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Amphiphilic chiral receptor as efficient chiral solvating agent for both lipophilic and hydrophilic carboxylic acids

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Abstract

Two amphiphilic chiral receptors **2a** and **2b** were designed and synthesized. Both are efficient chiral solvating agents for chiral carboxylic acids. In particular, **2a** is an excellent CSA not only for lipophilic guests, but also for some hydrophilic guests. It is the first CSA for the direct determination of the enantiomeric composition of hydrophilic chiral hydroxylated acid in protic polar solvent.

Keywords: Chiral solvating agent; Chiral recognition; High enantioselectivity; Amphiphilic receptor

Chiral carboxylic acids are basic building blocks of natural products and drug molecules as well as versatile functional synthons.[1–3] Due to their importance, there is a growing demand for the development of fast and accurate methods for determining enantiomeric excess (ee) and assigning the absolute configuration (AC) of these chiral compounds. Apart from other analytical methods such as chromatography[4] and capillary electrophoresis,[5] using chiral solvating agents (CSAs) on NMR spectroscopy is a satisfactory and convenient method to meet this demand,[6–8] and the method can also provide with direct structural and dynamic information of host–guest complexes in solution. Although the development of new CSAs continues to be an active area of research, and various synthetic receptors have been reported in the previous literatures,[9–18] the CSAs that can lead to clear baseline separation of the multiplet of the probe group in two enantiomers are rare. In addition, it has been known that almost all reported CSAs for carboxylic acids could only be used in the less polar solvents, such as deuterated chloroform and benzene so far. This can be ascribed to two reasons. First, most CSAs are only soluble in the less polar solvents due to the existence of the large aromatic groups in these molecules. Second, the noncovalent interactions between host and guest molecules for molecular recognition would be weakened remarkably by the competitive influence of protic solvents. So the discrimination toward hydrophilic guests could not be carried out by using these CSAs. That is why the hydrophilic compounds have to be changed to their lipophilic derivatives prior to discrimination. In fact, most of the bioactive compounds are chiral and hydrophilic and all of the recognition events in nature take place in aqueous medium. So the development of new CSAs which can be used in protic solvents, especially in water, is very important not only for the analysis of bioactive compounds but also for a better understanding and control of the major processes in nature. Therefore the design of the synthetic receptors that can be used as CSAs in protic solvents presents special challenge.

In our previous work,[18] the CSAs (**1a**, **1b**, and **1c**) (Fig. 1) have shown excellent enantioselective recognition ability for some chiral carboxylic acids. However, the acids suitable as the guests for discrimination are limited to lipophilic, and the enantioselective discrimination can be achieved only in the less polar solvents.

In this Letter, we report the design, synthesis, and property of new amphiphilic chiral solvating agents **2a**

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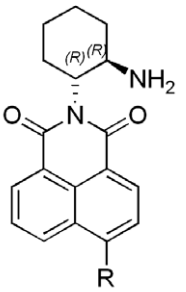


1a (1*R*, 2*R*)- R=H
1b (1*R*, 2*R*)- R=Br
1c (1*R*, 2*R*)- R=N(CH$_3$)$_2$

Fig. 1. (1*R*,2*R*)-1-(1′,8′-Naphthalimide)-2-aminocyclohexane and its 4′-derivatives.

and **2b**. NMR studies demonstrated that they were effective chiral solvating agents. In particular, **2a** not only leads to clear baseline separation of the multiplet of the probe groups in two enantiomers, but also is versatile for a wide range of chiral carboxylic acids including both lipophilic and hydrophilic carboxylic acids.

