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Visual chiral recognition of mandelic acid and α-amino acid derivatives by enantioselective gel formation and precipitation

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ABSTRACT

Novel chiral receptors based on L-phenylalanine and L-valine have been synthesized and their chiral recognition properties toward mandelic acid and *N*-tosyl α-amino acids are studied. The phenylalanine-based receptor undergoes enantioselective gel formation with *R*-mandelic acid and *N*-tosyl-D-valine, whereas the valine-linked receptor in their presence results in the formation of precipitates.

Chiral recognition of α-hydroxy and α-amino acids has received considerable attention in recent years because of their relevance to biology, organic synthesis, and asymmetric catalysis.[1] Considerable progress has been made in the design and development of synthetic receptors that can recognize these molecules with high enantioselectivity. Analytical techniques such as NMR, UV/Vis, and fluorescence spectroscopy have been commonly used to study the chiral recognition.[2] Recently, conventional visual detection methods, such as color change and precipitation, have gained significant importance in chiral discrimination.[3] Although supramolecular gel formation and collapsing have attracted much attention in recent years as a means of visual detection of anionic species,[4] there are only a few cases wherein their potential for chiral recognition has been realized. Zheng and co-workers have reported the recognition of chiral amines through enantioselective gel formation of the L-2,3-dibenzoyltartaric acid appended calix[4]arene.[5] Pu and co-workers have reported the chiral visual sensing of amino alcohols by enantioselective gel collapsing of the gels of chiral BINOL-terpyridine-Cu(II) complexes.[6] Tu et al. have used enantioselective metallogel collapsing for the chiral recognition of binaphthyl derivatives.[7] Further, Yashima and co-workers have reported the enantioselective gel formation ability of some poly(phenylacetylene)s bearing a cyclodextrin residue in response to a chiral amine, 1-phenylethylamine.[8]

Herein, we report novel acyclic chiral receptors **6a** and **6b** based on L-phenylalanine and L-valine which recognize enantiomers of mandelic acid and α-amino acid derivatives through enantioselective gel formation and precipitation.

Receptors **6a** and **6b** were synthesized as shown in Scheme 1. Compound **2** was synthesized by the hydrolysis of compound **1**.[9] α-Amino amides **5a** and **5b** were synthesized according to the literature procedure.[10] Thus, the reactions of N-boc-protected L-amino acids (phenylalanine and valine) with 2-naphthylamine in ethyl acetate in the presence of DCC followed by treatment with TFA in DCM gave compounds **5a** and **5b**, respectively. Treatment of compound **2** with triethylamine and ethyl chloroformate followed by refluxing with compounds **5a** and **5b** gave compounds **6a** and **6b**, respectively in 45–50% yields.

We studied the interaction of receptor **6a** and **6b** with tetrabutylammonium salts of *R*- and *S*-mandelic acid. We have found that receptor **6a** selectively forms a gel with *R*-enantiomer of mandelic acid salt in 10% DMSO/$CHCl_3$ (Fig. 1a). The gel formation by receptor **6a** (8.3×10^{-3} M) with TBA salt of *R*-mandelic acid was observed at 8.5×10^{-3} M solution of *R*-mandelate, whereas no gel formation was observed with *S*-mandelate even at its much higher concentration (up to 1.9×10^{-2} M). On the other hand, the interaction of receptor **6b** (9.0×10^{-3} M) having L-valine as a chiral center with *R*-mandelate (4.4×10^{-3} M) results in the formation of a precipitate, whereas with *S*-mandelate, the solution remains clear up to 2.2×10^{-2} M of *S*-mandelate (Fig. 1b). However, such property of gel/precipitate formation of a particular receptor was not observed with the solutions of their enantiomeric mixtures.

The gel which is formed from the interaction of **6a** with *R*-mandelic acid salt changes into solution phase upon heating, and the resultant solution reversibly changes to the gel upon cooling to

