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Application of Roof-Shape Amines as Chiral Solvating Agents for Discrimination of Optically Active Acids by NMR Spectroscopy: Study of Match−Mismatch Effect and Crystal Structure of the Diastereomeric Salts

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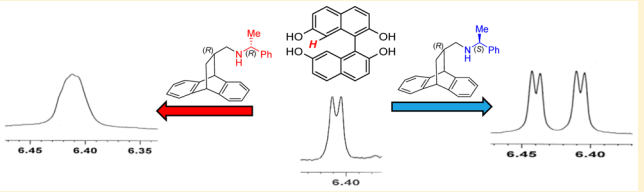
Supporting Information

ABSTRACT: Optically active roof-shape amines were prepared and scanned as chiral solvating agents to study molecular recognition of acids by NMR analysis. Three types of amines were studied to establish a match−mismatch effect for structurally diverse acid analytes. Single-crystal X-ray diffraction analysis was performed on the diastereomeric salts of roof-shape amines and both isomers of mandelic acid to establish molecular conformation and correlate the absolute configuration with the observed NMR shift. The present system also recognizes the two isomers of weakly acidic BINOL and its derivatives.



INTRODUCTION

Chiral molecules of different shapes, sizes, and functional groups have found a number of applications in diverse areas of modern chemistry, medicinal chemistry and material science. The relationship of their specific properties and chiral description has also been established by intense study. Because of the different pharmacological properties associated with the enantiomeric pair of the racemic compound the use of its optically pure form is becoming mandatory, particularly when used as drugs or as fragrance materials. Thus, establishing its optical purity by reliable techniques is becoming a vital consideration and a subject of active research in analytical sciences. The ratio of optical isomers of the test sample can be analyzed by different techniques such as chromatography,[1] mass spectrometry,[2] IR, UV and fluorescence spectroscopy,[3] CD, and electrophoresis,[4] etc. Some of these protocols may only succeed if a certain type of structural requirement or specific functional group is present in the analyte. In some cases, additional accessories, such as special chiral columns, are needed for the chromatography.

Nuclear magnetic resonance (NMR) spectroscopy offers an alternative method for fast, accurate, and reliable determination of optical purity of chiral molecules.[5] However, the regular NMR analysis of chiral compounds in an achiral environment (solvent) cannot differentiate the signals of the two enantiomers. The use of chiral solvents in NMR analysis has been explored with limited success.[6] For the NMR discrimination which can be conveniently measured; the enantiomers need to be derivatized to diastereomers, either by covalent bond formation or temporarily by noncovalent interactions. A traditional technique involving in situ preparation of diastereomeric lanthanide chelate complexes is one such widely used procedure.[7] Alternatively, this may also be done by the use of chiral derivatizing agents (CDA)[8] for formation of diastereomeric compounds.[9] The diastereomer formation for NMR analysis may be done by simply mixing the analyte and the chiral solvating agent (CSA) during the spectroscopic analysis.[10] Even though the use of proton NMR is more commonly employed, the focus on targeting other NMR active nuclei for the purpose of determining optical purity is increasingly being studied.[11−15] The two components, the sample under investigation, and the chirally pure CSA in the solution, interact with each other through noncovalent interactions like hydrogen bonding, halogen bonding, π-stacking, van der Waals interactions, etc. The effectiveness of a good CSA to distinguish the two isomers of the analyte primarily depends on combination of these supramolecular forces, and hence, they are quite sensitive and specific in their action. The selectivity of each CSA for specific substrates could be considered its limitation. Hence, there is constant need to design newer derivatives to scan for wider analytes for the NMR analysis.

A novel class of compounds resembling the shape of a roof was introduced and studied by Weber, while searching their applications as clathrate hosts with inclusion properties.[16] Such molecules find few applications in different areas ranging from medicinal chemistry to material science.[17] We have previously presented the synthesis and resolution of roof shape alcohols **I** and **II** and their derivatives (Chart 1).[18,19] The optically pure

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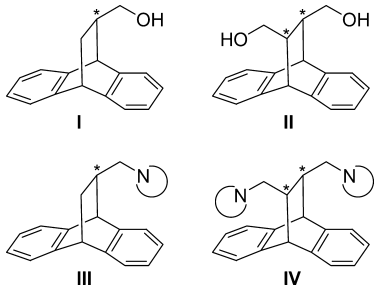
Chart 1. Roof-Shape Chiral Alcohols and Amines

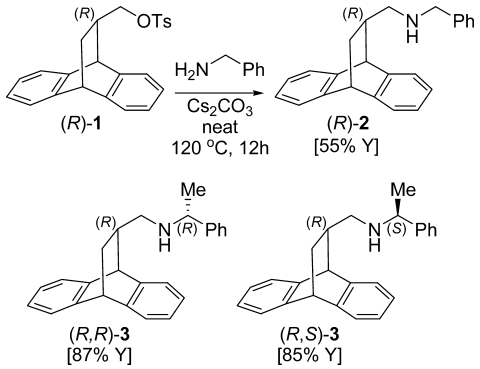


roof-shape alcohols were also converted to amines **III** and **IV** to be scanned as chiral solvating agents for discrimination of the signals of some optically active compounds in NMR spectroscopy,[19] while we also used **I** as a chiral auxiliary for asymmetric synthesis of α-halo acids.[18b]

RESULT AND DISCUSSION

In the present study, we have prepared optically pure roof-shape secondary amines and evaluated them as chiral solvating agents for the discrimination of signals of chiral acids by NMR spectroscopy. In the design, we have explored the possibility of introducing another aromatic system by choosing to attach benzyl amine with the aim of adding an additional supramolecular interaction in the form of π-stacking. With this aim, the chiral alcohol **I** was converted to its monotosylate (*R*)-**1**, and it was then treated with benzylamine to furnish chiral secondary amine (*R*)-**2** (Scheme 1). In order to study the

Scheme 1. Synthesis of Roof-Shape Amines



match−mismatch effect by changing the orientation of the aromatic ring of benzyl amine, we further prepared two more derivatives by selecting two enantiomers of the chiral benzyl amine. Roof-shape amine (*R*,*R*)-**3** was prepared by using (*R*)-α-phenylethylamine, and its diastereomer (*R*,*S*)-**3** was obtained by using (*S*)-α-phenylethylamine from (*R*)-**1** by a substitution reaction. One of the two aromatic rings of the rigid bicyclic roof shape portion of the CSA, second aromatic ring of the benzyl unit, and the second chiral center should control the orientation of its diastereomeric complex with acidic analyte for effective chiral discrimination by molecular recognition.

