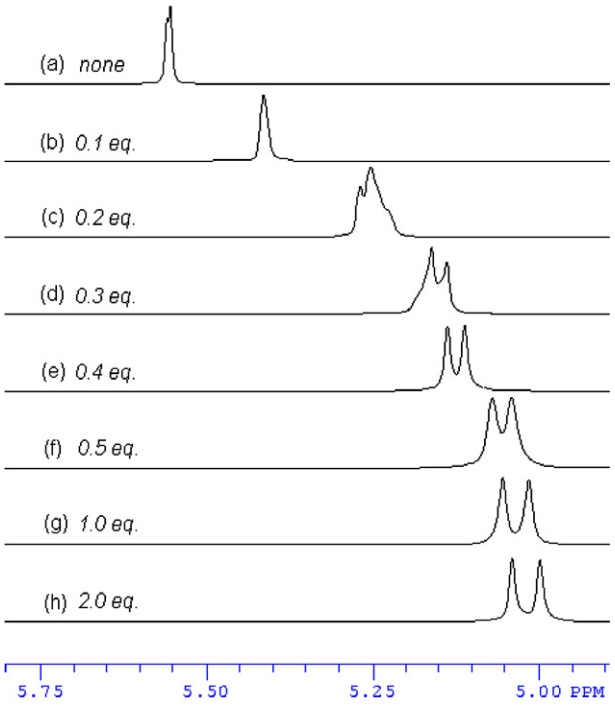

Figure 1. ^{1}H NMR spectra of *rac*-**7** in the presence of (+)-**1** in $CDCl_3$.

Figures 2 and 3 are the Job plots of (+)-**1** and (+)-**2** with (*R*)- and (*S*)-**7**, respectively. For compound (+)-**1**, a maximum was observed when the ratio of (+)-**1** versus (*R*)- or (*S*)-**7** was 1:1 ($X = 0.5$), which indicates that the host forms a 1:1 complex with (*R*)- or (*S*)-**7** (Fig. 2). As with compound (+)-**2**, a maximum appeared when (+)-**2** versus (*R*)- or (*S*)-**7** was 2:1 ($X = 0.67$), indicating that the host formed a 2:1 complex with (*R*)- or (*S*)-**7** under these conditions (Fig. 3). The chemical shift changes of (*R*)-**7** were greater than those of (*S*)-**7** in the presence of (+)-**1**, whereas the chemical shift changes of (*S*)-**7** were greater than those of (*R*)-**7** in the presence of (+)-**2**.

Next, we examined the relationship between the absolute configuration and the upfield shift of the proton signals of guest alcohols in the presence of (*S,S,S,S,S,S*)-(+)-**1** or (*S,S,S,S,S,S*)-(+)-**2**. In the case of compounds **5a**, **7**, **8**, and **9**, the α-methine proton ($C^{\alpha}H$) of the (*R*)-enantiomer appeared at a higher magnetic field than that of the (*S*)-enantiomer in the presence of (*S,S,S,S,S,S*)-(+)-**1** or (*S,S,S,S,S,S*)-(+)-**2** (Table 2).

In the case of relatively bulky guest compounds **14** and **15** having two benzene rings, the α-methine proton signal of the (*S*)-enantiomer appeared at a higher magnetic field than that of the (*R*)-enantiomer in the presence of (*S,S,S,S,S,S*)-(+)-**1**. In the NMR spectra of compound (**16**), α-methine proton signal of the (*S*)-enantiomer appeared at a higher magnetic field in the presence of (*S,S,S,S,S,S*)-(+)-**1**, while that of the (*R*)-enantiomer appeared at a higher magnetic field in the presence of (*S,S,S,S,S,S*)-(+)-**2**.

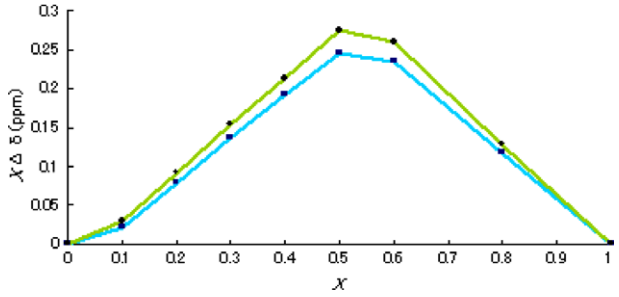

Figure 2. Job plots of (+)-**1** with (*R*)- and (*S*)-**7** [X = molar fraction of **1**, $\Delta\delta$ = chemical shift change of (*R*)- and (*S*)-**7**].

