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# $^1$H NMR spectrum simplification of phenyl compounds containing electronegative groups by intermolecular interactions

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**Abstract**

Resolutions of $^1$HNMR spectra of aromatic protons have been greatly improved by using simple alcohols, aliphatic amines and aliphatic acids as solvent-induced shift reagents. The hydrogen-bonding between the solvent and the solute molecules, and the self-association characteristics of the solvents are responsible for the spectrum resolution enhancement.


NMR spectroscopy, by virtue of its non-invasiveness and versatility, is one of the most powerful tools in structural elucidation. However, the application is sometimes hampered by resonance overlapping because much information could only be extracted from the resolved spectra. Many methods have been developed to overcome this problem.[1–8] One of the most simple and effective ways is to use chemical shift reagents. Lanthanide shift reagents (LSRs)[9–14] and aromatic solvent-induced shift reagents (ASIS)[3,15,16] are two of the most widely used chemical shift reagents. They simplify the spectra following the mechanisms of Lewis acid–base interaction and anisotropic ring effect, respectively. Although there are resolution improvements, the LSRs and the ASISs inherent line-broadening, low accessibility and low sample recoverability, these restrain their daily use. Therefore, finding new chemical shift reagents in NMR becomes important and necessary for NMR daily measurements.

Intermolecular interaction between solvent and solute is undoubtedly one of the essential factors in determining chemical shift. Therefore, it is possible to find some solvent-induced shift reagents for the spectrum resolution enhancement of the object compounds by taking the advantages of solute–solvent intermolecular interactions. Among all interactions, hydrogen-bonding is undoubtedly the most important one; it is common, strong enough and sufficiently directional. In this contribution, therefore, we attempted to use intermolecular hydrogen-bonding to achieve $^1$H NMR spectrum resolution enhancement of interest by choosing the appropriate compounds as solvent-induced shift reagents. The phenyl-containing compounds, especially that of monosubstituted ones, which are characterized by a featureless hump in normal $^1$H NMR with little definitive structural information obtainable, are the target of this contribution. For some polysubstituted phenyl compounds, the resonances of proton can be resolved even in $CDCl_3$. In the process of finding the potential solvent-induced shift reagents, the criteria below should be followed to achieve a good resolution: (1) solvent molecules should have electronegative functional groups enabling hydrogen-bond interaction; (2) no resonance overlapping to the aromatic regions; (3) easily accessible and easily being separated. Therefore, our focuses were put on aliphatic molecules having functional groups interacting with the target phenyl group containing compounds.

Nine solvent-induced shift reagents (**1**–**9**) presented in this contribution were found to have resolution enhancement on phenyl proton resonances of solutes (**10**–**15**) (Scheme 1). All the solute–solvent pairs shown above follow the same variation pattern on phenyl group

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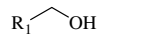
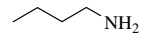
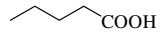
resonances. For convenience of discussion, as an example, benzyl alcohol (**14**)/1-octanol (**5**) solution system was chosen to be described in detail.

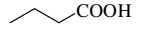
In $CDCl_3$, the phenyl protons resonances of benzyl alcohol (**14**) are crowded into a featureless hump in the region of 7.2–7.4 ppm (Fig. 1a); whereas in neat 1-octanol, they are well resolved into three separated multiplets (Fig. 1b). With base line separation, a first-order $^1H$ NMR spectrum of solute **14** is obtained. The magnitudes of the induced-shifts of solute phenyl protons vary in an order of $H_o > H_m > H_p$, which is similar to those induced by LSRs,[6] decreasing the magnitude with increasing distance from the hydroxyl functional group; and the magnitude of the influence falls away sharply with the distance. The pattern of these induced-shifts suggests the existence of intermolecular interactions between the solute–solvent pairs on the hydroxyl end of solute **14**. A significant 4.4 ppm downfield shift for hydroxyl proton of benzyl alcohol is observed from 1.86 ppm in $CDCl_3$ to 6.24 ppm in 1-octanol. Moreover, no spectrum resolution enhancement was observed when 1-octanol is replaced by *n*-octane as a solvent (Fig. 1c). It indicates that a strong intermolecular hydrogen-bonding interaction exists between the pairs, which induced prominent changes in the electron distribution of hydroxyl, and in the essentiality of the hydrogen-bonding in spectrum resolution.