Having prepared the three roof-shape secondary amines (*R*)-**2**, (*R*,*R*)-**3**, and (*R*,*S*)-**3** we examined different acidic substrates for a possible, detectable discrimination of the NMR signals in the analysis. The recognition study was conducted in $CDCl_3$ (400 MHz; 20 mM concentration; ratio of 1:1) with (*R*/*S*)-mandelic acid as the test substrate, targeting the $C_\alpha H$ proton of Ph*C*H*(OH)COOH. For such study, the degree of induced chemical shift ($\Delta\delta$) and nonequivalence ($\Delta\Delta\delta$) on the complex formation with CSA are measured. In this case, the signal of the $C_\alpha H$ proton shifted toward the upfield region in all three cases, while for (*R*)-**2** and (*R*,*R*)-**3** the signals also separated (Figure 1). However, in the case of (*R*,*S*)-**3** the signals did not resolve, and both $C_\alpha H$ protons of the diastereomeric salt appeared as one singlet (Figure 1 and Table 1).

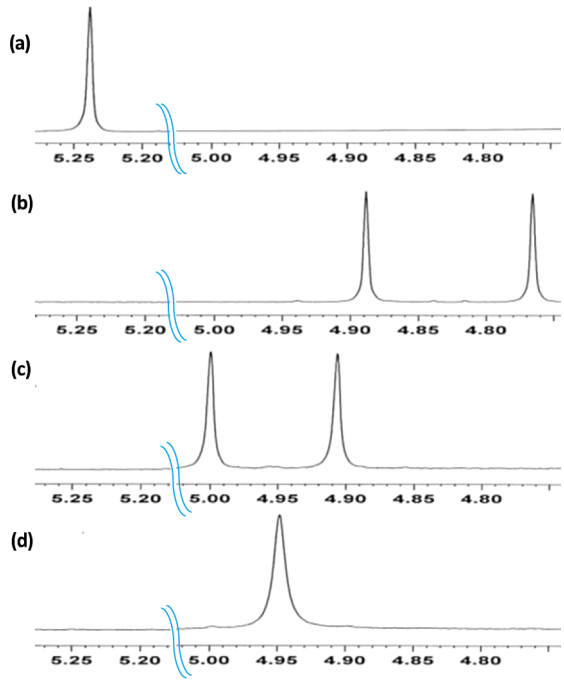


Figure 1. Separation of $C_\alpha H$ signals of (a) (*R*/*S*)-mandelic acid (b) with (*R*)-**2**; (c) with (*R*,*R*)-**3**; (d) with (*R*,*S*)-**3** (20.0 mM, $CDCl_3$, 400 MHz).

The probable mode of action for the recognition of substrates with amino CSA should involve its protonation followed by its complexation with carboxylate. The formation of the carboxylate anion was confirmed when the carbonyl stretch (1716 cm^{-1} for mandelic acid) disappeared in the FT-IR spectra of its mixture with (*R*)-**2** or (*R*,*R*)-**3**, and the new strong peaks appeared at 1624 and 1602 cm^{-1} (the COO^- stretch).[20] However, in the case of (*R*,*S*)-**3** all the three peaks were observed, possibly indicating incomplete complex formation.

In the case of α-chloropropanoic acid, all three roof-shape amines failed to distinguish the signals (entry 2, Table 1). We also examined derivatives of mandelic acid where the hydroxyl group was blocked by introducing suitable protecting groups. In the case of *O*-acetyl mandelic acid and *O*-methyl mandelic acid, we observed a similar pattern of selectivity, although the chemical shift nonequivalence ($\Delta\Delta\delta$) was much reduced (entries 3 and 4, Table 1). Similar selectivity was seen in the case of α-bromo phenylacetic acid (entry 5, Table 1), contrary to α-chloropropanoic acid, indicating the supporting role of aromatic ring in the molecular recognition. It is often advantageous to analyze a sample by targeting more than one nuclei to confirm the optical purity. Application of ^{19}F NMR spectra for structural determination has distinct advantages of fewer and sharper peaks compared to ^1H NMR. We extended our study for 4-trifluoromethylmandelic acid and compared the

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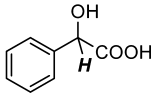
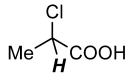
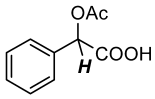
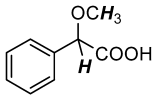
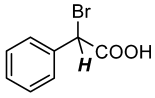
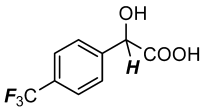
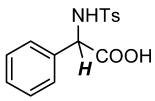
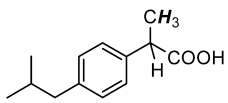
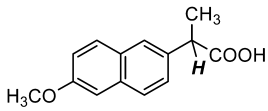
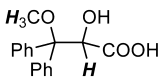
Table 1. Comparison of the Ability of CSA To Discriminate Signals of Chiral Acids

