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ARTICLE

A Versatile Ternary Ionic Complex for Chiral Discrimination of Molecules of Diverse Functionality Using ^{1}H NMR

Indrani Pal, Sachin Rama Chaudhari, and Nagarajarao Suryaprakash*

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The study reports a simple, efficient and versatile protocol developed for NMR spectroscopic enantiodiscrimination of molecules containing diverse functional groups, such as, amino alcohols, secondary alcohols, cyanohydrins, oxazolidones, diols, thiones and epoxides, by using a phosphorous based three component mixture. The simple mixing and shaking of enantiopure 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (BNPA), 4-(dimethylamino)pyridine (DMAP) and a chiral analyte in the solvent $CDCl_3$ served as a chiral solvating agent and resulted in well dispersed peaks for each enantiomer in the ^{1}H NMR spectrum. The discrimination could be achieved not only for the proton at the chiral centre, but also for multiple proton sites. The devised approach also permitted the precise measurement of enantiomeric excess (*ee*).

Introduction

Ever increasing demands of asymmetric synthesis and enantiopure molecules in the study of pharmaceuticals, natural products, biological molecules has accelerated the need for exploring simple, easy to use, cost effective and reliable methods for testing the enantiopurity of chiral compounds [1, 2]. Various analytical techniques are available to determine the enantiopurity of molecules, viz., HPLC, circular dichroism (CD), NMR spectroscopy, etc. However, since last few decades NMR spectroscopic discrimination of enantiomers has kept its footsteps forward as the most potential analytical tool compared to other available techniques [3]. In the solution NMR the enantiodiscrimination is achieved by converting the substrates to diastereomers employing any one of the enantiopure chiral auxiliaries, viz., chiral derivatizing agent (CDA), chiral solvating agent (CSA) or chiral lanthanide shift reagent (CLSR) [4]. It is also well known that there exists no unique chiral auxiliary applicable to molecules possessing different functional groups. Number of chiral auxiliaries is thus reported [5]. Each reported auxiliary is applicable to molecules possessing a particular functional group(s), and has its own advantages and limitations [6]. The superiority of CSA over other auxiliaries arises due to the formation of diastereomeric complexes through non-covalent interactions with the analyte. Not only it does not invoke any derivatization, it is also free from line broadening [7], which is generally observed when CLSR is employed. In addition the process of discrimination involves simple mix and shake of chiral analyte and the auxiliary.

The binapthol derivatives are very well documented as chiral discriminating agents. Although 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (BNPA) has been reported as a discriminating agent for primary amines, it fails to discriminate molecules containing other functionalities [8]. As the interaction of analyte with BNPA is non-covalent, we have introduced a simple protocol which involves mixing of an acid with a base, giving rise to an ion-pair complex. The addition of chiral analyte to this ion-pair complex results in a ternary ionic complex. The present study reports the versatile applicability of this new protocol in testing the enantiopurity of molecules of different functionalities, such as, amino alcohols, secondary alcohols, cyanohydrins, oxazolidones, diols, thiones and epoxides.

Experimental

All the commercially available chemicals were purchased from Sigma Aldrich and used as received. The ^{1}H NMR experiments were carried out using the Bruker AV-III 400 NMR spectrometer equipped with a TXI probe. The ^{1}H NMR spectra of a series of chiral amino alcohols and other molecules were obtained using a 1:1 and 2:2 molar mixture of optically pure BNPA and DMAP in the solvent $CDCl_3$ at room temperature (298 K). The chemical shifts were measured using TMS as an internal reference. Similar procedure was utilized to achieve discrimination in molecules of other functionalities.