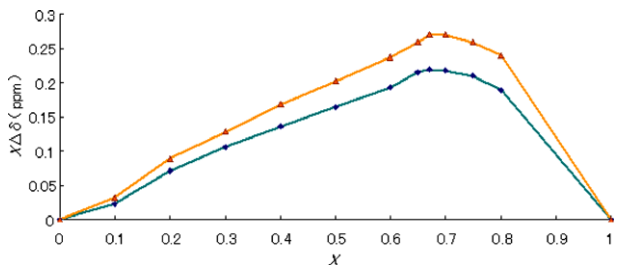

Figure 3. Job plots of (+)-**2** with (*R*)- and (*S*)-**7** [X = molar fraction of **2**, $\Delta\delta$ = chemical shift change of (*R*)- and (*S*)-**7**].

Table 2. The absolute configuration of the enantiomer that showed a more up-field shift in the ^{1}H NMR spectra in the presence of (+)-**1** or (+)-**2**

Alcohol	Host	Enantiomer showing more upfield shift
5a	(+)-**1**	(*R*)
7	(+)-**1**	(*R*)
7	(+)-**2**	(*R*)
8	(+)-**1**	(*R*)
9	(+)-**1**	(*R*)
9	(+)-**2**	(*R*)
14	(+)-**1**	(*S*)
15	(+)-**1**	(*S*)
16	(+)-**1**	(*S*)
16	(+)-**2**	(*S*)

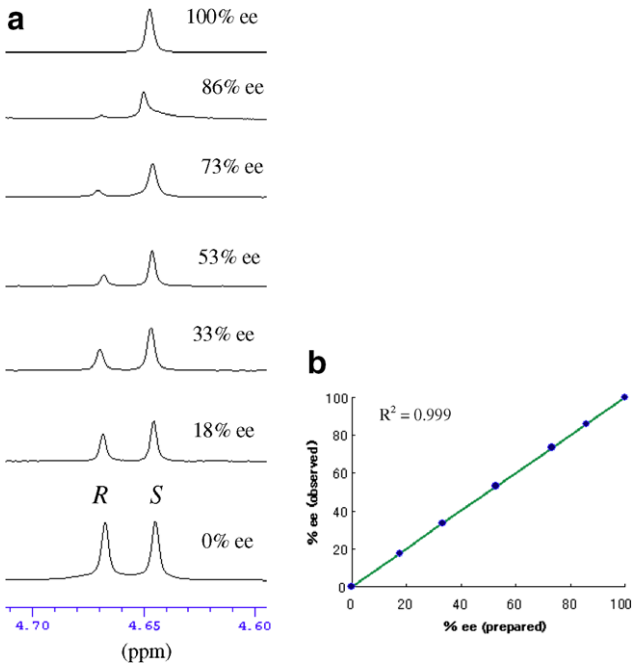

Figure 4. (a) Selected region of the 400 MHz ^{1}H NMR spectra of **16** of various enantiomeric purities in the presence of (*S,S,S,S,S,S*)-**1** (1 equiv). (b) Correlation between theoretical and observed % ee values.

Finally, we attempted to determine the enantiomeric excess (% ee) of the guest alcohol by integration of the corresponding $C^{\alpha}H$ NMR signal in the presence of chiral trianglamine. Samples containing different ee's of **16** were prepared and their NMR spectra in the presence of (+)-**1** measured (Fig. 4a). The excellent linear correlation ($R^2 = 0.999$) between theoretical and observed % ee values was observed (Fig. 4b).

3. Conclusions

In conclusion, chiral trianglamines **1** and **2** function as a useful chiral shift reagent for several types of secondary alcohols. In particular, compound **1** has a better chiral recognition ability than compound **2**. The study on the mechanism of the chiral recognition by chiral trianglamines (**1** and **2**) and the design of new macrocyclic amines are currently in progress.

4. Experimental

4.1. General method

^{1}H NMR spectra were recorded on JEOL JNM-GSX 400 spectrometer, with tetramethylsilane (TMS) as the internal standard. The optical rotations were measured with a ATAGAO AP-100 polarimeter.

Enantiomerically pure macrocyclic amines, (*S,S,S,S,S,S*)-(+)-**1**, (*S,S,S,S,S,S*)-(+)-**2**, and (*S,S,S,S,S,S*)-(+)-**3**, were prepared by the literature method.[7] (*S,S*)-(+)-**4** was also prepared by the literature method.[9]

4.2. NMR shift experiments

NMR shift experiments were performed on a JEOL JNM-GSX 400 spectrometer at 25 °C. Samples for analysis were prepared by mixing enantiomerically pure (+)-**1** or (+)-**2** with the guest alcohol of 1:1 or 2:1 molar ratio in $CDCl_3$.

Acknowledgments

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