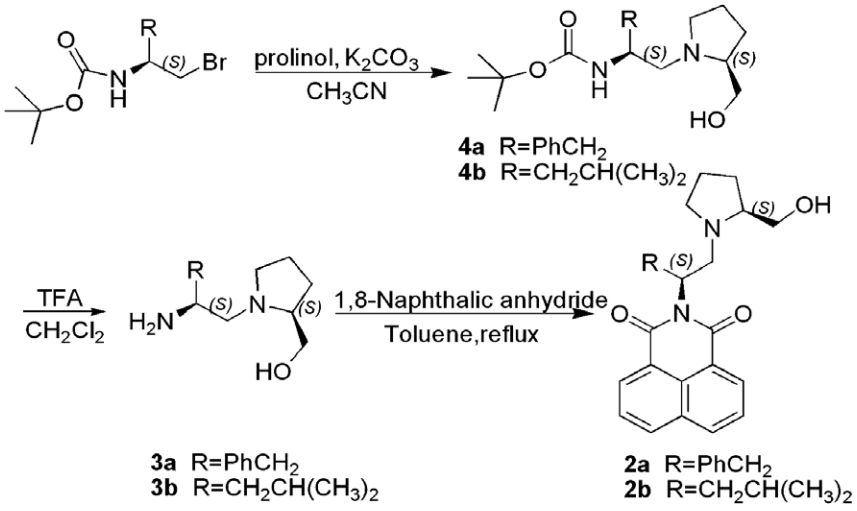
In our approach, chiral amino alcohols (1*S*,2*S*)-*N*-(1-(2-amino-3-phenylpropyl) pyrrolidin-2-yl) methanol (**3a**) and (1*S*,2*S*)-*N*-(1-(2-amino-4-methylpentyl) pyrrolidin-2-yl) methanol (**3b**) instead of (1*R*,2*R*)-1,2-diaminocyclohexane were used to react with 1,8-naphthalic anhydride to get new chiral receptors **2a** and **2b**. Comparing with **1a**, **1b**, and **1c**, the new chiral receptors **2a** and **2b** have one more functional group (primary hydroxyl group) and better flexibility. It was expected that the increased hydrophilic group might make them amphiphilic, which is important for them to be used as the CSAs in many test solvents, such as deuterated methanol, ethanol, acetonitrile, acetone, chloroform, and ethyl acetate. The existence of primary hydroxyl group and high flexibility would help **2a** and **2b** form more stable diastereoisomeric complexes through multiple weak, noncovalent interactions with the guests to overcome the competitive influence of protic solvents to molecular recognition.

The investigation reveals that chiral receptors **2a** and **2b** are amphiphilic, and they are effective chiral solvating agents. In particular, **2a** is an excellent CSA not only for lipophilic guests, but also for some hydrophilic guests, such as tartaric acid and lactic acid. To the best of our knowledge, **2a** is the first receptor which can be used as CSA for the direct determination of the enantiomeric composition of hydrophilic chiral hydroxylated acid in protic polar solvent. Therefore it may be applicable to bioanalytical problems.

The synthetic route for compounds **2a** and **2b** is outlined in Scheme 1. (*S*)-2-(Boc-amino)-3-phenylpropyl bromide or (*S*)-2-(Boc-amino)-4-methylpentyl bromide[19] was reacted, respectively, with 1 equiv of prolinol in the presence of K_2CO_3 in refluxing acetonitrile affording **4a** and **4b**. The treatment of **4a** or **4b** with TFA in CH_2Cl_2 furnished chiral amino alcohols **3a** and **3b** in 43.2% and 35.7% yield, respectively. Then **2a** and **2b** were obtained by condensation of **3a** or **3b** and 1,8-naphthalic anhydride in refluxing toluene with Dean–Stark trap, the yield was 21.3% and 31.5%, respectively. The structures of new chiral receptors **2a** and **2b** were characterized by ^{1}H NMR, ^{13}C NMR, IR, MS, and EA, respectively.

