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Chiral Solvating Agents for Cyanohydrins and Carboxylic Acids†

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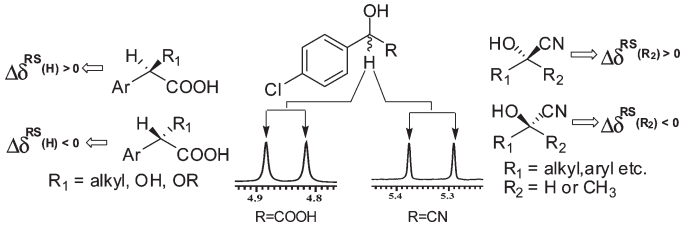

We have shown that a structure as simple as an ion pair of (*R*)- or (*S*)-mandelate and dimethylaminopyridinium ions possesses structural features that are sufficient for NMR enantiodiscrimination of cyanohydrins. Moreover, ^{1}H NMR data of cyanohydrins of known configuration obtained in the presence of the mandelate−dimethylaminopyridinium ion pair point to the existence of a correlation between chemical shifts and absolute configuration of cyanohydrins. Mandelate−DMAPH$^+$ ion pair and mandelonitrile form a 1:1 complex with an association constant of 338 M^{-1} (ΔG^0, −3.4 kcal/mol) for the (*R*)-mandelonitrile/(*R*)-mandelate−DMAPH$^+$ and 139 M^{-1} (ΔG^0, −2.9 kcal/mol) for the (*R*)-mandelonitrile/(*S*)-mandelate−DMAPH$^+$ complex. To understand the origin of enantiodiscrimination, the geometry optimization and energy minimization of the models of ternary complexes of (*S*)-mandelonitrile/(*R*)-mandelate/DMAPH$^+$ and (*S*)-mandelonitrile/(*S*)-mandelate/DMAPH$^+$ complexes was performed using DFT methodology (B3LYP) with the 6-31+G(d) basis set in Gaussian 3.0. Further, analysis of optimized molecular model obtained from theoretical studies suggested that (i) DMAP may be replaced with other amines, (ii) the hydroxyl group of mandelic acid is not necessary for stabilization of ternary complex and may be replaced with other groups such as methyl, (iii) the ion pair should form a stable ternary complex with any hydrogen-bond donor, provided its OH bond is sufficiently polarized, and (iv) α-H of racemic mandelic acid should also get resolved with optically pure mandelonitrile. These inferences were experimentally verified, which not only validated the proposed model but also led to development of a new chiral solvating agent for determination of ee of carboxylic acids and absolute configuration of aryl but not alkyl carboxylic acids.

Introduction

The ability of a host molecule to form geometrically different diastereomeric complexes with antipods of a chiral compound has been exploited for the discrimination of enantiomers by NMR.[1−5] While rigid structures with either built-in cages[6−12] or with strong conformational bias[12−16]

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have been among the most used hosts for NMR enantiodiscrimination, structurally flexible simpler structures[17−19] have also been shown to discriminate enantiomers in NMR with similar resolutions. Recently, we have shown that a much simpler structure, an ion pair of (*R*) or (*S*)-mandelate and dimethylamminopyridinium ion, possesses structural features which are sufficient for NMR enantiodiscrimination of cyanohydrins.[20] Moreover, ^{1}H NMR data of cyanohydrins of known configuration obtained in the presence of the mandelate−dimethylaminopyridinium ion pair pointed to the existence of a correlation between chemical shifts and absolute configuration of cyanohydrins. Here, we describe (a) these results in more detail and (b) significant extension of work leading to development of new chiral solvating agents for carboxylic acids. The mandelic acid−DMAP combination reagent has never been reported before, although use of *O*-acetyl- and *O*-methylmandelic acid as derivatizing agent for determination of ee of secondary alcohols has been described.[21]

The asymmetric cyanation of aldehydes and ketones to produce cyanohydrins is a highly versatile synthetic transformation. Homochiral cyanohydrins are of synthetic interest as they may be transformed into a number of key functional groups, such as α-hydroxy acids, primary and secondary *β*-hydroxyamines, α-aminonitriles, α-hydroxy ketones, α-hydroxy esters, etc., under conditions that conserve optical purity.[22] Many of these intermediates can be used in further stereoselective transformations. Recent advances in the field of chemical and enzymatic catalyst for asymmetric cyanohydrin synthesis are set to revolutionize the use of chiral cyanohydrins in organic synthesis.[22−27] This has resulted in an increased surge of interest in developing new simple, rapid, and steadfast new methods for ascertaining ee and absolute configuration of cyanohydrins.

Assigning the absolute configuration of cyanohydrins is not just an extension of the procedure for secondary or tertiary alcohols because of the complicating effects of cyano group.[28] Even though cyanohydrins appears to have some resemblance with the structure of secondary or tertiary alcohols, the presence of the strongly polar −CN substituent makes the geminal hydroxynitrile moiety a wholly novel situation from the structural point of view to which the NMR procedures previously described for secondary alcohols cannot be applied without a previous and rigorous validation.

Although there were few examples of the use of chiral derivatizing agents and solvating agents for determination of enantiomeric excess of cyanohydrins, there was no thorough study available for enantiodiscrimination of cyanohydrins that can be used for assigning absolute configuration until 2006, when Louzao et al. established the first derivative-based method for aldocyanohydrins,[28] which was later extended to include ketocyanohydrins as well.[29] In these reports, rigorous validation on MPA esters of cyanohydrins was done for determining absolute configuration. The method suffers from drawbacks typical of a derivatization method, viz. chances of resolution and racemization during derivatization and difficulties in recovering cyanohydrin after the analysis.

A recent interesting study of binary mixtures of pyridine and various carboxylic acids using noisy light-based coherent anti-Stokes Raman scattering ($I^{(2)}$CARS) has shown that in solution (i) acid−base reaction produces pyridinium cation and carboxylate anion in highly product favored reaction, (ii) pyridinium and acetate ions exist as ion pairs, and (iii) the propensity to exist as a pyridinium−carboxylate ion pair depends on the pK_a of acid and remains unaffected by the steric bulkiness of the carboxylic acid.[30] Crystal structures of several pyridine/carboxylic acid cocrystalline systems have shown that pyridinium cations interact with anions through a moderate to strong NH···O bond.[31] Since the second oxygen of carboxylate in the ion pair is available as a H-bond acceptor, a ternary complex with a H-bond donor becomes feasible.

The pK_a values of mandelic acid and acetic acid are not very different from each other; therefore, mandelic acid/DMAP mixture should exist primarily as an ion pair, mandelate−DMAPH$^+$, in solution. Due to the powerful electron-withdrawing effect of the cyano group, the O−H bond of the hydroxyl group of cyanohydrins is sufficiently polarized to be able to form a ternary complex with the mandelate−DMAPH$^+$ ion pair through the OH···O bond. On the basis of the foregoing arguments, we purposed a

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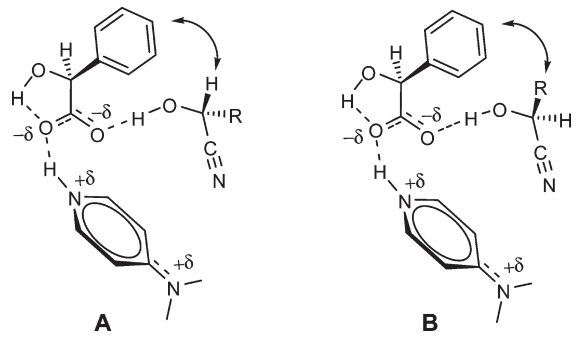

FIGURE 1. Hypothetical model showing ternary complexes of (*R*)-cyanohydrin and (*S*)-cyanohydrin with (*S*)-mandelate−DMAPH$^+$ ion pair. The H in complex A and the R group in complex B of cyanohydrin face the phenyl group of mandelate.

hypothetical model for ternary complex of mandelonitrile with mandelate−DMAPH$^+$ ion pair (Figure 1). In the hypothetical model of the ternary complex, the cylindrically compact, electronegative cyano group has been shown to prefer a position in space which is farthest from carboxylate but closer to the dimethylamino group of DMAP, where the Lewis basic nitrogen of cyano unit can interact with the partially positive nitrogen of amino group. Distortion of the aromatic character and stabilization of imino form has been demonstrated recently in a dimethylaminopyridinium salt.[32]