Results and discussion

Ternary Ion-pair Complex

To ascertain the enantiomeric discriminating ability of the developed ternary complex, initially the experiments were carried out on amino alcohols using enantiopure BNPA as the CSA. The ^{1}H NMR spectrum of racemic amino alcohol, (1*R*, 2*S* / 1*S*, 2*R*)-2-amino-1, 2-diphenylethanol, in the presence of 1 equiv. of CSA in $CDCl_3$ was thus obtained and the corresponding spectrum is reported in Fig. 1b. It is clearly evident that BNPA interacted with alcohol and yielded discrimination. Nevertheless, the chemical shift separation of -CH protons at the chiral centres (marked a and b in the structure) between the enantiomers is very small, indicating very weak interaction between amino alcohol and the BNPA. To induce stronger interaction, an one equivalent of DMAP was then added to the above solution. As a consequence the two enantiomers experienced different magnetic environments and the spectrum of protons a and b appeared as two doublets with nearly 2-fold enhancement in their chemical shift separation ($\Delta\delta^{R/S}$). The spectrum and the measured $\Delta\delta^{R/S}$ are reported in Fig. 1a.

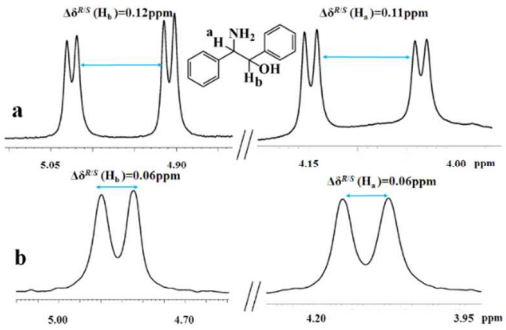

Figure 1: 400 MHz ^{1}H-NMR spectra of racemic (1*R*, 2*S* / 1*S*, 2*R*)-2-amino-1, 2-diphenylethanol (1 equiv.) with; a) BNPA+DMAP (1:1) in $CDCl_3$ and b) BNPA in $CDCl_3$.

Both DMAP and BNPA have definite roles in chiral discrimination of amino alcohols, viz., BNPA interacts with DMAP through a NH•••O type interaction and forms a chiral ion-pair of the type $DMAPH^+$ -BNPA. Subsequently each enantiomer of amino alcohol undergoes NH•••O and OH•••O type interaction with $DMAPH^+$-BNPA ion-pair. This interaction gets intensified between the amino alcohol and chiral $DMAPH^+$-BNPA ion pair to give rise to a ternary complex via multiple intermolecular H-bonding interacting groups of the ion pair and the analyte. This acid-base ion pair accepts protons from amino alcohol in order to stabilize the complex. The proposed ternary ion pair complex is reported in Fig. 2.

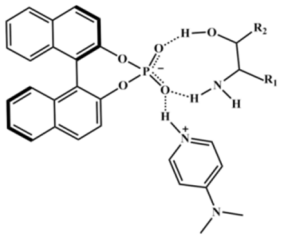

Figure 2: Illustration of the proposed ternary ion pair complex

Furthermore, on increasing the ratio of BNPA and DMAP from 1:1 to 2:2 the significant enhancement in the frequency separation and also improvement in the baseline resolution was observed. This result unambiguously established that the addition of DMAP promotes the interaction between amino alcohol and CSA to generate two different diastereomeric ternary complexes and also the resolution of the peaks a and b are significantly enhanced as reported in Fig.3.

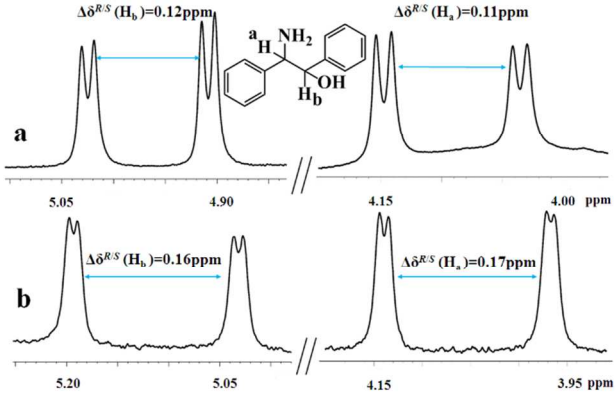

Figure 3: 400 MHz ^{1}H-NMR spectra of racemic (1*R*, 2*S* / 1*S*, 2*R*)-2-amino-1, 2-diphenylethanol (1 equiv) in; a) (2:2) BNPA:DMAP, and b) (1:1) BNPA:DMAP.