No	Substrates	nmr nucleus	(*R*)-**2**		(*R*,*R*)-**3**		(*R*,*S*)-**3**	
			(Δδ)[a]	(ΔΔδ)[b]	(Δδ)	(ΔΔδ)	(Δδ)	(ΔΔδ)
1		^{1}H	-0.411	0.123	-0.285	0.093	-0.289	--[c]
2		^{1}H	-0.048	--[c]	0.042	--[c]	-0.016	--[c]
3		^{1}H	-0.130	0.050	0.003	0.032	-0.041	--[c]
4		^{1}H (Cα)	-0.179	0.028	-0.055	0.043	-0.104	--[c]
		^{1}H (CH_3)	-0.167	0.003	0.060	0.049	-0.082	--[c]
5		^{1}H	-0.010	0.034	0.128	0.040	0.020	--[c]
6		^{1}H	-0.351	0.077	-0.356	0.062	-0.357	0.017
		^{19}F	-0.127	0.032	-0.094	0.076	-0.099	0.015
7		^{1}H (Cα)	-0.165	0.055	-0.201	0.070	-0.146	0.049
		^{1}H (CH_3)	-0.396	0.079	-0.353	0.074	-0.287	0.031
8		^{1}H	-0.038	0.015	0.007	0.019	-0.004	0.008
9		^{1}H	-0.050	--[c]	0.010	--[c]	-0.074	--[c]
10		^{1}H (Cα)	-0.135	0.039	-0.067	0.146	-0.056	0.006
		^{1}H (OCH_3)	-0.029	0.016	0.020	0.079	0.028	0.013

[a]Induced chemical shift (Δδ). [b]Nonequivalence (ΔΔδ). [c]Signals were not separated; (20.0 mM, $CDCl_3$, 400 MHz for H and 376 MHz for F NMR).

separation of signals in ^{1}H NMR for the C$_\alpha$*H* and ^{19}F NMR for CF_3 group (entry 6, Table 1). Although CSA (*R*)-**2** and (*R*,*R*)-**3** were almost equally effective where baseline separation of signals was observed, the CSA (*R*,*S*)-**3** showed relatively poor resolution.

Optically active natural and artificial amino acids have become an integral part of the design and synthesis of several biologically important molecules. Determination of optical purity of amino acids is becoming an important consideration. Recently, few chiral solvating agents have been studied to measure optical purity of amino acids by NMR analysis.[21] We also extended our study of the present CSAs to check the discrimination of the protons of the N-Ts derivative of phenyl glycine (entry 7, Table 1). In this case, the signals of the methyl group of N-Ts and C$_\alpha$*H* showed discrimination in ^{1}H NMR analysis. Almost similar selectivity was seen, where CSA (*R*,*S*)-**3** showed comparatively poor separation of both these signals. Next, we examined ibuprofen and naproxen, two commonly studied nonsteroidal anti-inflammatory drugs as substrates. The CSA (*R*)-**2** and (*R*,*R*)-**3** showed the same ability to recognize the isomers of ibuprofen, but the other was quite less effective, while all the three proved incapable of showing separation of signals of naproxen (entries 8 and 9, Table 1). The present system was then examined for relatively bulky 2-hydroxy-3-methoxy-3,3-diphenylpropanoic acid, which is an intermediate for few pharmaceuticals.[22] Signals of C$_\alpha$*H* and C$_\beta$O*CH*$_3$ of this compound were seen to have been resolved due to the complex formation between this racemic acid and the (*R*,*R*)-**3**, more

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than the other two derivatives (entry 10, Table 1). At this stage, we conclude that (*R*)-**2** and (*R*,*R*)-**3** were more effective in chiral recognition of mandelic acid and its derivatives compared to (*R*,*S*)-**3**. In most of the cases, we found the present roof-shape amine to be comparable or better than some of the reported chiral amine based CSAs (see Table 1 of the SI for the details). In order to further establish the role of the roof shape part of the secondary amine, we prepared the *N*-methyl derivative of (*R*)-α-phenylethylamine and scanned as CSA for the recognition of (±)-mandelic acid. We observed a small shift in signal (induced chemical shift; $\Delta\delta$ = −0.066 ppm) but there was no splitting of the signals ($\Delta\Delta\delta$ = 0 ppm).

An experiment was designed to determine the difference in binding ability of (*R*,*R*)-**3** with both the isomers of mandelic acid. For a constant concentration of (*R*,*R*)-**3** (20 mM), a varying amount of (*R*)-MA and (*S*)-MA was added in such a way that the molar ratio varied from 0.2, 0.5, 1.0, and 1.5. The change in the chemical shift ($\Delta\delta$) value for α-*H* proton of mandelic acid was plotted against the molar ratio of chiral mandelic acid (Figure 2). The negative values for $\Delta\delta$ suggest an

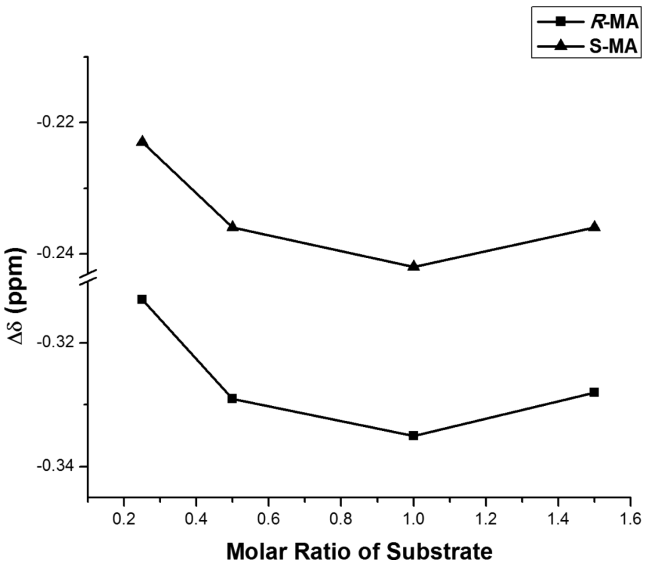

Figure 2. Graph showing the effect of different molar ratios of (*S*)-MA and (*R*)-MA with (*R*,*R*)-**3** upon change in chemical shift for the α-*H* proton of mandelic acid.

upfield shift of the signal. For both the isomers of MA, a minima is observed at molar ratio of 1.0 indicating maximum shift in δ value. However, the shift with (*R*)-MA is much more than that with (*S*)-MA indicating a stronger association of (*R*,*R*)-**3** with (*R*)-MA as compared to its association with (*S*)-MA.