^{1}H NMR spectroscopy was utilized to investigate the enantiomeric discriminating ability of **2a** and **2b**. We chose a broad variety of racemic chiral carboxylic acids as the guests, including lipophilic and hydrophilic carboxylic acids, which were mandelic acid **5** and some of its derivatives **6**–**9**, dibenzoyltartaric acid **10**, lactic acid **11**, tartaric acid **12**, and some N-protected L-amino acids, such as *p*-tolysulfonyl alanine (Ts-alanine) **13**, *p*-tolylsulfonyl valine (Ts-valine) **14**, *p*-nitrobenzenesulfonyl alanine (*p*-NBS-alanine) **15**, and 3,5-dinitrobenzoyl valine (DNB-valine) **16**. The structures of all guests were shown in Figure 2.

Table 1 summarized the chemical shift nonequivalences ($\Delta\Delta\delta$) of CH_3, CH, and NHTs of these guests in the



Scheme 1. The synthesis route of compounds **2a** and **2b**.

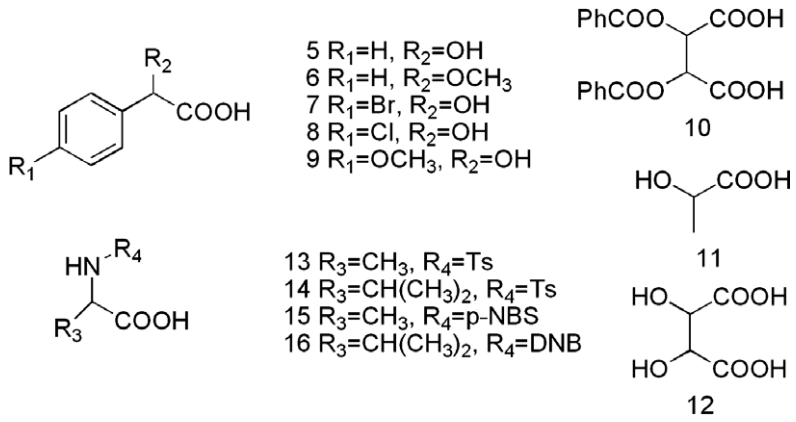


Fig. 2. The structure of guests used herein.

presence of compounds **2a** and **2b**, respectively. As shown in Table 1, in the presence of receptors **2a** and **2b**, there were large enough chemical shift nonequivalences to give baseline resolution of appropriate proton signals for almost all the chosen carboxylic acids measured on a 300 MHz NMR instrument. In the presence of compound **2a**, the $\Delta\Delta\delta$ of the methine proton of 1-methoxy-phenylacetic acid (MPAA) (**6**) was up to 84.3 Hz (see Fig. 3), and the $\Delta\Delta\delta$ of the methine proton of DNB-valine **16** was up to 74.1 Hz. The clear resolution of the multiplet peaks of the methine proton could be observed (see Fig. 4). Furthermore, as what we expected, the recognition of water soluble lactic acid **11** can also be achieved perfectly in $CDCl_3$ when **2a** is used as CSA. It means that the formation of stable host–guest diastereoisomeric complexes has facilitated the guest compound resolving in the test solvent. It is remarkable that even the enantiomers of racemic tartaric acid **12** can also be discerned clearly in the presence of receptor **2a**, the $\Delta\Delta\delta$ is 18.9 Hz in CD_3COCD_3 and 6.9 Hz in CD_3OD, respectively, (shown in Fig. 4), while in the same condition, **2b** did not show any discriminating ability toward the enantiomers of **12**. As far as we know, **2a** is the first receptor, which can be used as CSA for the direct determination of the enantiomeric composition of chiral hydroxylated acid in protic polar solvent. All the results reveal that chiral receptors **2a** and **2b** are excellent chiral solvating agents. Compared with **2b**, **2a** shows applicability toward a wider range of guests and in a broad variety of solvents.