The ternary ion-pair complex is also free from kinetic resolution, which is established by recording the spectrum at different time intervals. This is another significant advantage of the present protocol.

Effect of Solvent Polarity

To ascertain the effect of solvent polarity, if any, on the achievable separation between the two discriminated peaks, the experiments were also carried out in solvents of different polarities. It is observed that solvents capable of making hydrogen bonds, such as, methanol and DMSO resulted in less separation due to the possible hydrogen bonding with the complex. On the other hand, in non-polar solvents the modest separation is achieved but with more line broadening. Though chloroform and dichloromethane have almost comparable dipole moments the best separation with proper baseline resolution could be achieved in the chloroform solvent. Thus the studies were carried out in the solvent $CDCl_3$. All the relevant spectra are reported in the supporting information. The variation of the spectral resolution, that is the separation between the two doublets (-$CHNH_2$) of each enantiomer of 2-amino-1,2-diphenylethanol as a function of the solvent dipole moment is reported in Fig. 4.

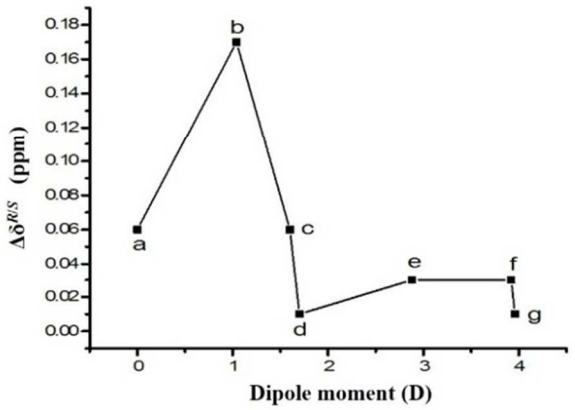

Figure 4: The plot of maximum $\Delta\delta^{R/S}$ (of -$CHNH_2$) obtained for racemic (1*R*, 2*S* / 1*S*, 2*R*)-2-amino-1, 2-diphenylethanol with the CSA as a function of the dipole moment of different of solvents; a) C_6D_6, b) $CDCl_3$, c) CD_2Cl_2, d) MeOD, e) CD_3COCD_3, f) CD_3CN and g) DMSO.

Applications to Diverse Chiral Molecules

The ^{1}H NMR spectra of a wide variety of amino alcohols were recorded for enantiodiscrimination. In each investigated molecule the discrimination could be achieved at number of proton sites. The measured differential values of chemical shifts of the discriminated peaks are assimilated in Table 1. For all the amino alcohols the reported $\Delta\delta^{R/S}$ values for different proton sites pertain to the one that gave excellent baseline resolution at ambient temperature (25 °C). Another major advantage of this CSA is its ability to yield discrimination at many other proton sites with a very good base line resolution.

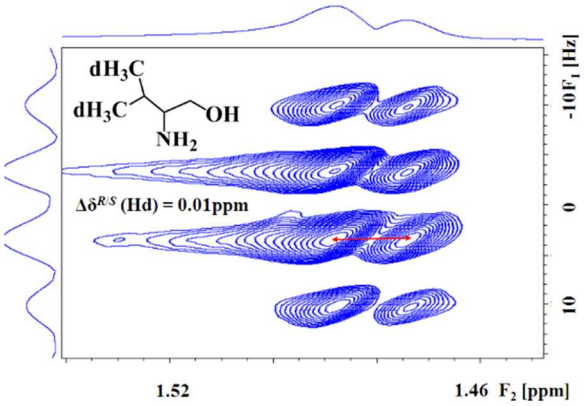

Figure 5: 400 MHz 2D *J*-resolved spectrum of racemic-2-amino-3-methyl-1-butanol

For few investigated molecules the measurement of precise chemical shift separation between the discriminated peaks was hampered due to complex spectral multiplicity pattern. In order to circumvent such a problem, earlier we have recommended the utilization of two dimensional *J*-resolved experiment, which is an extremely useful technique to obtain accurate chemical shifts, especially when there is severe overlap [9]. The typical spectrum for (rac)-2-amino-3-methyl-1-butanol is given in Fig 5, where the –CH_3 (d) peak is well resolved in 2D. All other spectra are reported in the supporting information.