The use of optically pure of 1,1′-binaphthyl-2,2′-diol (BINOL) and its derivatives in asymmetric synthesis and catalysis is now a very important subject.[23] There are only a few reports on the use of chiral solvating agents for establishing optical purity of BINOL and its derivatives in the literature. Even in these reports, BINOL and analogues were converted to their alkoxy derivative before being subjected to the CSA analysis.[24a] There is also one other report on the use of quinine as CSA to discriminate signals of isomers of BINOL in ^{1}H NMR.[24b] Since our present secondary amine based roof-shape CSAs were expected to be strongly basic in nature, we investigated them for weakly acidic BINOL or its derivatives. However, for BINOL all three were ineffective in separating the signals (entry 1, Table 2). Structurally similar 2,2′,7,7′-tetrahydroxy-1,1′-binaphthyl possessing a C_2-symmetric axis is also utilized in asymmetric chemistry.[25] The presence of two more easily accessible hydroxyl groups in this molecule may lead to better interactions with the CSA. This was supported by the observation that the CSAs (*R*)-**2** and (*R*,*S*)-**3** were able to separate the signal of the most shielded hydrogen attached to the C8 position while CSA (*R*,*R*)-**3** failed to resolve them (entry 2, Table 2). This hydrogen showed a clear doublet in the most upfield part of the aromatic region (δ 6.4), convenient for easy measurement (Figure 3). This hypothesis was confirmed when poor separations were seen when these two outside hydroxyl groups were either blocked as 7,7′-dimethoxy-2,2′-dihydroxy-1,1′-binaphthyl or in case of 6,6′-dibromo-2,2′-dihydroxy-1,1′-binaphthyl (entries 3 and 4, Table 2).

In another set of experiments, we examined 3,3′-dimethoxy-2,2′-dihydroxy-1,1′-binaphthyl and 3-methoxy-2,2,′3′-trihydroxy-1,1′-binaphthyl for the same study. Similar to the above observations, the latter one showed reasonable separation with (*R*,*S*)-**3** as against the other two (entries 5 and 6, Table 2).

Recently, chiral Brønsted acids such as phosphoric acid derivative 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate and its analogues have found wide uses as chiral catalysts.[26] We examined the effect of these CSAs by systematically studying the ^{31}P NMR and concluded the efficiency of (*R*)-**2** and (*R*,*S*)-**3** to be higher as against (*R*,*R*)-**3** (entry 7, Table 2). In all of the examples investigated in this class of compounds, (*R*)-**2** and (*R*,*S*)-**3** were more effective. Between them, the latter one (*R*,*S*)-**3** proved to be slightly superior class of CSA for binaphthyl system, while its diastereomer (*R*,*R*)-**3** was found more effective in the chiral recognition of derivatives of mandelic acid. Such a match−mismatch effect for controlling supramolecular interactions between diastereomeric chiral solvating agents for molecular recognition is noteworthy.

This molecular recognition was further studied to establish the linear relationship between the observed and actual values of % ee for establishing usefulness of the CSA (Figure 4). The observed % ee values were found to be within acceptable level of actual values, which confirms the accuracy of the analysis and possibility of the practical use in determination of sample of unknown purity.

Having established the efficacy of the three CSAs and collected information about the match-mismatch effect, we proceeded to understand the supramolecular interactions in depth. First, the experiments were run with nonracemic sample of mandelic acid with one known isomer excess with optically pure (*R*,*R*)-**3**. The signal of proton attached to the chiral center $C_\alpha H$ of (*R*)-mandelic acid [(*R*,*R*)-**3**·*R*-MA] appeared more upfield. The solution of the equimolar mixture of (*R*,*R*)-**3** with (*R*)-mandelic acid in acetonitrile was left for slow evaporation, and the crystals obtained were subjected to X-ray diffraction study.[27] Similarly, a mixture of (*R*,*R*)-**3** with (*S*)-mandelic acid was allowed to give a crystal of its diastereomeric salt [(*R*,*R*)-**3**·*S*-MA] for the similar analysis. The sample of [(*R*,*R*)-**3**·*R*-MA] crystallized in monoclinic chiral space group $P2_1$. The crystal structure contained one molecule each of (*R*,*R*)-**3** with (*R*)-mandelic acid along with a molecule of acetonitrile in the asymmetric unit (Figure 5). The hydrogen attached to the chiral carbon of (*R*)-mandelic acid appears to be laying on top of one of the aromatic rings of the roof-shape bicyclic framework. The shortest perpendicular distance between the

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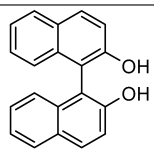
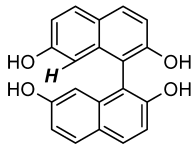
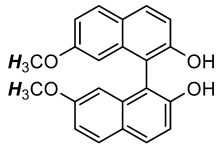
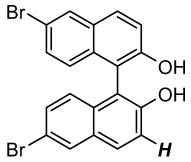
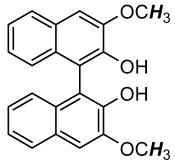
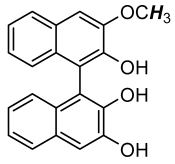
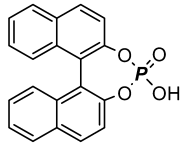
Table 2. Comparison of the Ability of CSA To Discriminate Signals of Chiral BINOL Derivatives