Results and Discussion

To test this hypothesis, we recorded ^{1}H NMR of racemic mandelonitrile (30 mM) in the presence of 1 molar equiv of (*S*)-mandelic acid and DMAP in $CDCl_3$. We were pleased to note that α-H of two enantiomers of racemic mandelonitrile appeared as well-resolved singlets ($\Delta\Delta\delta$ = 0.084 ppm) in approximate 1:1 ratio based on integral values. ^{1}H NMR data was collected on 300 MHz spectrometer. Chemical shifts (ppm) are internally referenced to TMS signal (0 ppm). α-H of racemic mandelonitrile appeared as singlet at δ 5.532 (Figure 2a), whereas in the presence of 1 molar equiv of mandelate−DMAPH$^+$ ion pair, its two enantiomers suffered an unequal upfield shift and appeared as two singlets at δ 5.435 and 5.351(Figure 2 b). DMAP or mandelic acid alone caused no shift in resonance of α-H proton. Although no covalent bond formation was expected, it was confirmed by recovery of mandelonitrile from samples after recording of NMR. Thus, after removal of $CDCl_3$, sample was dissolved in diethyl ether, which was sequentially washed with 2% sodium bicarbonate, dilute hydrochloric acid, and brine solution. Removal of solvent under reduced pressure on a rotary evaporator resulted in >90% recovery of mandelonitrile. Under similar conditions, α-H of (*R*)- and (*S*)- mandelonitrile appeared as singlets at δ 5.436 (Figure 2 c) and δ 5.353 (Figure 2d), respectively. These results clearly show that mandelate−DMAPH$^+$ ion pair is an effective chiral solvating agent for mandelonitrile. Since baseline separation of α-H of two enantiomers of racemate has occurred, ee of mandelonitrile can be obtained from integral values of α-H.

NMR enantiodiscrimination of a variety of racemic cyanohydrins derived from aliphatic and aromatic aldehydes and ketones with (*S*)-mandelate−dimethylaminopyridinium ion pair was studied (Figure 3). Racemic cyanohydrins were synthesized by reaction of the corresponding aldehyde or ketone with potassium cyanide in the presence of sodium metabisulfite.[33] Excellent baseline separation occurred in all cases with $\Delta\Delta\delta$ in the range of 0.055−0.112 ppm for all aldehyde cyanohydrins studied. The baseline separation occurred, even when the methine proton appeared as a doublet, triplet, or quartet (cyanohydrins **9**−**14**, Figure 3). Excellent baseline separation coupled with the fact that resolved singlets for aldehyde cyanohydrins appeared in the least complex region of ^{1}H NMR suggested that the mandelic acid/DMAP mixture can be used for the accurate determination of the optical purity of these compounds. The $\Delta\Delta\delta$ for ketone cyanohydrins was of the order of 0.010−0.031 ppm (cyanohydrins **15**−**19**, Figure 3). The magnitude of resolution for ketone cyanohydrins was less compared to aldehyde cyanohydrins but sufficient for the determination of optical purity of these compounds. There was some improvement in resolution in all examples except pyridin-4-yl ketone when NMRs were recorded in C_6D_6 instead of $CDCl_3$. No resolution occurred when DMSO-d_6 was used as solvent instead of $CDCl_3$.

Determination of Absolute Configuration of Cyanohydrins. Having demonstrated enantiodiscrimination of cyanohydrins, our next goal was to investigate the suitability of the method for the determination of their absolute configuration. The NMR spectral behavior of a series of cyanohydrins of known absolute configuration was studied using DMAP in combination with (*R*)- or (*S*)-mandelic acid to find the existence of any correlation between the absolute configuration and the NMR chemical shifts. Optically active cyanohydrins were synthesized using commercially available Me-HNL, (*S*)-selective hydroxynitrile lyase from *Manihot esculenta* and Pa-HNL, and (*R*)-selective hydroxynitrile lyase from *Prunus amygdalus*.

$\Delta\delta^{RS}$ values, obtained with (*R*)- and (*S*)-mandelic acid, respectively, for several aldo- and ketocyanohydrins of known configuration are shown in Table 1. Aldehyde cyanohydrins **20**−**23**, **26**, **30**, and **31**, which have the same spatial relationship, showed a positive $\Delta\delta^{RS}$ value, whereas cyanohydrins **24**, **25**, and **27**−**29** with opposite spatial arrangement showed negative $\Delta\delta^{RS}$ values. Similarly, ketone cyanohydrins **32**, **34**, **35**, and **37**, which are configurationally related to **1**, showed positive $\Delta\delta^{RS}$ values, whereas cyanohydrins, **33**, **36**, and **38**, which are configurationally related to **24**, showed negative $\Delta\delta^{RS}$ values. Moreover, the enantiomers of **20**, **21**, **23**, **30**, **32**, and **34**, which are configurationally related to **24**, exhibited negative $\Delta\delta^{RS}$ values. Similarly, the enantiomers of **25** and **27**, which are configurationally related to **20**, showed positive $\Delta\delta^{RS}$ value. Thus, the $\Delta\delta^{RS}$ sign is characteristic for this enantiomeric series and can be used for the assignment of absolute configuration. However, the $\Delta\delta^{RS}$ value for pyridine compound **26** was poor compared to other aldehyde cyanohydrin series. Since basic nitrogen on pyridine can alter the nature of complex formation, assignment of absolute configuration in the pyridine series may not be reliable.

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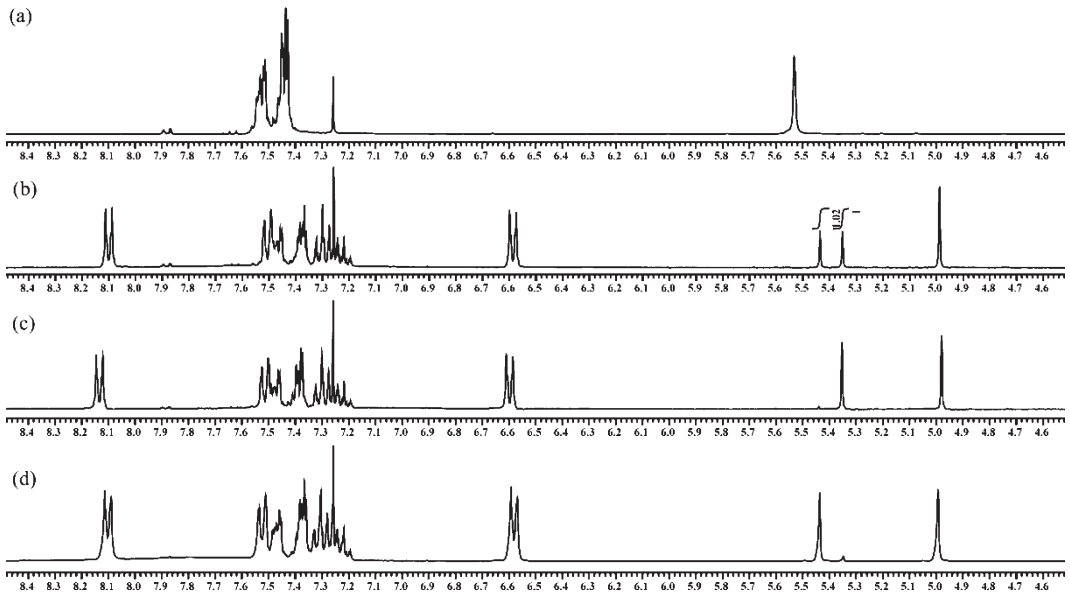

FIGURE 2. NMR enantiodiscrimination of mandelonitrile with (*S*)-mandelate−DMAPH$^+$ ion pair. Partial ^{1}H NMR spectra (300 MHz) of (a) (*R*,*S*)-mandelonitrile in $CDCl_3$ and (b−d) (*R*,*S*)-, (*R*)-, and (*S*)-mandelonitrile, respectively, in the presence of 1 molar equiv of (*S*)-mandelic acid and DMAP.