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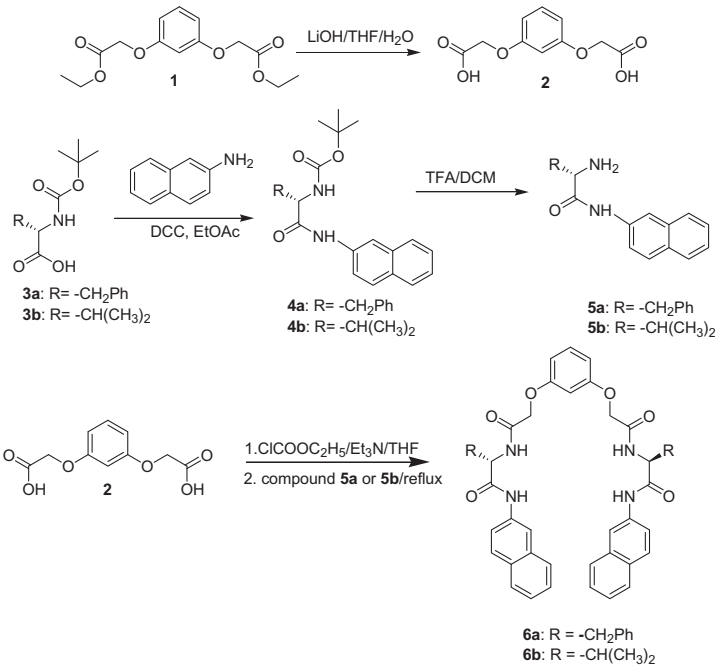

Scheme 1. Synthesis of compounds **6a** and **6b**.

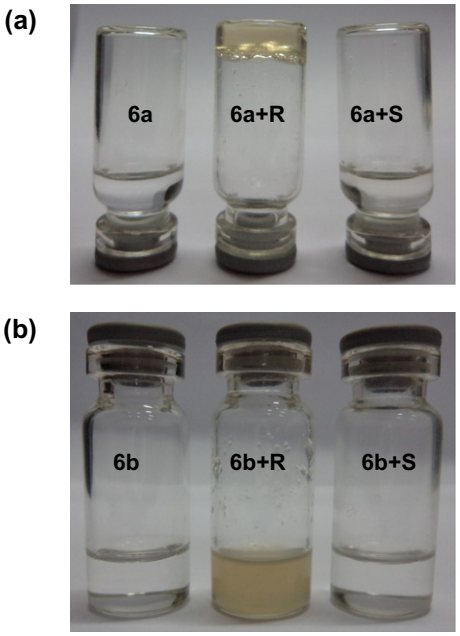

Figure 1. (a) photograph of the organogel formed by receptor **6a** (8.3×10^{-3} M) in (10%) DMSO/$CHCl_3$ with TBA salt of *R*-mandelic acid (8.5×10^{-3} M); (b) photograph of the precipitate formed by receptor **6b** (9×10^{-3} M) in (10%) DMSO/$CHCl_3$ with TBA salt of *R*-mandelic acid (9×10^{-3} M).

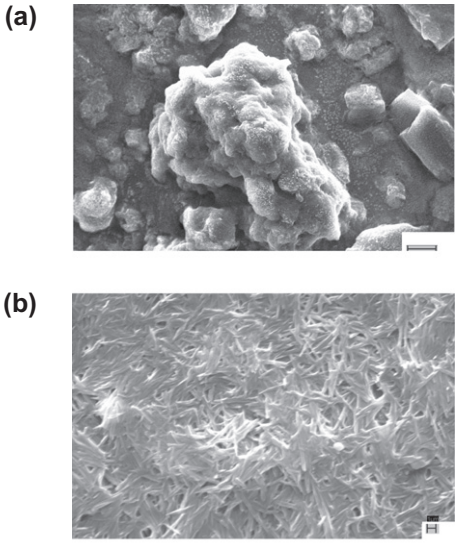

Figure 2. (a) SEM image of the gel formed by receptor **6a** with TBA salt of *R*-mandelic acid; scale bar: 10 μm. (b) SEM image of the precipitate formed by receptor **6b** with TBA salt of *R*-mandelic acid; scale bar: 1 μm.

room temperature, showing that the gel formation and collapsing are thermoreversible. The [T_{gel}] was found to be 49 °C.

To know the aggregation behavior of the gel and the precipitate formed by receptors **6a** and **6b** with *R*-mandelic acid salts, microscopic studies were carried out. The SEM images of these showed different aggregation patterns. The morphology of the gel was not well defined (Fig. 2a), whereas the precipitate showed a fibrous morphology (Fig. 2b).

The TEM image of the gel formed by receptor **6a** in the presence of *R*-mandelic acid salt showed a nano-size spherical morphology. The average diameter of spherical particles is in the range of 30–40 nm (Fig. 3).