No	Substrates	nmr nucleus	(*R*)-**2**		(*R*,*R*)-**3**		(*R*,*S*)-**3**	
			(Δδ)[a]	(ΔΔδ)[b]	(Δδ)	(ΔΔδ)	(Δδ)	(ΔΔδ)
1		^{1}H	0.007	--[c]	0.010	--[c]	0.011	--[c]
2		^{1}H	-0.015	0.019	0.005	--[c]	0.017	0.032
3		^{1}H	-0.008	0.004	-0.004	0.005	-0.003	0.002
4		^{1}H	0.005	0.011	0.001	0.018	-0.002	0.005
5		^{1}H	0.002	--[c]	0.001	--[c]	--[d]	--[c]
6		^{1}H	-0.033	--[c]	-0.014	--[c]	-0.014	0.007
7		^{31}P	+0.529	0.205	-0.114	--[c]	-0.739	0.341

[a]Induced chemical shift (Δδ). [b]Nonequivalence (ΔΔδ). [c]Signals were not separated. [d]No shift; (20.0 mM, $CDCl_3$, 400 MHz for H and 161 MHz for P NMR).

plane passing through this ring and the hydrogen is 4.18 Å, and it is observed to be shifting upfield region due its shielding effect in ^{1}H NMR analysis. The C−O bond lengths (∼1.24−1.25 Å) in the COOH group show that proton transfer has occurred from *R*-MA to amine moiety of the (*R*,*R*)-**3**, revealing that the complex is salt (see the SI for a detailed discussion on crystal structure). In general, two molecules of (*R*,*R*)-**3** linked to the two molecules of *R*-MA through N−H···O hydrogen-bonding interactions to generate the tetrameric assembly which formed an extended chain assembly along the *b*-axis. The neighboring chains along the *bc*-diagonal were linked through acetonitrile molecules via C−H···N interactions (H···N = 2.714 Å, N···C = 3.427 Å /C−H···N = 134°) between the N atom of the guest acetonitrile and C−H aromatic proton of the (*R*,*R*)-**3** moiety and other van der Waals forces between the host and the guest molecules. This reveals that acetonitrile molecules play a vital role in fusing the neighboring helical chains, thereby inducing its crystallization.

The complex [(*R*,*R*)-**3**·*S*-MA] also crystallized in monoclinic chiral $P2_1$ space group containing two molecules of each component in the asymmetric unit. The crystal structure of [(*R*,*R*)-**3**·*S*-MA] (Figure 6) is isostructural to the [(*R*,*R*)-**3**·*R*-MA] structure. The C−O bond lengths (∼1.24−1.26 Å) in the COOH group show that proton transfer has occurred from *S*-MA to the amine moiety of the (*R*,*R*)-**3** revealing that the complex is salt. Similar to the crystal structure of [(*R*,*R*)-**3**·*R*-MA], two molecules of each *S*-MA and (*R*,*R*)-**3** constitute a tetrameric structure through hydrogen-bonding interactions,

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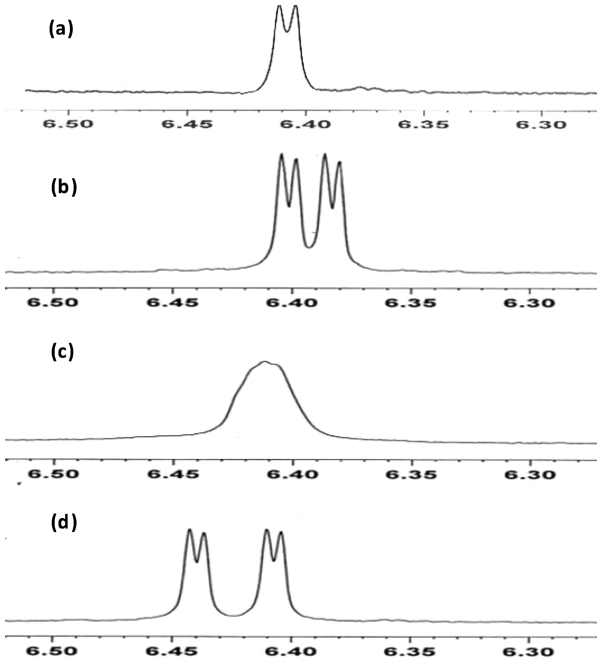

Figure 3. Separation of C_8H signal of (a) 2,2′,7,7′-tetrahydroxy-1,1′-binaphthyl (b) with (*R*)-**2**; (c) with (*R*,*R*)-**3**; (d) with (*R*,*S*)-**3** (20.0 mM, $CDCl_3$, 400 MHz).

which is extended along the *a*-axis to generate the chain structure. The neighboring chains are loosely connected to each other roughly along the *b*-axis via hydrophobic interactions. To the best of our knowledge, there are very few reports on the crystal study of the structure of the salt of test substrate and the CSA to understand the supramolecular interactions.[28] The experimental observations of shielding and deshielding effects in the two pairs in ^{1}H NMR analysis corroborated well with the information obtained from these crystal structures, even though one needs to be cautious in comparing the two.

Hence, in this paper we present preparation of three optically pure roof shape secondary amines, study of their applications for discrimination of signals of chiral acidic compounds by NMR spectroscopy, and evaluation of their match and mismatch effect of the diastereomers on the molecular recognition. We have also investigated the two pairs of diastereomeric salts by single-crystal X-ray diffraction analysis to establish the conformation of the hydrogen attached to the chiral carbon of mandelic acid. In one pair, we observed shielding effect due to its position above the aromatic ring of the bicyclic roof shape moiety, while in other the hydrogen is oriented away resulting in downfield shift in NMR analysis.