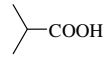
Even though all resolutions originate from hydrogen-bonding interactions, difference on the magnitude of chemical shift variations still exists due to the hydrogen-bond strength. To evaluate the discrimination ability of the solvents mentioned above, parameters of chemical shift difference $\Delta\delta_1$ ($\Delta\delta_1 = \delta_{Ho} - \delta_{Hp}$) and $\Delta\delta_2$ ($\Delta\delta_2 = \delta_{Hm} - \delta_{Hp}$) were proposed. Table 1 presents $\Delta\delta_1$ and $\Delta\delta_2$ of benzyl alcohol in solvents **1**–**9**, and the most significant resolution enhancement was observed in butan-1-amine with the largest $\Delta\delta_1$ and $\Delta\delta_2$. For solvent molecules with the same alkyl chain, the discrimination ability decreases in the order of amine (**6**) > alcohol (**4**) > acid (**7**), which is consistent with their relative hydrogen-bond basicity.[17,18] It seems that the stronger the hydrogen-bond, the more effective the resolving power. In comparison of alcohols (**1-5**) and acids (**7**–**9**) with different chain lengths, similar results were observed. The resonances of phenyl protons are better resolved in long chain alcohol or acid with relatively higher hydrogen-bond basicity which suggests that the solvent acts as a hydrogen-bond donor in these interactions. Considering that the influence of hydrogen-bonding may convey alone the hydrocarbon chain, the chemical shifts of $H_\alpha$ next to the functional groups of solvent and solute were compared between them in neat and in solution. A relative downfield shift of 0.149 ppm for solute **14** and an upfield shift of 0.013 ppm for solvent **5** were observed. The hydroxyl protons which take part in the hydrogen-bonding

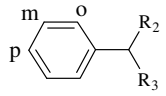
**1-5** 

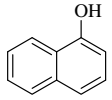
**6** 

**7** 

**8** 

**9** 

**10-15** 

**16** 

**1**. $R_1$= -H, **2**. $R_1$= -$CH_3$,
**3**. $R_1$=-$C_3H_5$, **4**. $R_1$= -$C_5H_{11}$,
**5**. $R_1$=-$C_7H_{15}$

**10**. $R_2$ = -H; $R_3$ =-Cl
**11**. $R_2$ = -H; $R_3$ = -$NH_2$
**12**. $R_2$ = -H; $R_3$ = -Br
**13**. $R_2$ = -$CH_3$; $R_3$ = -$NH_2$
**14**. $R_2$= -H ; $R_3$ = -OH
**15**. $R_2$ = -$OCH_3$; $R_3$ = -COOH

Scheme 1. List of solvent molecules (**1**–**9**) and solute molecules (**10**–**16**).