Further, to get more insight into the binding behavior of receptor **6a** with enantiomers of mandelic acid salts, ^{1}H NMR experiment was carried out. The changes in the spectrum of receptor **6a** on addition of *R*- and *S*-mandelic acid salts (1.1 equiv) have been shown in Figure 4. It is observed that in both cases, there is a similar downfield shift in the -NH_b protons of receptor **6a** on addition of the enantiomers of mandelic acid salt. However, there is a significant difference in the downfield shifts of the chiral –CH protons of the enantiomers of mandelic acid salt. In the presence of *R*-mandelate, the chiral –CH of mandelic acid salt shifted from 4.77 ppm to 4.89 ppm, whereas in the case of *S*-mandelate,

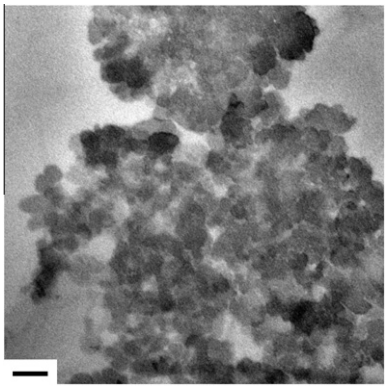

Figure 3. TEM image of the gel formed by receptor **6a** with TBA salt of *R*-mandelic acid; scale bar: 100 nm.

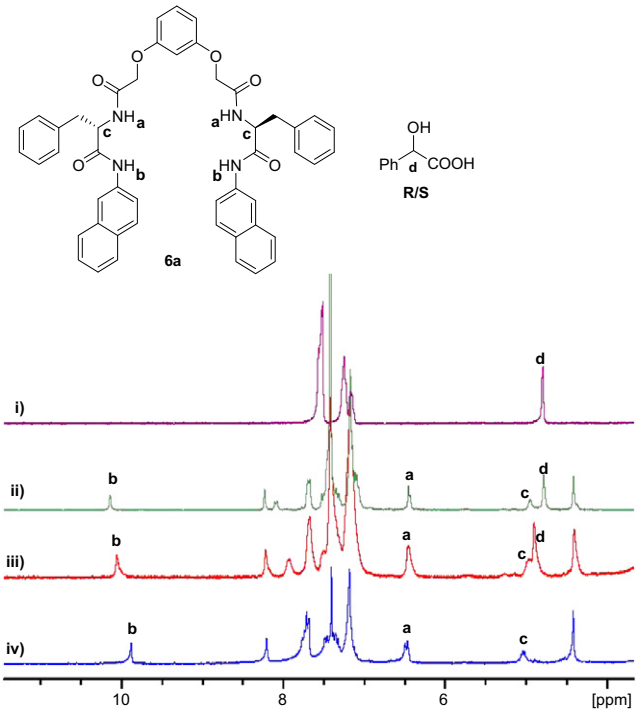

Figure 4. ^{1}H NMR spectra in (10%) DMSO-d_6/$CDCl_3$ (i) TBA salt of *R*(−)-mandelic acid; (ii) receptor **6a** (10 mM) + *S*-mandelic acid salt (1.1 equiv); (iii) receptor **6a** (10 mM) + *R*-mandelic acid salt (1.1 equiv); (iv) receptor **6a** (10 mM).

it is unaltered and appeared at 4.77 ppm. This difference in the NMR patterns clearly indicates that the chiral –CH proton of the *R*-isomer is involved in hydrogen bonding with **6a** perhaps through C––H––O interaction.

The proposed binding models for the interaction of TBA salts of *R*- and *S*-mandelic acid with receptor **6a** are given in Figure 5. In the case of *R*-mandelate, the chiral –CH proton is hydrogen-bonded with C═O groups of the receptor, and hence the OH group is free to interact with the solvents particularly DMSO to induce gel formation. Whereas, in the case of *S*-mandelate, the OH group is oriented toward carbonyl groups of the receptor and may be hydrogen-bonded (C═O––H––O–C). Hence, it is not free for the interaction with the solvents to initiate the gel formation. The NMR titration with *S*-mandelic acid salt revealed 1:1 complexation with *K*a, 150 ± 15 M^{-1}, calculated by WinEQNMR software[11] (see Supplementary data).

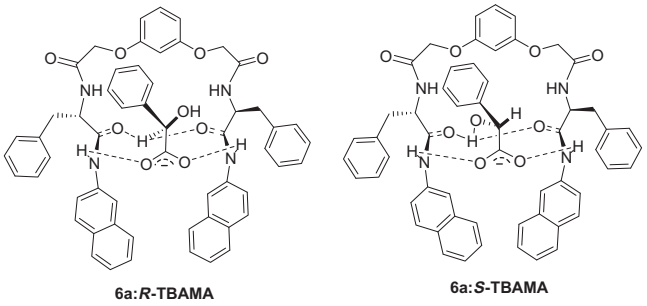

Figure 5. Proposed binding models for the interaction of TBA salts of *R*- and *S*-mandelic acid with receptor **6a**.

For the *R*-isomer, due to gel formation, binding constant could not be determined. The *K*a for **6b**:*S*-mandelate was found as 30 ± 3 M^{-1}.