Table 1
Chemical shift nonequivalences ($\Delta\Delta\delta$, 300 MHz) for 1:1 diastereoisomeric complexes of **2a** and **2b** with racemic guests in $CDCl_3$ at 25 °C

Guest	Probe group	$\Delta\delta$ (Hz)		$\Delta\Delta\delta$ (Hz)	
		2a	**2b**	**2a**	**2b**
5	C*H*	−0.575	−0.830	39.3	17.4
		−0.706	−0.888		
6	C*H*	−0.235	−0.351	84.3	19.8
		−0.516	−0.417		
	CH_3	−0.105	−0.200	23.4	13.5
		−0.183	−0.245		
7	C*H*	−1.010	−1.047	15.6	21.6
		−1.062	−1.119		
8	C*H*	−0.639	−0.972	53.4	19.5
		−0.817	−1.037		
9	C*H*	−0.681	−0.889	45.6	25.8
		−0.747	−0.975		
10	C*H*	−0.461	−0.527	18.9[a]	26.7[a]
		−0.524	−0.616		
11	CH_3	−0.256	—[b]	49.5	—[b]
		−0.421			
12[c]	C*H*	0.119	0.124	6.9	0
		0.096			
12[d]	C*H*	0.344	0.215	18.9	0
		0.152			
13	CH_3	−0.280	−0.643	39.0	20.4
		−0.410	−0.711		
	N*H*Ts	0.466	0.08	72.0	109.8
		0.226	−0.286		
14	CH_3	−0.25	−0.413	44.7	62.7
		−0.399	−0.602		
	N*H*Ts	0.243	0.135	69.6	97.8
		−0.011	−0.191		
15	CH_3	−0.349	—[b]	33.0	—[b]
		−0.596			
16	C*H*(CH_3)$_2$	−0.28	—[b]	74.1	—[b]
		−0.39			

[a] The molar ratio of CSA and guest is 2:1.
[b] The peaks of hosts overlapped with the peaks of the probe groups of guests.
[c] The deuterated solvent is CD_3OD.
[d] The deuterated solvent is CD_3OCD_3.

The ^{1}H NMR spectra of hosts **2a** and **2b** with some optical pure guests in a variety of ratios in $CDCl_3$ at a constant total concentration of 3.0×10^{-3} M were obtained. The stoichiometric ratio of the host–guest complexes was determined according to the Job's method of continuous variations.[20] The Job plots of **2a** with (*R*)-mandelic acid and (*S*)-mandelic acid were illustrated in Figure 5, showing a minimum of $\Delta\delta X$ at $X = 0.5$, which indicated that a 1:1 instantaneous complex was formed. The Job plots we have got indicated that hosts **2a** and **2b** form 1:1 instantaneous complexes with all these enantiomerically pure guests, respectively.

We also obtained the titration curves of hosts **2a** and **2b** with these enantiomerically pure guests, respectively. The association constants of the above complexes were