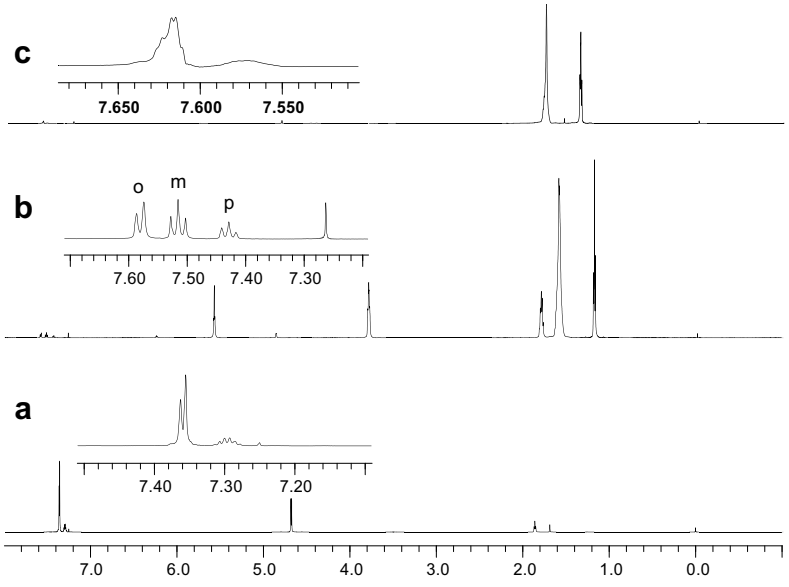



Fig. 1. The $^1H$ NMR spectra (Varian INOVA-600, 600 MHz; 298 K) of benzyl alcohol in (a) $CDCl_3$, (b) normal (nondeuterated) 1-octanol and (c) normal octane; with inset of expanded aromatic parts.

Table 1
The chemical shift differences of phenyl protons ($\Delta\delta_1$ and $\Delta\delta_2$) in benzyl alcohol with different solvent in solutions with mole ratio of 1:40

| Solvent | $\Delta\delta_1$ (ppm) | $\Delta\delta_2$ (ppm) |
|---|---|---|
| **1** | 0.099 | 0.079 |
| **2** | 0.124 | 0.082 |
| **3** | 0.135 | 0.080 |
| **4** | 0.144 | 0.084 |
| **5** | 0.151 | 0.087 |
| **6** | 0.188 | 0.104 |
| **7** | 0.125 | 0.074 |
| **8** | 0.115 | 0.068 |
| **9** | 0.113 | 0.067 |

interaction experience the largest induced shift, with an increase of 0.372 ppm for **14** and a decrease of 0.036 ppm for **5**. These shift variations indicate that the solute molecules are hydrogen-bond donor, while the solvent molecules are hydrogen-bond acceptor. In these solute–solvent pairs, the hydrogen-bond donor/acceptor interaction model works and the hydrogen-bonding capabilities modulate the extent of the resolution.

Further evidences in supporting the intermolecular interaction-induced resolution were carried out. Solute molecules other than benzyl alcohol (**14**) as benzyl chloride (**10**), benzyl amine (**11**), benzyl bromide (**12**), 1-phenylethanamine (**13**) and 2-methoxy-2-phenylacetic acid (**15**) were tested. The phenyl proton resonances of these solute were also simplified by the solvent-induced shift reagents mentioned above, with the same resolution enhancement pattern as $H_o > H_m > H_p$ followed. For solutes in 1-octanol, the phenyl protons of **15** experience the largest shift changes, while that of **10** the smallest (Fig. 2). These differences are in agreement with the variation of hydrogen-bond acidity of solutes. The more acidic the hydrogen-bond of the solute, the better the resolution shown.

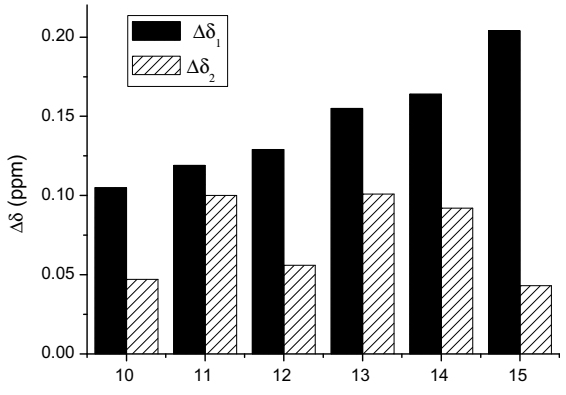



Fig. 2. The chemical shift differences $\Delta\delta_1$ and $\Delta\delta_2$ of aromatic protons of different solute molecules (**10**–**15**) which dissolved in neat 1-octanol with the mole ratio of 1:40.