EXPERIMENTAL SECTION

***N*-Benzyl-1-((12*R*)-9,10-dihydro-9,10-ethanoanthracen-12-yl)methanamine ((*R*)-2).** A mixture of **1** (0.30 g, 7.69 mmol), cesium carbonate (0.54 g, 15.3 mmol), and benzylamine **2** (0.16 g, 15.3 mmol) was taken in a dry round-bottom flask and heated under nitrogen (120 °C, 12 h). After completion of the reaction, cold water was added to the reaction mixture, which was then extracted with ethyl acetate (3 × 25 mL). The organic layer was collected, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain the crude product. The product was purified by column chromatography over silica gel using light petroleum ether and ethyl acetate as eluent to obtain the product (*R*)-**2** as a colorless oil (0.13g, 55%): $[\alpha]_D$ +14.6 (*c* = 1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.32 (m, 3H), 7.31−7.29 (m, 3H), 7.28−7.23 (m, 3H), 7.15−7.09 (m, 4H), 4.38−4.37 (d, *J* = 2.0 Hz, 1H), 4.28−4.27 (t, *J* = 2.4 Hz, 1H), 3.81−3.78 (d, *J* = 13.2 Hz, 1H), 3.74−3.70 (d, *J* = 13.2 Hz, 1H), 2.36−2.33 (br s, 1H), 2.33−2.29 (dd, *J* = 11.2 Hz, 5.6 Hz, 1H), 2.22−2.17 (dd, *J* = 11.2, 5.6 Hz, 1H), 2.16−2.11 (m, 1H), 2.04−1.98 (m, 1H), 1.18−1.14 (ddd, *J* = 12.0, 4.4, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 143.8, 143.7, 140.5, 39.9, 128.4(2C), 128.2(2C),

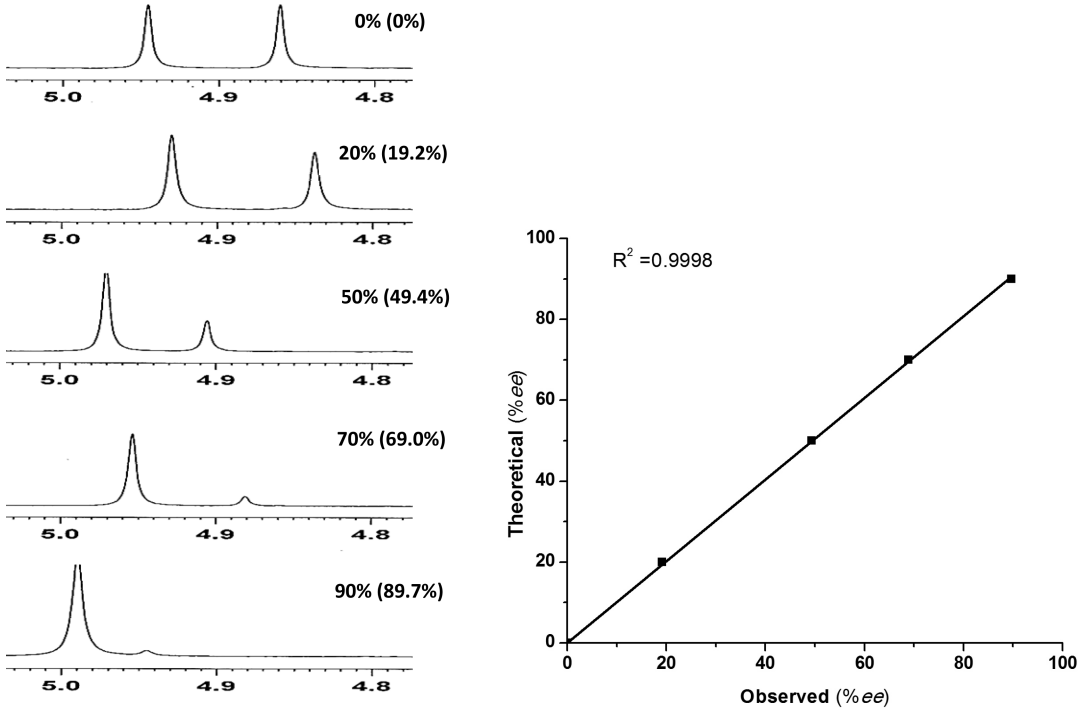

Figure 4. Selected region of ^{1}H NMR spectra of scalemic mixture of mandelic acid in the presence of (*R*,*R*)-**3**; values in parentheses are observed by NMR (left) and its correlation between theoretical and observed % ee values (right).