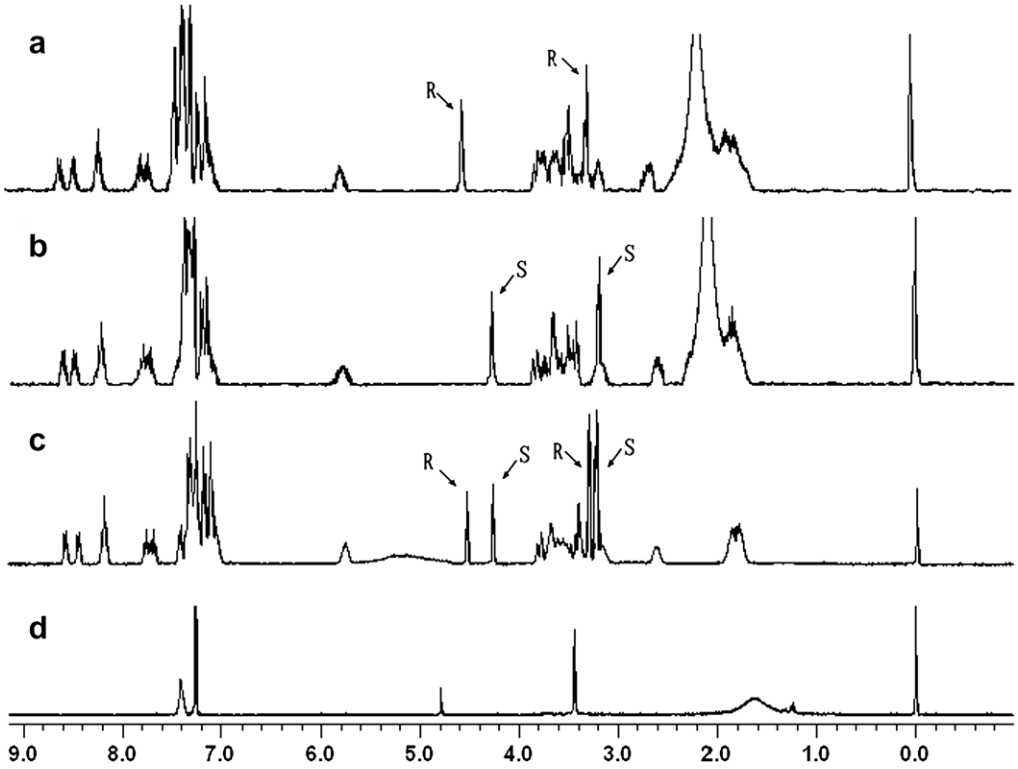


Fig. 3. ^{1}H NMR spectra of equimolar mixtures (20 mM each) of MPAA/compound **2a**. (a) (*R*)-MPAA and compound **2a**; (b) (*S*)-MPAA and compound **2a**; (c) (*R*)/(*S*)-MPAA and compound **2a**; (d) (*R*)/(*S*)-MPAA without compound **2a**.

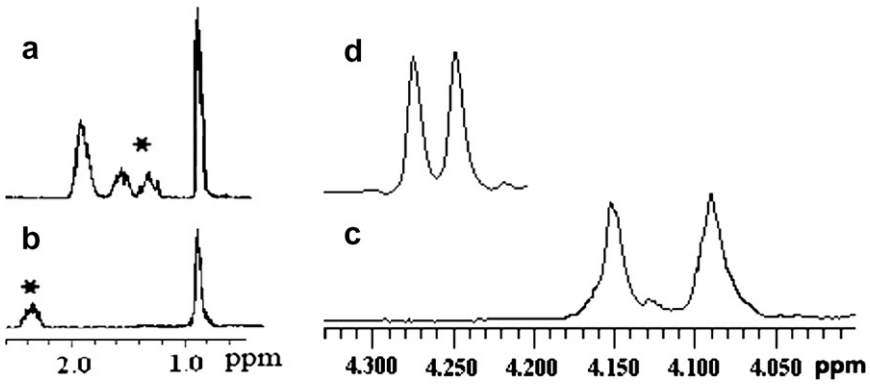


Fig. 4. ^{1}H NMR (300 Hz, $CDCl_3$, 25 °C, ppm referred to TMS as external standard) spectral regions corresponding to CH proton absorptions of racemic guest (20 mM): (a) equimolar mixture **2a**/DNB-valine, (b) free racemic DNB-valine, (c) mixture **2a**/tartaric (2:1) in CD_3OD, (d) mixture **2a**/tartaric (2:1) in CD_3OCD_3 ∗Probe signal.

determined from the titration curves by a nonlinear least-squares fitting method (Table 2). It showed that host **2b** bound guests stronger than host **2a** did for its flexibility, and the (*S*)/(D)-enantiomer was more strongly bound to **2a** or **2b** than the (*R*)/(L)-enantiomer. Particularly, the ratio between the association constant of the complex formed from host **2a** and (*S*)-mandelic acid and that from host **2a** and (*R*)-mandelic acid ($K_{a(S)}/K_{a(R)}$) exceeds 10.