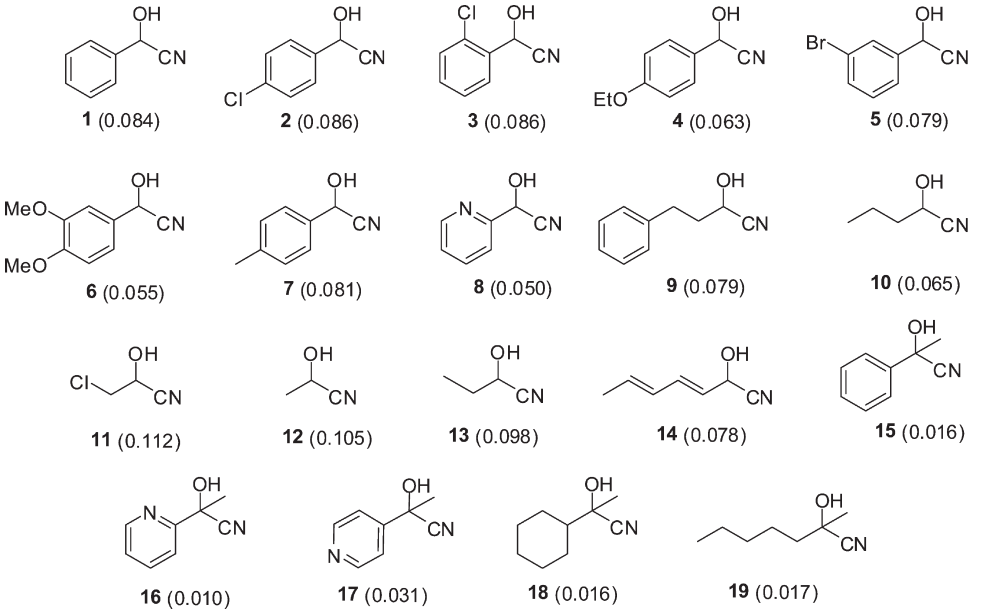

FIGURE 3. NMR enantiodiscrimination of *rac*-cyanohydrins in the presence of (*S*)-mandelate−DMAPH$^+$ ion pair. $\Delta\Delta\delta$ values for α-H or α-CH_3 are shown in parentheses.

Characterization of the Ternary Complex between Cyanohydrin and Mandelate−DMAPH$^+$ Ion Pair. An NMR method as described previously was used to determine the stoichiometry of the complex.[34,35] The ^{1}H NMR spectra of (*S*)-mandelate−DMAPH$^+$ ion pair with (*R*)-mandelonitrile in various ratios in $CDCl_3$, keeping the total concentration constant at 40 μM, were recorded. It was found that the α-H of mandelonitrile underwent a variable upfield shift depending upon the ratio of mandelonitrile and ion pair. The Jobs plot of $\Delta\delta X_i$ (the product of the chemical shift change and the mole fraction) versus the mole fraction (X_i) of (*R*)-mandelonitrile in the mixture was obtained from these values (Figure 4). A maxima was observed when the ratio of (*S*)-mandelate−DMAPH$^+$ ion pair versus (*R*)-mandelonitrile was 1:1 (X_i = 0.5), which indicated 1:1 complex formation between (*R*)-mandelonitrile and (*S*)-mandelate−DMAPH$^+$ ion pair.

Stability constants can be determined by NMR spectrometry when the species are in rapid exchange on the NMR time scale and when there is a variation in the chemical shift of a suitable nucleus on formation of the complex species.[36]

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TABLE 1. Correlation between Chemicals Shifts and Absolute Configuration of Cyanohydrins[a]

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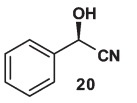
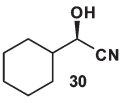
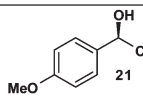
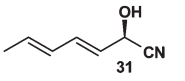
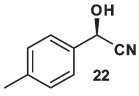
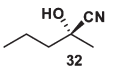
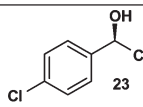
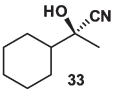
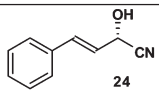
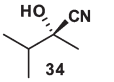
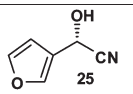
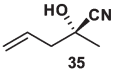
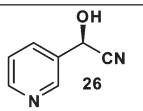
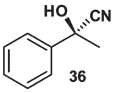
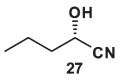
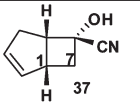
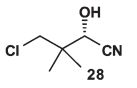
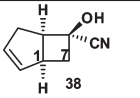
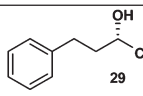
1	 20	+ 0.086	11	 30	+ 0.083
2	 21	+0.085	12	 31	+ 0.078
3	 22	+ 0.095	13	 32	+ 0.017
4	 23	+ 0.089	14	 33	- 0.021
5	 24	- 0.068	15	 34	+ 0.020
6	 25	- 0.073	16	 35	+ 0.016
7	 26	+ 0.010	17	 36	- 0.022
8	 27	- 0.085	18	 37	+ 0.021
9	 28	- 0.080	19	 38	- 0.021
10	 29	- 0.082	-	-	-

[a] $\Delta\delta^{RS}$ ($\Delta\delta^{R} - \Delta\delta^{S}$) values for α-H of **20-31**, α-CH_3 of **32**−**36** and 7-endo H of **37** and **38** are shown. Opposite $\Delta\delta^{RS}$ sign for enantiomers of **20**−**22**, **25**, **27**, **30**, **32**, and **34** was obtained.

A solution of mandelate−$DMAPH^+$ ion pair in $CDCl_3$ was placed in 19 5 mm NMR tubes. A predetermined quantity of a concentrated solution of mandelonitrile in $CDCl_3$ was added to each of 18 tubes so that finally solutions with desired relative amounts (equiv) of the mandelonitrile versus ion pair were obtained. The concentration of ion pair was always maintained at 20 mM. Volume and concentration changes were taken into account during analysis. Plots of concentration versus chemical shift are shown in Figure 5. An association constant (K_a) of 338 M^{-1} (ΔG^0, −3.4 kcal/mol) for (*R*)-mandelonitrile/(*R*)-mandelate−$DMAPH^+$ complex and 139 M^{-1} (ΔG^0, −2.9 kcal/mol) for (*R*)-mandelonitrile/(*S*)-mandelate−$DMAPH^+$ complex was obtained by nonlinear least-squares fitting for the ^{1}H NMR titration curve using the WinEQNMR program.[36] Values of ΔG^0 were calculated using the equation $\Delta G^0 = -RT \ln K_a$.

Proposed Model. Modeling studies were performed to understand the origin of enantiodiscrimination. Justification provided by our previous report[20] has been taken as base for this study. Although the molecular mechanics optimized models obtained in our previous study were able to explain enantiodiscrimination, they showed large differences in the calculated and experimentally observed δ and $\Delta\delta^{RS}$ values (for example, (*S*)-lactonitrile showed a $\Delta\delta^{RS}$ deviation of 1.92 ppm), when subjected to computational estimation of chemical shifts in implicit chloroform medium (IEFPCM method)[37] using the

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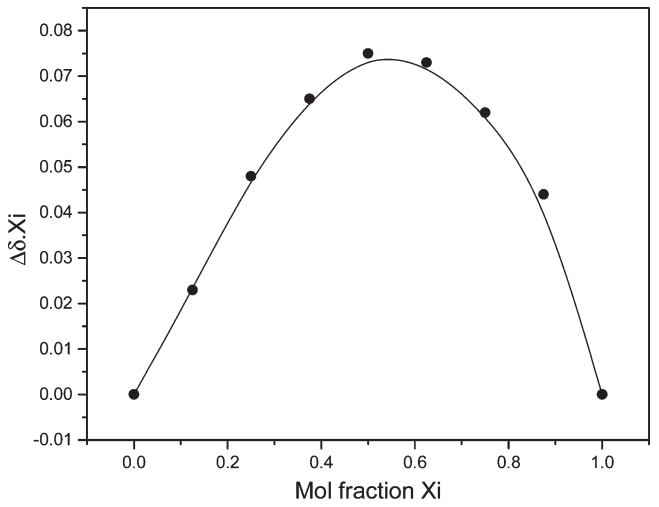

FIGURE 4. Jobs plot for the complexation of mandelate−DMAPH$^+$ ion pair with (*R*)-mandelonitrile. Δδ is the shift (ppm) for α-H of mandelonitrile. Maxima at 0.5 mol fraction indicated 1:1 complexation.