The organogel was also characterized by FTIR spectroscopy. The FTIR spectrum of receptor **6a** shows two sharp characteristic N–H stretching bands at 3425 and 3272 cm^{-1} and a carbonyl band at 1661 cm^{-1}. After the gel formation with TBA salt of *R*-mandelic acid, the NH bands change into a broad band, whereas the carbonyl band shifts from 1661 cm^{-1} to 1650 cm^{-1}. The shift in the carbonyl stretching frequency to lower frequency (11 cm^{-1}) after the gel formation indicates that the amide group is involved in the interaction through H-bonding during the gel formation. The precipitate formed by **6b** and TBA salt of *R*-mandelic acid was also characterized by ^{1}H NMR and FTIR. The ^{1}H NMR spectrum of the precipitate in DMSO-d_6 showed 1:1 complex formation. The IR spectrum of the precipitate shows the shift in the carbonyl band from 1650 cm^{-1} to 1629 cm^{-1} (see Supplementary data).

We also examined the behavior of receptors **6a** and **6b** toward TBA salts of various *N*-tosylated α-amino acids listed in Table 1. We have found that these receptors show chiral discrimination between D- and L-enantiomers of *N*-tosylvaline salts. The receptor **6a** forms a partial gel, whereas receptor **6b** forms a precipitate with TBA salt of *N*-tosyl-D-valine, respectively. No discrimination between the enantiomers was observed with other amino acid derivatives. The binding constants for receptors **6a** and **6b** with TBA salt of *N*-tosyl-L-valine were found to be 250 ± 25 M^{-1} and 50 ± 5 M^{-1}, respectively.

The SEM image of the gel formed by **6a** and TBA salt of D-valine indicated a folded sheet like morphology (Fig. 6a), whereas the precipitate formed by **6b** and D-valine salt showed a fibrous morphology (Fig. 6b).

The FTIR spectral studies of the partial gel and the precipitate were also conducted. The gel formation shows the shift in the C–O stretching frequency from 1661 cm^{-1} to 1648 cm^{-1}. In the precipitate formation the shift of the carbonyl band is from 1650 cm^{-1} to 1645 cm^{-1}. The ^{1}H NMR spectrum of the precipitate in DMSO-d_6 showed 1:1 complex formation between **6b** and TBA salt of *N*-tosyl derivative of D-valine.

In addition, we also synthesized the receptors with D-phenylalanine and D-valine, and studied their gel/precipitate formation behavior with TBA salts of the enantiomers of mandelic acid and *N*-tosylvaline. It is found that these receptors form similar gel or precipitate with the opposite enantiomers.

Table 1
Response of receptors **6a** and **6b** with TBA salts of various *N*-tosylated amino acids

	L	D	L	D	L	D
Receptor **6a**	PG	PG	Sol	PG	PG	PG
Receptor **6b**	P	P	Sol	P	P	P

PG: Partial gel; P: Precipitate.

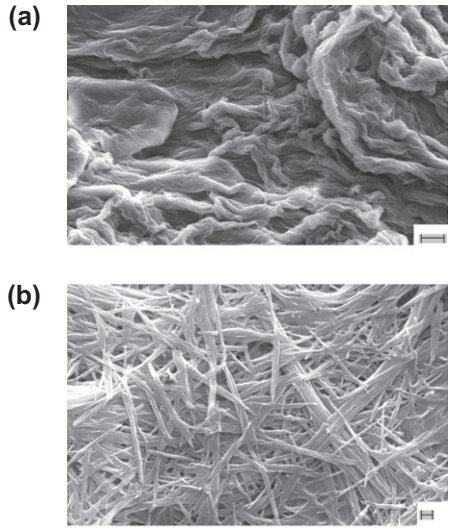

Figure 6. (a) SEM image of the gel formed by receptor **6a** with TBA salt of D-valine; scale bar: 10 μm. (b) SEM image of the precipitate formed by receptor **6b** with TBA salt of D-valine; scale bar: 1 μm.

In conclusion, chiral receptors based on L-phenylalanine and L-valine have been synthesized. These receptors show enantioselective discrimination toward TBA salts of the enantiomers of mandelic acid and *N*-tosylvaline in terms of gel formation or precipitation. The L-phenylalanine-based receptor on interaction with TBA salts of *R*-mandelic acid and *N*-tosyl-D-valine leads to gel formation, whereas the receptor with L-valine on their interaction results in the formation of precipitates. The receptors with D-phenylalanine and D-valine show enantioselective gel/precipitate formation with the opposite enantiomers. Hence, these systems may find their application in the visual sensing of enantiomers of mandelic acid and *N*-tosylvaline through gel formation or precipitation of their TBA salts.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.025.

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