Moreover, polyaryl compound such as 1-napthanol (**16**) have been tested in 1-butyamine (**6**). As shown in Figure 3, the overlapped resonance of protons 5 and 6 in $CDCl_3$ is resolved in 1-butylamine. It was found that the chemical shifts of protons near the hydroxyl group experience large downfield shift comparing to that, as proton 4 and 10, far away from it. This variation is in agreement with the result discussed above.

Two other samples of solutes in 1-octanol were performed to make further discussion. Toluene, with no electronegative functional group, shows no discrimination in phenyl proton resonances when dissolved in 1-octanol. This former makes further evidences on the mechanism of hydrogen-bonding induced shift. And for cinnamic acid, the overlapping of phenyl protons resonances remains, while the two vinyl protons experience the largest induced-shift in 1-octanol, with the shift difference between them increased 0.13 ppm comparing to that in $CDCl_3$ solution. It can be presumed that the distance between the functional groups and the probed protons determines the magnitudes of resonance separation, which is similar to that of LSRs works.

Generally, molecules of these amphiphilic solvent shifting reagents (**1**–**9**) in neat tend to self-associate via hydrogen-bonding and form clusters of different sizes.[19–21] Therefore, as ASIS,[7] it is very unlikely that only the solvent–solute pair is responsible for the observed shift. It is probably the hydrogen-bond interaction between the

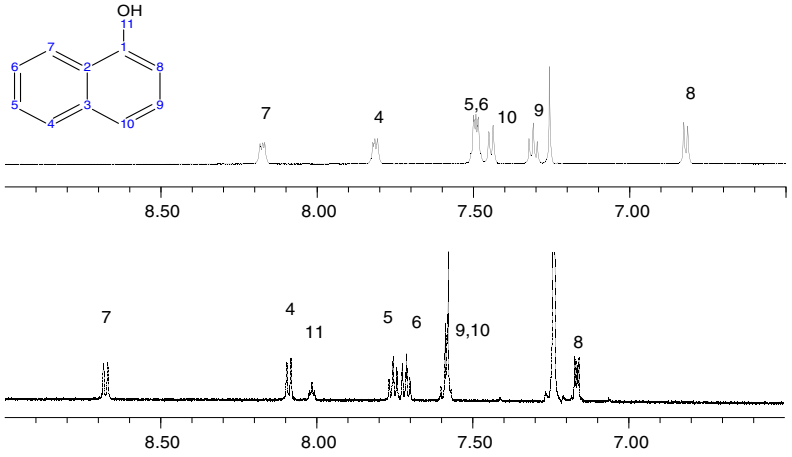



Fig. 3. The expanded NMR spectra of aromatic parts of 1-napthanol (**16**) in $CDCl_3$ (bottom) and in 1-butylamine (**6**) (upper).

solvent clusters and a single solute molecule that results in the observed resolution enhancement. Three experiments were carried out to prove this assumption.

Firstly, no resolution enhancement was observed for benzyl alcohol when the molar ratio of 1-octanol in bi-solvent system of 1-octanol and $CDCl_3$ is small. And it was not until the molar ratio of 1-octanol versus $CDCl_3$ reaches 1:1, the spectrum resolution of phenyl proton resonances was shown. And a well baseline separation was observed when the molar ratio is above 5:2. As the concentration of 1-octanol increases, the resolution becomes more pronounced. And secondly, previous studies[22,23] suggested that solute molecules tend to take a preferential orientation in the microheterogeneous solvent aggregates, which may facilitate the hydrogen-bonding interaction. Nuclear Overhauser effect (NOE) measurements were performed on benzyl alcohol/1-octanol system to give some clues to this solution character in our system. NOE enhancements on aromatic protons of benzyl alcohol especially $H_p$ were seen when proton of methyl on 1-octanol–$CH_3$ (1) irradiated. Moreover, irradiation of the –OH proton resonance of 1-octanol leads to 12% NOE enhancement of the alpha-proton $H_b$ of solute and a reversed peak of the –OH proton ($H_a$) of it, which indicates that the proton exchange exists between both the hydroxyl protons (Fig. 4). These prove that solute molecules reorient themselves in solvent aggregates, with its hydrophilic group pointing towards the hydrogen-bonded region of solvent aggregates while its phenyl groups reside in the nonpolar regions. And this is consistent with the results of the orientation of aromatic molecules by surfactant micelles[23] and our previous research on the preferential solvation of solute molecules in 1-octanol solution.[24] The reorientation facilitates the hydrogen-bond interaction between the solute and the solvent aggregate. Lastly, in water solvent the resonance overlapping of benzyl alcohol is not well resolved even though water molecules are very capable of forming hydrogen-bonding. All these results proved that the solvent aggregation is probably the sufficient condition in achieving well resolved spectrum.