GIAO algorithm[38] and B3LYP/6-311+G(2d,p) method, thereby prompting us to reinvestigate the modeling studies. The modeling studies were performed with Gaussian03 software.[39] Initial geometry optimization on the ternary complexes was carried out using molecular mechanics method in Chem3D software and a few models of the ternary complex were chosen for optimization using the density functional theory (DFT) method with the B3LYP/6-31+G(d) basis set.[40] All of the optimization studies were carried out in the gas phase. The optimized models were employed to computationally estimate chemical shifts in implicit chloroform medium (IEFPCM method)[37] using the GIAO algorithm[38] and B3LYP/6-311+G-(2d,p) method. As NMR experimental studies have been carried out in chloroform solvent, GIAO calculations were performed in chloroform solvent for reliable comparison. Calculated chemical shifts for α-H of nitrile are reported as ppm from the value calculated for TMS after conversion from shielding values.

The optimized space-filling model representations are shown in Figure 6. Whereas the α-H of nitrile experiences

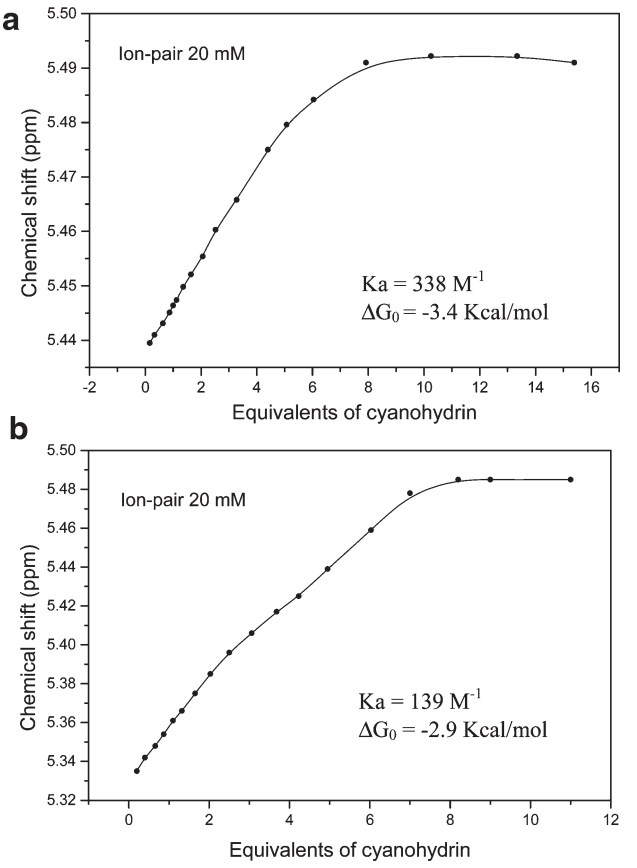

FIGURE 5. ^{1}H NMR titration data obtained for the complexation of (a) (*R*)-mandelate−DMAPH$^+$ ion pair as host and (*R*)-mandelonitrile as guest; (b) (*S*)-mandelate−DMAPH$^+$ ion pair as host and (*R*)-mandelonitrile as guest. K_a was obtained by nonlinear least-squares fitting for the ^{1}H NMR titration curve using WinEQNMR program.[36] ΔG^0 was calculated using equation $\Delta G^0 = -RT \ln K_a$.

anisotropic shielding due to the phenyl ring of mandelate in (*S*)-nitrile/(*R*)-mandelate−DMAPH$^+$ complexes, no such shielding is experienced by the α-H of nitrile in (*S*)-nitrile/(*S*)-mandelate−DMAPH$^+$ complexes. Thus, the $\Delta\delta^{RS}$ value for (*S*)-mandelonitrile should be negative, which is consistent with the experimental observation. The calculated $\Delta\delta^{RS}$ sign in NMR based on models in Figure 6 was in agreement with the experimentally observed results (Table 2). The calculated δ values for α-H of nitrile for all models in Figure 6 were within ±0.28−0.73 ppm compared to the experimentally observed values. Thus, the δ values for α-H of nitrile calculated based on models in Figure 6 were in good agreement with the experimentally observed values. According to models shown in Figure 6, the aryl ring of DMAP is not important for shielding. This observation was supported by the fact that the substitution of DMAP with aliphatic triethylamine or *N*-ethyl-*N*-isopropyl-2-propanamine did not result in any appreciable change in δ or ΔΔδ values for α-H of mandelonitrile (Table 3). *rac*-Mandelonitrile in the presence of (*S*)-mandelic acid showed resonance peaks corresponding to two enantiomers at δ 5.44 and 5.35 with DMAP; 5.38 and 5.26 with triethylamine, and 5.40 and 5.30 with *N*-ethyl-*N*-isopropyl-2-propanamine as base.

In fact, triethylamine gave the best ΔΔδ values out of various amines tested (Table 3). Neither triethylamine nor

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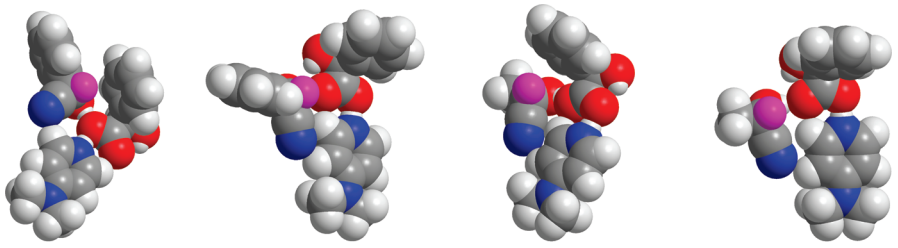

FIGURE 6. Space-filling representations for ternary complexes (a) (*S*)-mandelonitrile/(*R*)-mandelate−DMAPH$^+$, (b) (*S*)-mandelonitrile/(*S*)-mandelate−DMAPH$^+$, (c) (*S*)-lactonitrile/(*R*)-mandelate−DMAPH$^+$, and (d) (*S*)-lactonitrile/(*S*)-mandelate-DMAPH$^+$. α-H of nitrile is shown in purple. Similar conformations were obtained for (*R*)-mandelonitrile and (*R*)-lactonitrile complexes (see the Supporting Information).

TABLE 2. Calculated δ and $\Delta\delta^{RS}$ Values (in ppm) for Various Complexes of Mandelonitrile and Lactonitrile with Mandelate−DMAPH$^+$ Ion Pair[a−c]

entry	nitrile	δ with (*R*)-acid	δ with (*S*)-acid	$\Delta\delta^{RS}$
3	(*S*)-mandelonitrile	5.65 (5.35)	6.19 (5.44)	−0.54 (−0.09)
4	(*R*)-mandelonitrile	6.26 (5.44)	5.63 (5.35)	+0.63 (+0.09)
5	(*S*)-lactonitrile	4.75 (4.34)	5.04 (4.45)	−0.29 (−0.11)
6	(*R*)-lactonitrile	5.16 (4.45)	4.72 (4.35)	+0.43 (+0.10)

[a]See the Experimental Section for the method of calculating chemical shifts. [b]Calculated chemical shifts for α-H of nitrile are reported as ppm from the value calculated for TMS after conversion from shielding values. [c]Experimentally observed values are shown in parentheses.

TABLE 3. Enantiomeric Discrimination ($\Delta\Delta\delta$, in ppm) of Mandelonitrile with (*S*)-Mandelic Acid in the Presence of Various Amines

entry	amine	$\Delta\Delta\delta^a$ (ppm)
1	triethylamine	0.124
2	*N*-ethyl-*N*-isopropyl-2-propanamine	0.096
3	aniline	0
4	pyridine	0.009
5	5-ethyl-2-methylpyridine	0.032
6	2,6-dimethylpyridine	0.032
7	4-(*N*,*N*-dimethylamino)pyridine (DMAP)	0.084

[a]α-H of mandelonitrile.

DMAP caused any racemization of mandelonitrile for 6 h (usually a few minutes are sufficient to complete the experiment). However, we recommend the use of DMAP because it is less likely to cause any racemization of cyanohydrins.