Table 1: Measured $\Delta\delta^{R/S}$ values of discriminated protons for different amino alcohols.

Entry	Amino alcohol	Chemical shift difference ($\Delta\delta^{R/S}$) (ppm)
1		a = 0.01 b = 0.03 c = 0.04 d = 0.09 e = 0.07
2		a = 0.16 b = 0.09 c = 0.10 d = 0.05 e = 0.03 f = 0.03
3		a = 0.15 b = 0.10 c = 0.01 d = 0.10
4		a = 0.17 b = 0.16
5		a = 0.07 b = 0.05 c = 0.04
6		a = 0.04 b = 0.18 c = 0.26 d = 0.14
7		a = 0.12 b = 0.14 c = 0.04 d = 0.03
8		a = 0.32 b = 0.23 c = 0.20 d = 0.04
9		a = 0.11 b = 0.09 c = 0.02 d = 0.08 e = 0.01 f = 0.01 g = 0.01
10		a = 0.01 b = 0.04 c = 0.01 d = 0.02

The new ternary ion protocol developed also serves as a versatile CSA for testing the enantiopurity of molecules of other functionalities, viz., cyanohydrins, thiones, oxazolidones, secondary alcohols, diols, and epoxides. This is demonstrated on various molecules adapting the similar protocol discussed above for amino alcohols. All the molecules yielded discrimination with a good base line resolution. The discrimination achieved for different protons in these molecules are reported in Table 2.

Table 2: Measured $\Delta\delta^{R/S}$ values of discriminated protons in other molecules of different functionality.

Entry	Molecules	Chemical shift difference ($\Delta\delta^{R/S}$) (ppm)
11		a = 0.07 b = 0.05 c = 0.22
12		a = 0.04
13		a = 0.02
14		a = 0.26 b = 0.08 c = 0.19
15		a = 0.13 b = 0.37 c = 0.02
16		a = 0.02
17		a = 0.02 b = 0.03
18		a = 0.03 b = 0.03 c = 0.03
19		a = 0.03 b = 0.03
20		a = 0.01 b = 0.01 c = 0.01 d = 0.01
21		a = 0.02 b = 0.02 c = 0.02

It may be pointed out that even for the molecules reported in Table 2, the utility of BNPA alone failed to give any discrimination. However, the chiral ion pair $DMAPH^+$-BNPA yielded good discrimination, proving this to be an excellent solvating agent.

Enantiomeric excess (*ee*) Measurement

The method is finally utilized for the precise measurement of *ee*. For such a purpose the different scalemic mixtures of (1*R*, 2*S*) and (1*S*, 2*R*)-2-amino-1, 2-diphenylethanol in *S*-1, 1'-binapthyl-2, 2'-hydrogenphosphate and DMAP were prepared with appropriate gravimetric ratios. The spectra obtained for different scalemic mixtures are given in Fig 6. The *ee* was calculated by the ratiometric analysis of the integral areas of the peaks of $-C(H)NH_2$ that yielded the precise values of excess of one form over the other and are reported in Table 3. The measured *ee* values are in excellent agreement with the gravimetrically prepared scalemic mixtures within the experimental error.

Table 3: The experimentally determined and laboratory prepared scalemic ratios of (1*R*, 2*S*)-2-amino-1, 2-diphenylethanol and (1*S*, 2*R*) - 2-amino-1, 2-diphenylethanol. The $-C(H)NH_2$ peak was chosen to measure *ee*.

Entry	Integration $I_R : I_S$	Gravimetrically prepared excess of *R*-enantiomer	$ee\,\% = \frac{I_R - I_S}{I_R + I_S} \times 100$ Experimentally measured enantiomeric excess
a	1.000 : 0.014	98	97.24
b	1.000 : 0.052	90	90.11
c	1.000 : 0.110	80	80.18
d	1.000 : 0.250	60	60.00
e	1.000 : 0.430	40	39.86
f	1.000 : 0.660	20	20.48
g	1.000 : 1.500	-20	-20.00
h	1.000 : 2.336	-40	-40.04
i	1.000 : 3.986	-60	-59.89
j	1.000 : 8.889	-80	-79.77
k	1.000 : 46.887	-96	-95.83

Note: Negative value indicates an excess of (1*S*, 2*R*)-enantiomer.