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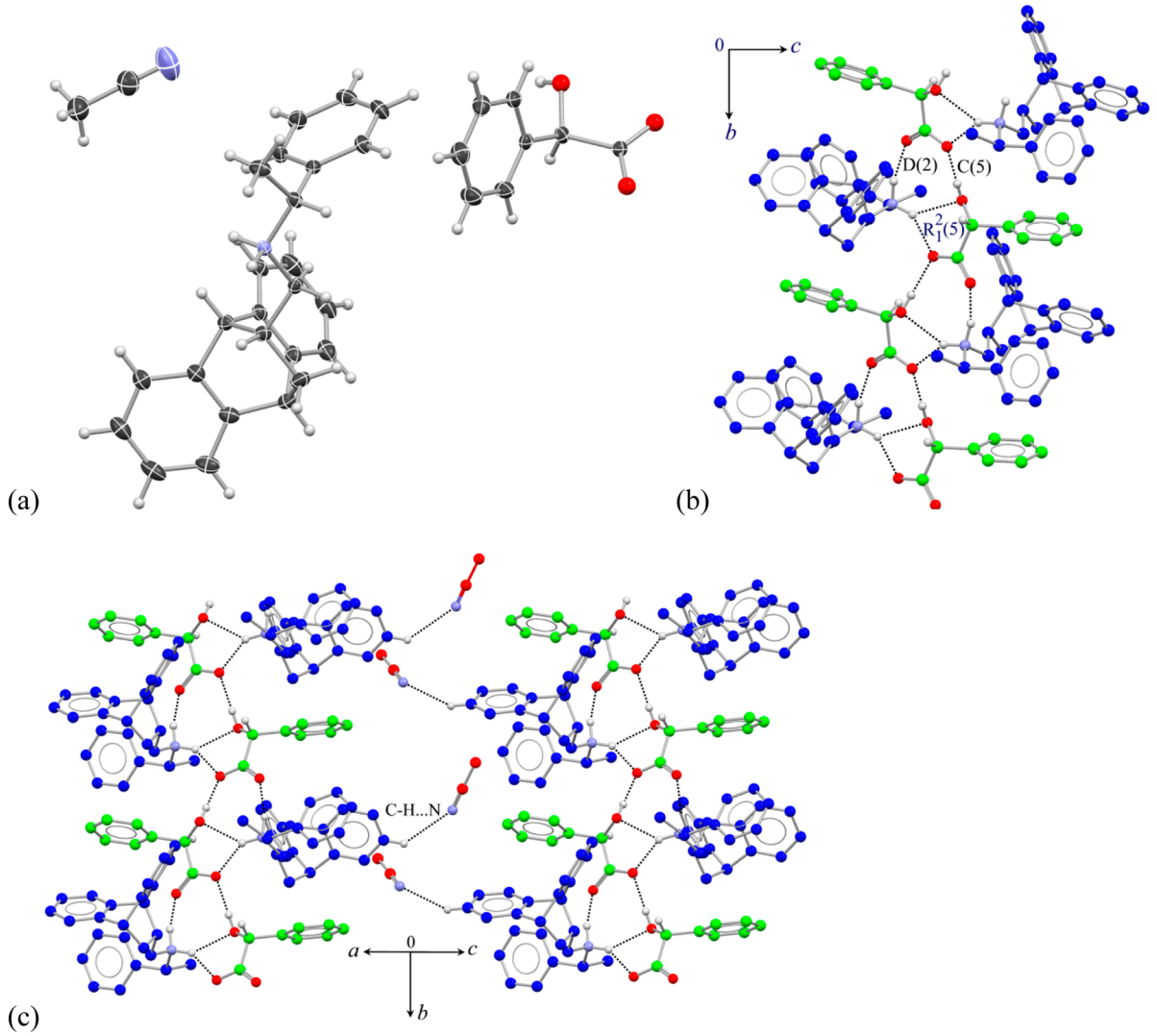

Figure 5. (a) ORTEP view of (*R*,*R*)-**3**·*R*-MA salt. The displacement ellipsoids are drawn at a 30% probability level, and H atoms are shown as small spheres of arbitrary radii. (b) Association of the (*R*,*R*)-**3** (blue) molecules to the O−H···O hydrogen bonded helical chain of *R*-MA (green) through N−H···O hydrogen-bonding interactions generating an extended chain assembly. (c) Linking of the neighboring helical chains through acetonitrile molecules via C−H···N interactions.

127.1, 125.8, 125.6(2C), 125.5, 125.3, 123.5, 123.4, 123.0, 54.0, 53.8, 46.7, 44.1, 38.6, 33.1; IR (neat) ν 3064.9, 3022.4, 2939.1, 2862.8, 2815.3, 1603.4, 1583.8, 1455.2, 1199.9, 1114.2, 747.4, 698.7, 555.7 cm^{-1}; MS (DIP-EI) *m*/*z* 236.3 (9), 325.2 (51), 324.2 (31), 177.9 (100), 119.9 (94), 90.8 (82); HRMS (TOF ES+) *m*/*z* calcd for $C_{24}H_{24}N$ $[M + H]^+$ 326.1903, found 326.1898.

(*R*)-*N*-(((12*R*)-9,10-Dihydro-9,10-ethanoanthracen-12-yl)-methyl)-1-phenylethan-1-amine ((*R*,*R*)-3). The synthetic procedure was similar to the one described above using (*R*)-α-phenylethylamine instead of benzylamine. The product (*R*,*R*)-**3** was obtained as a white solid on purification using column chromatography on silica gel (0.23 g, 87%): mp 102−104 °C; $[\alpha]_D$ +49.1 (*c* = 1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.31 (m, 5H), 7.28−7.25 (m, 2H), 7.22−7.20 (m, 1H), 7.17−7.14 (m, 1H), 7.13−7.09 (m, 2H), 7.08−7.02 (m, 2H), 4.37−4.36 (d, *J* = 2.0 Hz, 1H), 4.24−4.23 (t, *J* = 2.4 Hz, 1H), 3.71−3.66 (q, *J* = 6.4 Hz, 1H), 2.24−2.19 (dd, *J* = 11.2, 5.6 Hz, 1H), 2.08−2.01 (br s, 1H), 1.98−1.92 (m, 2H), 1.38−1.36 (d, *J* = 6.4 Hz, 3H), 1.10−1.06 (ddd, *J* = 11.7, 4.0, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 144.3, 143.8, 140.5, 128.4(2C), 126.8, 126.6(2C), 125.7, 125.6, 125.5, 125.4, 125.3, 123.5, 123.4, 122.9, 58.4, 52.7, 46.6, 44.2, 39.1, 33.1, 24.7; IR (KBr) ν 3065.4, 3017.9, 2957.8, 2891.3, 2819.8, 1598.7, 1489.4, 1465.1, 1172.9, 1129.7, 755.7, 704.7, 590.6, 555.9 cm^{-1}; MS (DIP-EI) *m*/*z* 339.3 (28), 338.4 (21), 323.6 (37), 177.9 (100), 134.2 (39), 104.9 (82); HRMS (ESI) *m*/*z* calcd for $C_{25}H_{26}N$ $[M + H]^+$ 340.2060, found 340.2055.