Further analysis of molecular models shown in Figure 6 suggested the following points. (i) The hydroxyl group of mandelic acid may not be necessary for stabilization of the ternary complex; thus, it should be possible to replace the −OH group with other groups such as methyl. Aromatic ring appears to be essential for differential shielding of α-H of (*R*)- and (*S*)-madelonitrile. (ii) The ion pair should form a stable ternary complex with any hydrogen-bond donor, provided its OH bond is sufficiently polarized to form a hydrogen bond; e.g., optically active mandelic acid in the presence of DMAP should be able to resolve another carboxylic acid. (iii) The α-H of racemic mandelic acid should also get resolved with optically enriched mandelonitrile, but not with lactonitrile. These inferences were experimentally validated as given below.

Mandelic Acid Can Be Substituted with Other Chiral Aromatic Acids. Using DMAP as base, various optically pure acids were tested for their ability to enantiodifferentiate methine proton of racemic mandelonitrile. The results are summarized in Table 4. The best results were obtained with (*S*)-MTPA (entry 6, Table 4), which showed a $\Delta\Delta\delta$ value of 0.115, compared to 0.084 ppm obtained with (*S*)-mandelic acid. The presence of an aryl group was found to be essential as aliphatic acids (entry 8−10, Table 4) failed to cause any enantiodifferentiation. Optically active amines (*R*)-1-phenylethanamine and (*R*,*R*)-1,2-diphenylethane-1,2-diamine in combination with achiral phenylacetic acid failed to cause any enantiodifferentiation. A combination of (*S*)-mandelic acid and (*R*,*R*)-1,2-diphenylethane-1,2-diamine gave $\Delta\Delta\delta$ of 0.046 ppm, which was not superior to a combination of (*S*)-mandelic acid and triethylamine or DMAP. This indicated that the chirality of acid and not amine is important for the enantiodifferentiation of cyanohydrins.

TABLE 4. Enantiomeric Discrimination ($\Delta\Delta\delta$, in ppm) of Mandelonitrile with Various Carboxylic Acids (1 molar equiv) in the Presence of DMAP

entry	carboxylic acid	$\Delta\Delta\delta^a$ (ppm)
1	(*S*)-2-hydroxy-2-phenylacetic acid (mandelic acid)	0.084
2	(*S*)-2-(6-methoxynaphthalen-2-yl)-propanoic acid (naproxen)	0.030
3	(*R*)-2-(3-chlorophenyl)-2-hydroxyacetic acid	0.048
4	(*S*)-2-phenylpropanoic acid	0.031
5	(*S*)-2-methoxy-2-phenylacetic acid	0.041
6	(*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (MTPA)	0.115
7	(*S*)-2-phenylbutanoic acid	0.030
8	(*S*)-2-methylbutanoic acid	0.0
9	(*S*)-2-hydroxy-4-methylpentanoic acid	0.0
10	(*S*)-2-cyclohexyl-2-hydroxyacetic acid	0.0

[a]α-H of mandelonitrile.

We applied the computational model described above for mandelic acid to MTPA. The optimized space-filling model representations are shown in Figure 7. The calculated δ values for α-H of mandelonitrile in (*S*)-mandelonitrile/(*S*)-MTPA−DMAPH$^+$ complex was 5.42, which corresponded well with the experimentally observed value of 5.39. The calculated δ value for α-H in (*S*)-mandelonitrile/(*R*)-MTPA−DMAPH$^+$ complex was 6.03, which showed a deviation of only 0.52 ppm from the experimentally observed value of 5.51. Thus, the δ values for α-H of mandelonitrile calculated based on models in Figure 7 were in good agreement with the experimentally observed values.

A range of cyanohydrins were tested using readily available (*S*)-naproxene, (*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid (**39**), in presence of DMAP (Table 5). The magnitude of resolution of cyanohydrins with (*S*)-naproxene in presence of DMAP was in the range of 0.006−0.041, which was inferior compared to a combination of (*S*)-mandelic acid and DMAP.

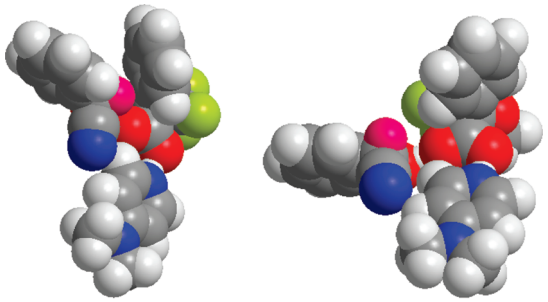

FIGURE 7. Space-filling representations for ternary complexes (a) (*S*)-mandelonitrile/(*S*)-MTPA-DMAPH$^+$ and (b) (*S*)-mandelonitrile/(*R*)-MTPA-DMAPH$^+$. α-H of mandelonitrile is shown in purple.

TABLE 5. Enantiodiscrimination of Cyanohydrins with (*S*)-Naproxen (39)−DMAPH$^+$ Ion Pair

entry	cyanohydrin	resolution $\Delta\Delta\delta^a$ (ppm)
1	mandelonitrile	0.030
2	4-chloromandelonitrile	0.035
3	2-chloromandelonitrile	0.029
4	4-ethoxymandelonitrile	0.025
5	3-bromomandelonitrile	0.041
6	3,4-dimethoxymadelonitrile	0.029
7	4-methylmandelonitrile	0.023
10	3-chloro-2-hydroxypropanenitrile	0.032
12	2-hydroxybutanenitrile	0.029
13	2-hydroxy-2-phenylpropanenitrile	0.006
15	2-hydroxy-2-(pyridin-4-yl)propanenitrile	0.006
16	2-cyclohexyl-2-hydroxypropanenitrile	0.007

^{a}α-H of mandelonitrile.

The mandelate−DMAPH$^+$ ion pair should form a ternary complex with any hydrogen bond donor, provided its OH bond is sufficiently polarized to form a hydrogen bond. Such compounds should also face enantiodiscrimination in ^{1}H NMR. Thus, racemic 2-chloromandelic acid was resolved ($\Delta\Delta\delta$ = 0.008 at 25 °C and 0.014 at −40 °C for α-H) with (*S*)-mandelic acid−DMAPH$^+$ ion pair, lending further support to the proposed model.

Mandelic acid should also get resolved with optically active mandelonitrile. This was found to be true and formed the basis for development of a new method for determination of ee of carboxylic acids. Chiral carboxylic acid is an important functionality present in natural products, biological molecules, metabolic intermediates, and pharmaceuticals. Rapid developments in the area of search for new chemical and biological catalysts aided by high-throughput combinatorial techniques for enantioselective synthesis of chiral carboxylic acids has given rise to an increasing demand for simple, easy to use, cheap, and reliable methods for the determination of enantiomeric purity of these compounds.[41−47] In recent years, many chiral shift reagents,[4] such as amines,[48−50] diamines,[51−54] amides,[12,55] and macrocyclic compounds,[8,10,56−59] have been described for determination of ee of chiral carboxylic acids by ^{1}H NMR.

We started our investigation by recording ^{1}H NMR of racemic mandelic acid in the presence of 1 molar equiv each of (*R*)-mandelonitrile and DMAP at 20 °C in $CDCl_3$. The singlet due to the methine proton of both enantiomers of mandelic acid suffered unequal upfield shift and appeared as two well-resolved singlets at δ 4.96 and 4.98 ($\Delta\Delta\delta$ = 0.015 ppm). The resolution was increased to $\Delta\Delta\delta$ = 0.017 when (*R*)-mandelonitrile was substituted with (*R*)-4-methoxymandelonitrile, whereas resolution was decreased when (*R*)-mandelonitrile was substituted with either (*R*)-4-methylmandelonitrile ($\Delta\Delta\delta$ = 0.013) or (*R*)-4-choloromandelonitrile ($\Delta\Delta\delta$ = 0.011). Thus, (*R*)-4-methoxymandelonitrile in the presence of DMAP was selected as the reagent of choice for further studies.