From the data in Table 2, it is clear that mandelic acid exhibited much stronger bonding ability toward chiral hosts **2a** and **2b** than the other guests did. The results imply that the hydroxyl group in mandelic acid may play an important role for the formation of host–guest complex. Host **2a** may bind in situ to each enantiomer of mandelic acid through noncovalent intermolecular forces as the major driving force of molecular recognition. The possible interaction models (Fig. 6) between host **2a** and each enantiomer of mandelic acid were established through theoretical calculation based on PM3 of MOPAC 2007 software. The most stable forms are shown in Figure 6.

From Figure 6 we can see that the ionpairing interaction formed from the carboxylic group in (*R*) or (*S*)-mandelic acid and the tertiary amine in host **2a** is a major force for the formation of host–guest complexes. This is well

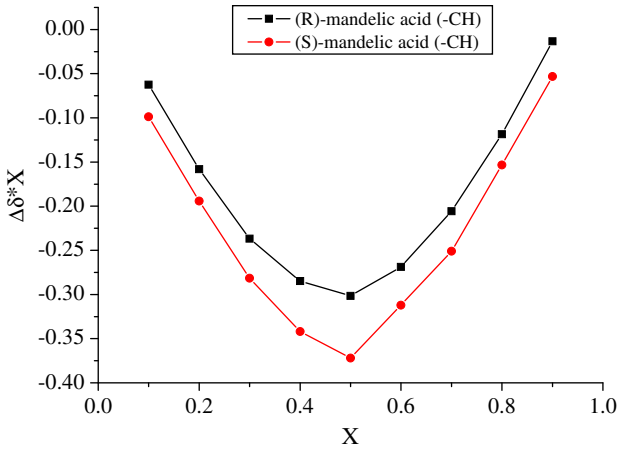


Fig. 5. Job plots of **2a** with (*R*)- and (*S*)-mandelic acid [X = molar fraction of mandelic acid, $\Delta\delta$ = chemical shift change of the methine of (*R*)- and (*S*)-mandelic acid].

Table 2
Association constants K_a (mol/L)$^{-1}$ of **2a** and **2b** with chiral carboxylic acids

Entry	CSA	Guests	K_a	K_a (*S* or D)/ K_a (*R* or L)
1	**2a**	(*R*)-Mandelic acid	$(1.1 \pm 0.07) \times 10^4$	>10
2	**2a**	(*S*)-Mandelic acid	$>10^5$	
3	**2b**	(*R*)-Mandelic acid	$(1.6 \pm 0.4) \times 10^4$	>6
4	**2b**	(*S*)-Mandelic acid	$>10^5$	
5	**2a**	(*R*)-MPAA	$(2.2 \pm 0.03) \times 10^2$	1.72
6	**2a**	(*S*)-MPAA	$(3.8 \pm 0.01) \times 10^2$	
7	**2b**	(*R*)-MPAA	$(2.3 \pm 0.04) \times 10^2$	1.74
8	**2b**	(*S*)-MPAA	$(4.0 \pm 0.04) \times 10^2$	
9	**2a**	Ts-(D)-valine	$(3.5 \pm 0.2) \times 10^3$	2.92
10	**2a**	Ts-(L)-valine	$(1.2 \pm 0.01) \times 10^3$	
11	**2b**	Ts-(D)-valine	$(4.9 \pm 0.01) \times 10^3$	1.01
12	**2b**	Ts-(L)-valine	$(4.9 \pm 0.01) \times 10^3$	