There was an excellent correlation between the experimentally measured *ee* values with those expected from the gravimetric preparation as reported in Fig. 6.

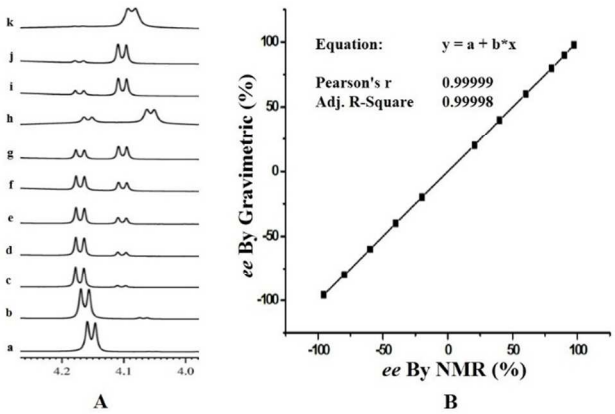

Figure 6: (A) ^{1}H-NMR spectra of cis-2-amino-1,2-diphenylethanol in *S*-1,1'-binapthyl phosphoric acid and DMAP in $CDCl_3$; a) 99% (1*R*, 2*S*) & 1% (1*S*, 2*R*), b) 95% (1*R*, 2*S*) &5% (1*S*,2*R*), c) 90% (1*R*, 2*S*) & 10% (1*S*, 2*R*), d) 80% (1*R*, 2*S*) & 20% (1*S*,2*R*), e) 70% (1*R*, 2*S*) &30% (1*S*, 2*R*), f) 60% (1*R*, 2*S*) & 40 % (1*S*, 2*R*), g) 40% (1*R*, 2*S*) & 60% (1*S*, 2*R*) h) 30% (1*R*, 2*S*) & 70%(1*S*, 2*R*) i) 20% (1*R*, 2*S*) & 80% (1*S*, 2*R*), j) 10% (1*R*, 2*S*) & 90% (1*S*, 2*R*), k) 2% (1*R*, 2*S*) & 98% (1*S*, 2*R*). (B) Linear correlation between *ee* values determined experimentally with those expected by gravimetric preparation.

Conclusions

The novel and versatile protocol involving the ternary ion-pair complex has been introduced for the enantiodiscrimination of molecules of diverse functionality. The developed protocol has been convincingly demonstrated on number of aliphatic and aromatic amino alcohols, secondary alcohols and cyanohydrins, diols, epoxides where optically pure solvating agent 1, 1'-binapthyl-2, 2'-hydrogenphosphate (BNPA) alone fails to discriminate. The addition of DMAP as a third reagent had the significant effect on discrimination. The protocol also permitted the precise measurement of enantiomeric excess (*ee*). In circumstances when the spectra are severely overlapped consequent to closely resonating protons, the two dimensional *J*-resolved experiments aided in their unravelling and precise determination of *ee* by ratiometric analysis of the integral areas of the contours. The additional advantage of 2D-*J* resolved experiment is that the experiments can be carried out at lower concentrations of CSA.

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NMR Research Centre,
Solid State and Structural Chemistry,
Indian Institute of Science,
Bangalore, India.

Electronic Supplementary Information (ESI) available: [The NMR spectra are given in the supporting information]. See DOI: 10.1039/b000000x/

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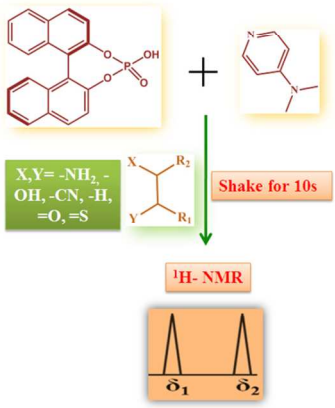

A Novel Chiral Solvating Agent for Enantiodiscrimination by NMR Spectroscopy
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