The observed resonance in NMR is the average of resonances of complexed and uncomplexed species present in solution at equilibrium. The magnitude of $\Delta\delta$ is expected to increase with increase in the concentration of the 1:1 complex with respect to uncomplexed species. Since the 1:1 complex is in equilibrium with its components in solution, adding excess chiral solvating agent to the sample should push the equilibrium in favor of the 1:1 complex. Accordingly, the resolution was improved to $\Delta\Delta\delta$ = 0.025 when the ratio of (*R*)-4-methoxymandelonitrile was increased to 2.5 molar equiv (Figure 8). Further, a significant improvement in resolution occurred when the probe temperature was reduced to −40 °C. At a probe temperature of −40 °C, $\Delta\Delta\delta$ was 0.044 with 1 molar equiv and 0.054 with 2.5 molar equiv of (*R*)-4-methoxymandelonitrile.

A range of racemic α-substituted phenylacetic acids were tested using 1 and 2.5 equiv of (*R*)-4-methoxymandelonitrile at 20 or −40 °C. The ratio of DMAP was kept constant at 1 molar equiv in all cases. Baseline separation for methine proton occurred in all examples of α-substituted phenylacetic acids derivatives studied under all conditions. However, maximum resolution occurred when 2.5 equiv of (*R*)-4-methoxymandelonitrile was used at −40 °C. Under these conditions, $\Delta\Delta\delta$ was in the range of 0.030−0.058 ppm for mandelic acid derivatives (entries 1−4; Table 6). When −OH of mandelic acid was replaced with Br, $\Delta\Delta\delta$ was of the order

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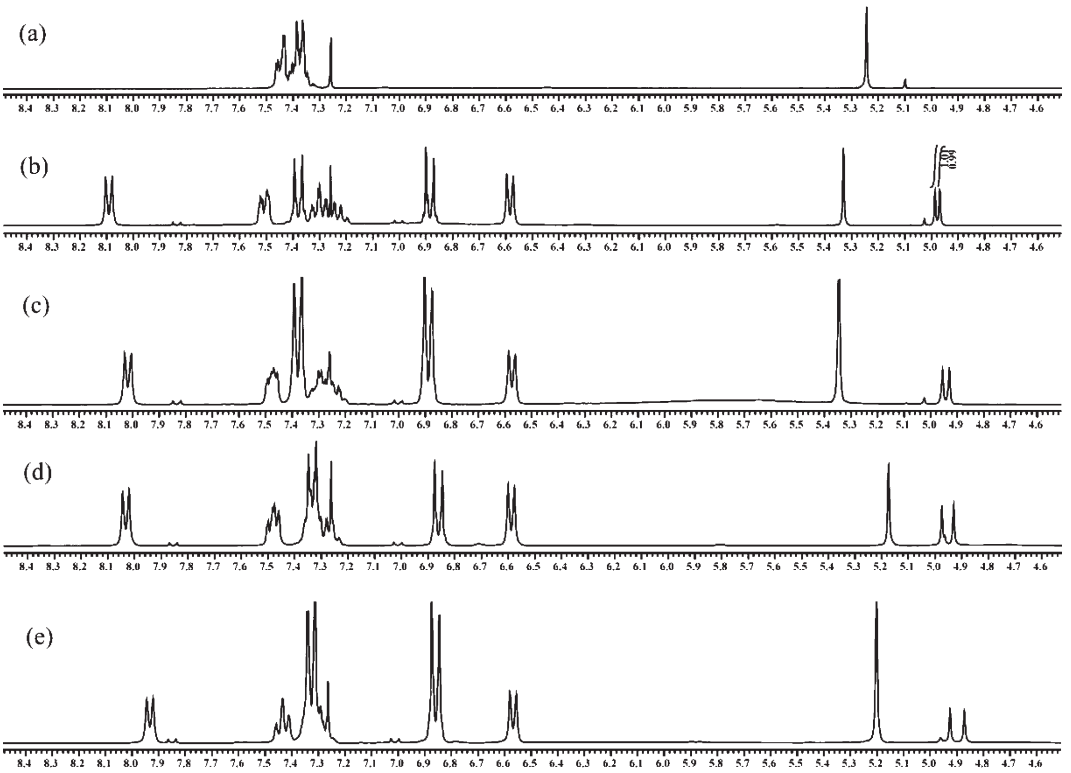


FIGURE 8. NMR enantiodiscrimination of (*R,S*)-mandelic acid with (*R*)-4-methoxymandelonitrile in presence of DMAP. Partial ^{1}H NMR spectrum (300 MHz) of (*R,S*)-mandelic acid in $CDCl_3$ (a); (*R,S*)-mandelic acid in the presence of 1 molar equiv each of DMAP and (*R*)-4-methoxymandelonitrile at 20 °C (b) and −40 °C (d); (*R,S*)-mandelic acid in presence of 1 molar equiv DMAP and 2.5 molar equiv of (*R*)-4-methoxymandelonitrile at 20 °C (c) and −40 °C (e).

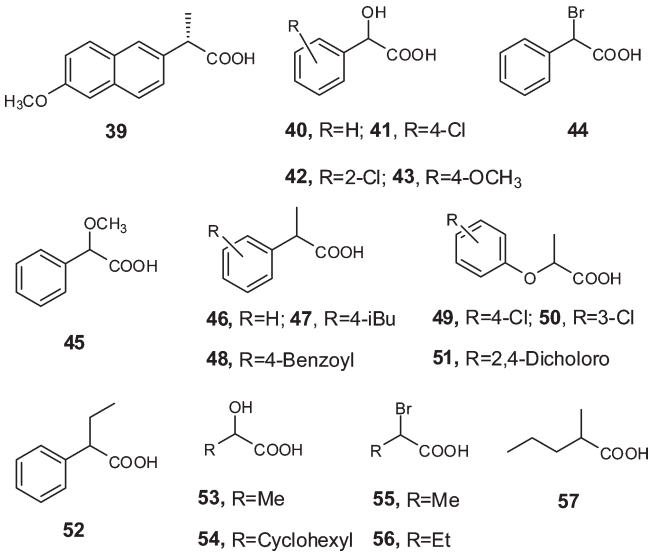
of 0.071 ppm (entry 5, Table 6). The resolution was increased to 0.082 when −OH of mandelic acid was replaced with $-OCH_3$ (entry 6, Table 6). It is significant to note that in addition to the methine proton located at asymmetric carbon, the $-OCH_3$ protons at the para position of phenyl were also resolved ($\Delta\Delta\delta$ = 0.030 ppm; entry 4, Table 6).

Resolution of Racemic 2-Phenyl- and 2-Phenoxypropanoic Acids in the Presence of DMAP. Determination of ee of 2-phenyl- and 2-phenoxypropanoic acids by ^{1}H NMR methods is more difficult because in these cases the resonance due to methine proton appears as quartet due to coupling with methyl group and as a consequence merger of signals occurs. When 2.5 equiv of (*R*)-4-methoxymandelonitrile and a probe temperature of −40 °C were used, $\Delta\Delta\delta$ values in the range of 0.041−0.078 ppm (entries 7−12, Table 6) were obtained, which are sufficient for the determination of ee of these compounds. In all of these examples, the doublet due to the methyl group of propanoates was also resolved with $\Delta\Delta\delta$ values in the range of 0.021−0.032 ppm. In the case of 2-phenylbutanaote, the $\Delta\Delta\delta$ value for triplet of methine proton was 0.085 (entry 13, Table 6). It was interesting to note that the signals of aromatic protons at the ortho position in 2-(4-cholorophenoxy)- and 2-(2,4-dicholorophenoxy)propanoic acids also suffered unequal shift and were resolved with $\Delta\Delta\delta$ values of 0.031 and 0.056 ppm, respectively (entries 10 and 12, Table 6).