(*S*)-*N*-(((12*R*)-9,10-Dihydro-9,10-ethanoanthracen-12-yl)-methyl)-1-phenylethan-1-amine ((*R*,*S*)-3). The synthetic procedure is similar to the one described above using (*S*)-α-phenylethylamine instead of benzylamine. The product (*R*,*S*)-**3** was obtained as pale yellow liquid on purification using column chromatography on silica gel (0.22 g, 85%): $[\alpha]_D$ −17.5 (*c* = 1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.24 (m, 9H), 7.12−7.09 (m, 4H), 4.37−4.36 (d, *J* = 1.6 Hz, 1H), 4.24−4.23 (t, *J* = 2.4 Hz, 1H), 3.69−3.64 (q, *J* = 6.8 Hz, 1H), 2.17−2.16 (m, 1H), 2.05−2.03 (m, 2H), 2.02−1.94 (m, 1H), 1.38−1.36 (d, *J* = 6.8 Hz, 3H), 1.09−1.06 (ddd, *J* = 12.0, 4.0, 2.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 144.1, 143.82, 143.80, 140.6, 128.4(2C), 126.9, 126.6(2C), 125.8, 125.6(2C), 125.5, 124.2, 123.5, 123.3, 123.0, 58.3, 52.5, 46.6, 44.2, 38.7, 33.1, 24.1; IR (neat) ν 3065.4, 3022.1, 2936.9, 2863.5, 1602.2, 1461.0, 1123.6, 851.1, 725.2, 704.2, 595.64, 501.4 cm^{-1}; MS (DIP-EI) *m*/*z*) 339.3 (8), 178.1 (25), 97.1 (35), 69.2 (60), 68.6 (100); HRMS (TOF ES+) *m*/*z* calcd for $C_{25}H_{26}N$ $[M + H]^+$ 340.2060, found 340.2060.

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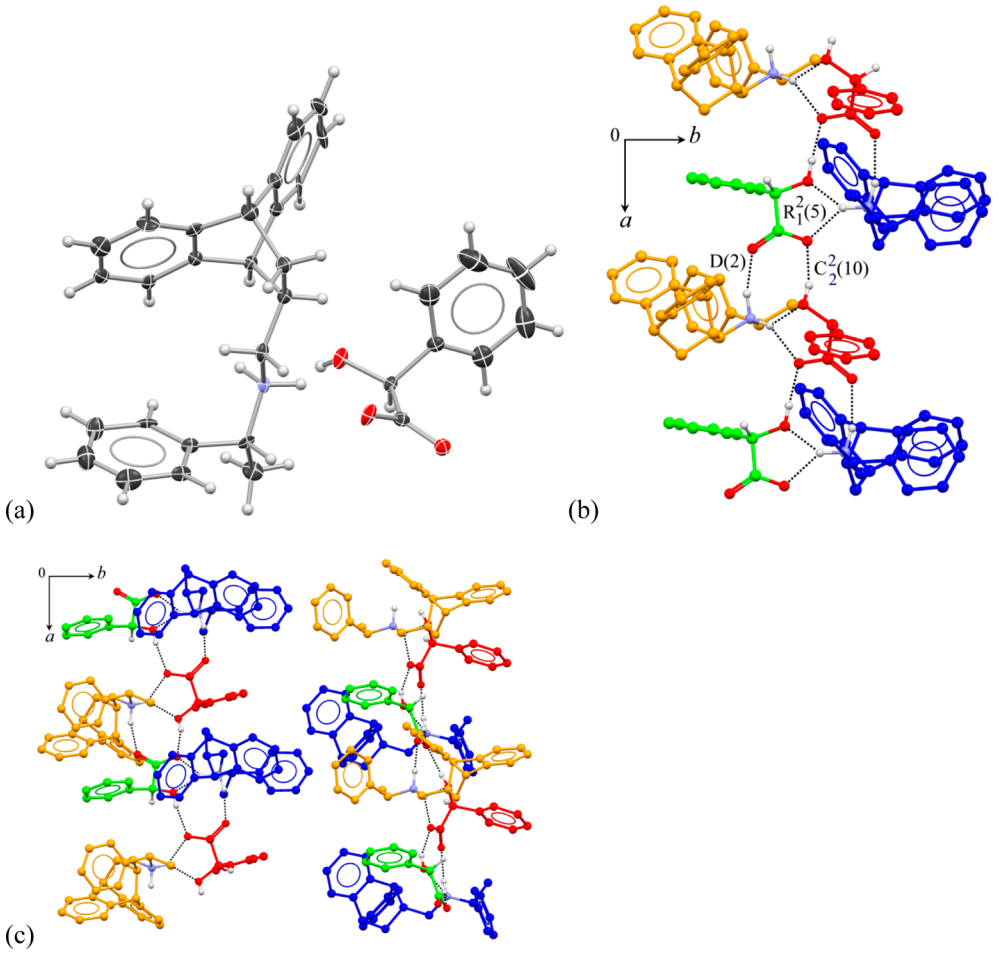

Figure 6. (a) ORTEP view of (*R*,*R*)-**3**·*S*-MA salt. The displacement ellipsoids are drawn at 40% probability level, and H atoms are shown as small spheres of arbitrary radii. (b) Association of the symmetry-independent (*R*,*R*)-**3** molecules to the O−H···O hydrogen-bonded helical chain of *S*-MA (green and red) through N−H···O hydrogen-bonding interactions generating an extended chain assembly. (c) Linking of the neighboring helical chains through van der Waals forces.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00935.

X-ray data for (*R*,*R*)-**3**·(*R*)-mandelic acid salt (CIF)

(*R*,*R*)-**3**·(*S*)-mandelic acid salt (CIF)

Details of CSA study, spectral reproductions, and X-ray structure data (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Prof. Vishwakarma Singh on the occasion of his 65th birthday.

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