consistent with the results of NMR experiment. The ^{1}H NMR spectra of equimolar host **2a** and (*R*) or (*S*)-mandelic acid showed that the methine proton signals of (*R*) and (*S*)-mandelic acids were shifted upfield by 0.55 and 0.68 ppm, respectively, while the proton signals of methine and methylene adjacent to the nitrogen atom of the tertiary amine in host **2a** were shifted downfield by about 0.4 ppm due to the strong ionpairing interaction between host and guest molecules. In addition, the hydrogen-bonding between the carboxyl group in the guest molecule and the primary hydroxyl group in host **2a**, as well as the π–π interaction between host and guest molecules, is also important forces for achieving cooperative binding. From Figure 6 we found that there was another hydrogen-bonding between the carboxyl and α-hydroxyl groups in mandelic acid, which may be helpful to facilitate the formation of ionpairing interaction. The interaction models may explain why hosts **2a** and **2b** can facilitate lactic acid resolving in $CDCl_3$ for the test. It is known that the stability of the host–guest complexes could be weakened remarkably in protic polar solvent. The clear discerning of the enantiomers of tartaric acid **12** can be achieved even in protic polar solvent (CD_3OD), which means the formation of the stable host–guest complexes from the enantiomers of **12** and **2a** in the test condition. The possible reason is that the more functional groups (one more hydroxyl and one more carboxyl groups) and the flexibility of tartaric acid may be suitable for it to form more stable host–guest complex with **2a** through multiple noncovalent interactions, decreasing efficiently the influence of protic polar solvent to molecular recognition. Although both **2a** and **2b** are amphiphilic chiral receptors and all can form stable host–guest complexes with tartaric acid, but only **2a** can discriminate the enantiomers of it efficiently. It may be due to the presence and the suitable position of the phenyl group in **2a**, in the two complexes formed, respectively, from the two enantiomers of **12** and **2a**, the two corresponding probe groups of the guests may locate at different points in space around the phenyl group of the host molecule, and the anisotropic effect of the phenyl group would play an important role for chemical shift nonequivalence. As to **2b** as the CSA, the corresponding probe groups in the two complexes formed, respectively, from the two enantiomers of **12** and **2b** may locate far from the naphthalene ring and carbonyl groups of host **2b**, so that the anisotropic effect of the naphthalene ring and carbonyl groups could not play any role for chemical shift nonequivalence. When mandelic acid was used as the guest, which brings an phenyl group, the corresponding probe groups of the two enantiomers may locate at different points in space near the naphthalene ring or carbonyl

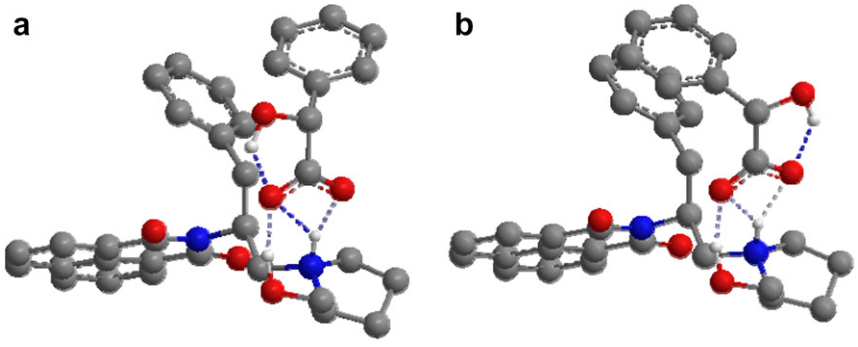


Fig. 6. The possible most stable models for the interaction between (a) **2a** and (*R*)-mandelic acid, (b) **2a** and (*S*)-mandelic acid based on PM3 of MOPAC 2007 software.

groups of host **2b**, which may be caused by the π–π interaction between host and guest compounds. In this case, the discerning of the enantiomers of the guests can be achieved in ^{1}H NMR spectra.

In conclusion, we have designed and synthesized a new class of chiral solvating agents **2a** and **2b** derived from chiral amino alcohol and 1,8-naphthalic anhydride. They are amphiphilic and efficient CSAs. In particular, **2a** shows excellent ability to discriminate the enantiomers of a broad range of carboxylic acids, including hydrophilic carboxylic acid even in protic polar solvent. This implies that it may be used in biological and medical systems.

Acknowledgment

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