Resolution of Racemic Aliphatic Carboxylic Acids in the Presence of DMAP. Next, resolution of aliphatic carboxylic acids with 4-methoxylmandelonitrile in the presence of DMAP was studied. The quartet due to the methine proton of racemic lactic acid showed a $\Delta\Delta\delta$ value of 0.011 ppm with 1 equiv and 0.018 ppm with 2.5 equiv of (*R*)-4-methoxymandelonitrile at 20 °C, which was improved to 0.030 and 0.040, respectively, at −40 °C (entry 14, Table 6). The doublet due to the methyl group was also resolved, but the maximum $\Delta\Delta\delta$ obtained was 0.009 with 2.5 equiv of (*R*)-4-methoxymandelonitrile at −40 °C. When the methyl group of lactic acid was substituted with cyclohexyl group, increased resolution was observed with a $\Delta\Delta\delta$ value of 0.041 and 0.054 for methine doublet, with 1 and 2.5 equiv of **2**, respectively, at −40 °C (entry 15, Table 6). However, with 2.5 equiv of (*R*)-4-methoxymandelonitrile, there was some overlap of the methine doublet with the methoxy signal of (*R*)-4-methoxymandelonitrile. When −OH of lactic acid was replaced with Br, the resolution was decreased; the maximum $\Delta\Delta\delta$ value of 0.023 was obtained with 2.5 equiv of (*R*)-4-methoxymandelonitrile at −40 °C (entry 16, Table 6). The resolution obtained with 2-bromobutyric acid and 2-methylpentanoic acid was poor (entries 17 and 18, Table 6). Increasing the ratio of (*R*)-4-methoxymandelonitrile and decreasing the probe temperature to −40 °C resulted only in a marginal increase in $\Delta\Delta\delta$ value in these examples.

Resolution of Carboxylic Acids in the Presence of Triethylamine. To further improve resolution of carboxylic acid, especially in the case of 2-phenyl- and 2-phenoxypropanoic acids, DMAP was substituted with triethylamine, which gave the best resolution in the case of cyanohydrins. The ratio of triethylamine was kept constant at 1 molar equiv in all cases. Baseline separation for methine proton occurred with 1 molar equiv of (*R*)-4-methoxymandelonitrile at 20 °C in all examples of mandelic acid derivatives studied, with

TABLE 6. Resolution ($\Delta\Delta\delta$, in ppm) of Racemic α-Substituted Phenylacetic Acids, 2-Phenyl- and 2-Phenoxypropanoic Acids, and Aliphatic Caroboxylic Acids in the Presence of (*R*)-4-Methoxymandelonitrile and DMAP



		(*R*)-4-methoxymandelonitrile (1.0 equiv) $\Delta\delta$ (ppm)[a]		(*R*)-4-methoxymandelonitrile (2.5 equiv) $\Delta\delta$ (ppm)[a]	
entry	acid	20 °C	−40 °C	20 °C	−40 °C
1	**40**	0.017	0.044	0.025	0.054
2	**41**	0.019	0.053	0.029	0.068
3	**42**	0.024	0.023		0.030
4	**43**	0.018	0.047	0.026	0.058
		0.009; OCH_3	0.021; OCH_3	0.015; OCH_3	0.030; OCH_3
5	**44**	0.010	0.045	0.022	0.071
6	**45**	0.021	0.056	0.037	0.082
7	**46**	0.016	0.048	0.025	0.072
		0.006; H3	0.024; H3	0.013; H3	0.031; H3
8	**47**	0.013	0.048	0.030	0.078
		0.0; H3	0.024; H3	0.011; H3	0.032; H3
9	**48**	0.013	0.041	0.024	0.066
		0.003; H3	0.020; H3	0.007; H3	0.024; H3
10	**49**	0.016	0.037	0.023	0.050
		0.006; H3	0.009; H3	0.013; H3	0.021; H3
		0.009; H2′, H5′	0.028; H2′, H5′	0.014; H2′, H5′	0.031; H2′, H5′
11	**50**	0.011	0.024	0.022	0.046
		0.0; H3	0.0; H3	0.009; H3	0.021; H3
12	**51**	0.014	0.033	0.023	0.041
		0.010; H3	0.018; H3	0.022; H3	0.023; H3
		−; H6′[b]	0.047; H6′	0.024; H6′	0.056; H6′
13	**52**	0.014	0.049	0.026	0.085
		0.006; H3	0.024; H3	0.013 H3	0.038 H3
14	**53**	0.011	0.030	0.018	0.040
		0.002; C3	0.008; C3	0.005; C3	0.009; C3
15	**54**	0.013	0.041	0.024	0.054
16	**55**	0.009	0.014	0.017	0.023
17	**56**	0.007		0.010	0.008
18	**57**		0.006		0.008

[a] δ for H2 unless stated otherwise. [b] Peaks merged.

improvement in resolution in most of the examples (entries 1−4, Table 7). In the case of 2-phenyl- and 2-phenoxypropanoic acids, baseline separation was achieved using 2.5 equiv of 4-methoxymandelonitrile and at a probe temperature of −40 °C (entries 5−11, Table 7). $\Delta\Delta\delta$ values in the range of 0.084−0.123 ppm were obtained, which are sufficient for the determination of ee of these compounds and better than resolution obtained with DMAP. Aliphatic carboxylic acids with (*R*)-4-methylmandelonitrile in the presence of triethylamine gave a resolution of 0.004−0.024 ppm (entries 12−14, Table 7).

Determination of Absolute Configuration of Carboxylic Acids. A procedure that is often used for determination of absolute configuration is to look for the presence of specific trends in the shifts that correlate with the absolute configuration of the substrate.[3,5] The assumption is that, if the trends are consistent among a series of compounds with known configurations, then they will be consistent for an unknown compound with a similar structure. Applying empirical trends such as these, we have described above the development of a method for the determination of absolute configuration of cyanohydrins. On the basis of the analysis

TABLE 7. Resolution (ΔΔδ, in ppm) of Racemic 2-Phenyl- and 2-Phenoxypropanoic Acids and Aliphatic Carboxylic Acids in Presence of (*R*)-4-Methoxymandelonitrile and Triethylamine

entry	acid	(*R*)-4-methoxy mandelonitrile (1.0 equiv), 20 °C ΔΔδ[a] (ppm)	(*R*)-4-methoxy mandelonitrile (2.5 equiv), −40 °C ΔΔδ[a] (ppm)
1	**40**	0.021	0.054
2	**41**	0.024	0.084
3	**43**	0.019	0.057
		0.009; OCH3	0.032; OCH3
4	**45**	0.026	0.103
5	**46**	0.023	0.085
		0.138; H3	0.057; H3
6	**47**	0.024;	0.088;
		0.014; H3	0.057; H3
7	**48**	0.024	0.098
		0.010; H3	0.046; H3
8	**49**	0.025	0.093
		0.013; H3	0.034; H3
		0.013; H2′, H5′	0.047; H2′, H5′
9	**50**	0.023	0.123
		0.011; H3	0.040; H3
10	**51**	0.025	0.084
		0.013; H3	0.060; H3
		0.013; H6′	0.088; H6′
11	**52**	0.026	0.102
		0.013; H3	0.052; H3
12	**55**	0.013	0.024
13	**56**	0.005	
14	**57**	0.004	0.008

[a]ΔΔδ for H2 unless stated otherwise.

of ^{1}H NMR data of cyanohydrins of known configuration obtained in the presence of the mandelate−DMAPH$^+$ ion pair, we have shown the existence of a correlation between chemical shifts and the absolute configuration of cyanohydrins. In these cases, the chiral solvating agent, i.e., ion pair, caused a significant difference in chemical shift for two enantiomers of the substrate, i.e., cyanohydrin.

We have described above the enantiodiscrimination of carboxylic acids with chiral mandelonitriles in the presence of DMAP (Table 6). Although the resolution obtained was sufficient for the determination of ee of these compounds, the magnitude was not sufficient to look for correlation between chemical shift values and absolute configuration. However, moieties on the substrate that may cause a specific trend in the shifts in the resonance of chiral derivatizing agent have also been used for assigning absolute configuration.[3] A chiral derivatizing agent (CDA) could be thought of as CSA where all the solute is in the complexed form; therefore, the principles developed for CDAs can be applied to CSAs as well, as only the magnitude of resolution is expected to be lower with CSAs as compared to CDAs.