In conclusion, by taking the advantages of intermolecular interaction, $^1$H NMR spectrum resolution was achieved by solvent-induced shift reagent. Some shift reagents were found having resolution enhancement ability on aromatic region of $^1$H NMR by hydrogen-bond interaction between solute–solvent pairs. Hydrogen-bonding ability of the interaction pairs and anisotropic effect of solvents are regarded as two essential factors in resolution achieving, with the former is the necessary condition while the latter is the sufficient condition. And this can also answer the question of why $CDCl_3$ solvent shows no resolution on these compounds due to its relative weak hydrogen-bond ability and isotropic character.

Even though these solvents are not as effective as some LSRs, their considerable effect, low price and a relative littler amount of detected compounds needed[25] make them very attractive in daily experiments. In addition, the use of deuterated solvent is not mandatory because shift reagents of many kinds could be chosen to avoid resonances overlapping. On one hand, following the idea of interaction-induced-shift for spectrum resolution, some other intermolecular interaction as electric sufficient/deficient interaction or Lewis acid–base interaction could be utilized in shift reagent design. And, if a chiral environment is provided, chiral recognition would be much more easily realized. Hydrophobic effect was once used by Wenzel, etc. to realize enantioselective and spectrum resolution of aromatic compound by calix[4]resorcarenes.[26] On the other hand, some association characters of molecules can be obtained as the cluster formation of these molecules provides assistance to discrimination process.

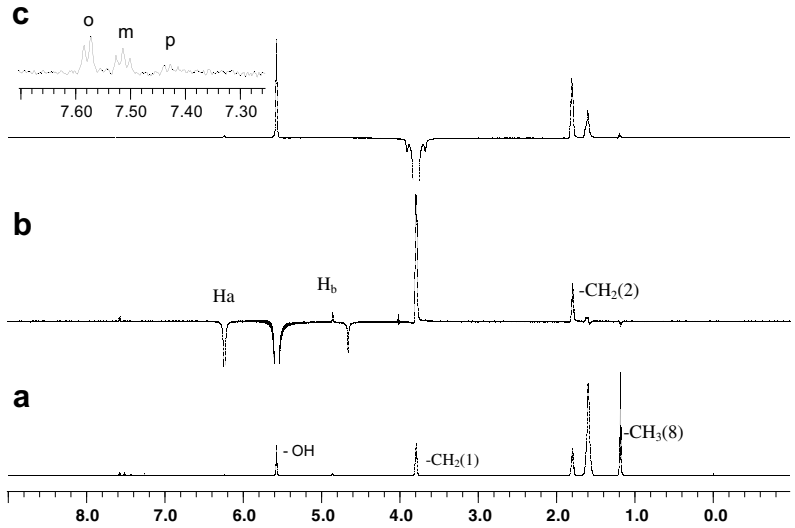



Fig. 4. The $^1$H NMR spectrum (Varian INOVA-600, 600 MHz; 298 K) of benzyl alcohol in 1-octanol with mole ratio of 1:40 (a), and the corresponding NOESY1D spectra when saturated hydroxyl proton of 1-octanol (b) and the alpha proton of 1-octanol with the expended phenyl region as inset part (c). Ha presents the hydroxyl proton of benzyl alcohol while $H_b$ presents the alpha proton of it.

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