Accordingly, the $\Delta\delta^{RS}$ value of −0.082 (α-H of 4-methoxymandelonitrile) was obtained with (*S*)-mandelic acid and +0.085 with (*R*)-mandelic acid using 4-methoxymandelonitrile in the presence of DMAP. Encouraged by these results, we pursued this method further. It occurred to us that obtaining two NMRs for each sample, one with optically pure (*R*)-mandelonitrile and the other with optically pure (*S*)-mandelonitrile, to obtain $\Delta\delta^{RS}$ values may not be necessary; instead, a single NMR using (*R*)- or (*S*)-mandelonitrile of lower ee may be sufficient. Thus, we prepared solution of 4-methoxymandelonitrile containing (*R*)- and (*S*)-enantiomers in a ratio of approximately 85:15 (70% ee) by diluting a solution of optically pure (*R*)-4-methoxymandelonitrile with an appropriate amount of racemic 4-methoxymandelonitrile. The actual *R* to *S* ratio was determined by ^{1}H NMR method described above. Using (*R*)-4-methoxymandelonitrile of 70% ee, we determined the $\Delta\delta^{RS}$ values for (*R*)- and (*S*)-mandelic acid, which were found to be +0.0586 and −0.0618, respectively. Although the $\Delta\delta^{RS}$ values were compromised to some extent compared to values obtained when optically pure (*R*)- and (*S*)-4-methoxymandelonitriles were used, these values are sufficient to look for existence of any trend in a series of carboxylic acids. $\Delta\delta^{RS}$ values obtained with a series of optically pure carboxylic acids with (*R*)-4-methoxymandelonitriles, ee 70%, in the presence of DMAP are given in Figure 9. No change in sign of $\Delta\delta^{RS}$ was observed when these values were obtained using optically pure (*R*)- and (*S*)-4-methoxymandelonitrile; only the magnitude of resolution was higher by ∼0.020 ppm in all examples studied. Under these conditions, all carboxylic acids, which are spatially related to (*S*)-mandelic acid, showed a negative $\Delta\delta^{RS}$ value, whereas those related to (*R*)-mandelic acid showed a positive $\Delta\delta^{RS}$ value. Thus, the $\Delta\delta^{RS}$ sign appears to be characteristic for this enantiomeric series and possibly can be used for the assignment of absolute configuration.

Conclusions

Mandelic acid in the presence of DMAP is an effective chiral solvating agent (CSA) for the determination of ee and absolute configuration of cyanohydrins. Resolutions of the order of 0.055−0.112 ppm (16.5−33.6 Hz) for aldocyanohydrins and 0.016−0.031 ppm (4.8−9.3 Hz) for ketocyanhydrins on 300 MHz NMR were obtained. The magnitude of resolution for ketone cyanohydrins was less compared to aldehyde cyanohydrins but sufficient for the determination of optical purity of these compounds. A model has been

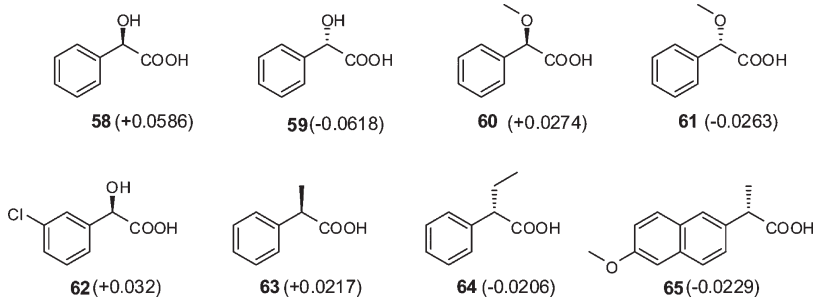


FIGURE 9. Correlation between chemical shifts and absolute configuration of carboxylic acids. $\Delta\delta^{RS}$ ($\Delta\delta^R - \Delta\delta^S$) values in ppm for α-H of nitrile are shown in parentheses.

proposed on the basis of molecular modeling studies. Several inferences drawn from the proposed model were experimentally verified, including that (i) DMAP may be replaced with other amines, (ii) the hydroxyl group of mandelic acid is not necessary for stabilization of ternary complex and may be replaced with other groups such as methyl, (iii) the ion pair should form a stable ternary complex with any hydrogen bond donor, provided its OH bond is sufficiently polarized, and (iv) α-H of racemic mandelic acid should also get resolved with optically pure mandelonitrile, which not only validated the proposed model but also led to development of new CSA for determination of ee of aryl and alkyl carboxylic acids. Resolutions of the order of 0.021−0.085 ppm (6.3−25.5 Hz) for aryl carboxylic acids and 0.008−0.057 ppm (2.4−17.1 Hz) for aliphatic carboxylic acids on 300 MHz NMR were obtained, which are sufficient for accurate determination of ee of these compounds. CSA appears to be suitable for the determination of absolute configuration of aryl carboxylic acids but not for aliphatic carboxylic acids.

Experimental Section

Stoichiometry of the complex. NMR method as described previously was used to determine the stoichiometry of the complex.[34,35] The ^{1}H NMR spectra of the (*S*)-mandelate−DMAPH$^+$ ion pair with (*R*)-mandelonitrile in a various ratios in $CDCl_3$ at a constant total concentration of 40 μM were recorded. It was found that the α-H of mandelonitrile underwent a variable upfield shift depending upon the ratio of mandelonitrile and ion pair. Jobs plot of $\Delta\delta X_i$ (the product of the chemical shift change and the mole fraction) versus the mole fraction (X_i) of (*R*)-mandelonitrile in the mixture were obtained.

Determination of Stability Constants. A 20 mM solution of mandelate−-DMAP$^+$ ion pair in $CDCl_3$ was placed in 19 5 mm NMR tubes. A predetermined quantity of a concentrated solution of mandelonitrile in $CDCl_3$ was added to each of 18 tubes so that finally solutions with desired relative amounts (equiv) of the mandelonitrile versus ion pair were obtained. Volume and concentrations changes were taken into account during analysis. The concentration of the ion pair was always maintained at 20 mM. Plots of concentration versus chemical shift were obtained. An association constant for (*R*)-mandelonitrile/(*R*)-mandelate−DMAPH$^+$ complex and (*R*)-mandelonitrile/(*S*)-mandelate−DMAPH$^+$ complex was obtained by nonlinear least-squares fitting for the ^{1}H NMR titration curve using the WinEQNMR program.[36] Values of ΔG^0 were calculated using equation $\Delta G^0 = -RT \ln K_a$.

Modeling Studies. The modeling studies were performed with Gaussian03 software.[39] Initial geometry optimization on the ternary complexes was carried out using the molecular mechanics method in Chem3D software, and a few models of the ternary complex were chosen for optimization using the density functional theory (DFT) method with the B3LYP/6-31+G(d) basis set.[40] All of the optimization studies were carried out in the gas phase. The optimized models were employed to computationally estimate chemical shifts in implicit chloroform medium (IEFPCM method)[37] using the GIAO algorithm[38] and B3LYP/6-311+G(2d,p) method. As NMR experimental studies have been carried out in chloroform solvent, GIAO calculations were performed in chloroform solvent for reliable comparison. Calculated chemical shifts for α-H of nitrile are reported as ppm from the value calculated for TMS after conversion from shielding values.

Substitution of DMAP with Other Amines. (*S*)-Mandelic acid (18 μmol) and $CDCl_3$ (0.6 mL) were mixed in 5 mm NMR tube and amine (18 μmol) added to it. Mandelonitrile (18 μmol) was added, and ^{1}H NMR data was collected on a JEOL ACX 300 MHz spectrometer. Chemical shifts (ppm), internally referenced to TMS signal (0 ppm), were obtained.

Substitution of (*S*)-Mandelic Acid with Other Carboxylic Acids. Carboxylic acid (18 μmol) and $CDCl_3$ (0.6 mL) were mixed in a 5 mm NMR tube, and DMAP (18 μmol) added. Cyanohydrin (18 μmol) was added, and ^{1}H NMR data was collected on JEOL ACX 300 MHz spectrometer. Chemical shifts (ppm) internally referenced to TMS signal (0 ppm) were obtained.

Chiral Solvating Agent for Carboxylic Acids. Carboxylic acid (18 μmol) and $CDCl_3$ (0.6 mL) were mixed in a 5 mm NMR tube, and DMAP or triethylamine (18 μmol) was added. (*R*)-4-Methoxymandelonitrile (18 or 45 μmol) was added, and ^{1}H NMR data were collected on a JEOL ACX 300 MHz spectrometer. Chemical shifts (ppm) internally referenced to TMS signal (0 ppm) were obtained.

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Supporting Information Available: Cartesian coordinates for models in Figures 6 and 7; tabulated partial ^{1}H NMRs showing resolution of carboxylic acid and ^{1}H NMRs for cyanohydrins **1**−**19** and carboxylic acids **39**−**56** in presence of chiral shift reagent. This material is available free of charge via the Internet at http://pubs.acs.org.