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# The qualitative probing of hydrogen bond strength by diffusion-ordered NMR spectroscopy

Gurpreet S. Kapur,† Eurico J. Cabrita and Stefan Berger*

*Institut für Analytische Chemie, Universität Leipzig, Johannisallee 29, D-04103, Leipzig, Germany*

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**Abstract**

The feasibility of using diffusion-ordered NMR spectroscopy (DOSY) as a useful probe to qualitatively understand the relative strength of hydrogen bonds between various components in a mixture and a ligand in non-aqueous solutions has been demonstrated. $^{1}$H-detected DOSY and $^{31}$P-detected DOSY were used.


*Keywords:* hydrogen bonding; diffusion-ordered spectroscopy; DOSY; NMR; diffusion coefficients.

The study of molecular association is of paramount importance to understand solution structures. Hydrogen bonds are not only considered as playing a determinant role in solution structures, but are also of crucial importance to all biochemical processes. NMR-based techniques have been in use for many years to characterise hydrogen bonding.[1] Using NMR spectroscopic techniques, the hydrogen bonding is mostly manifested such as characteristic downfield shift of the proton resonance, e.g. in carbohydrates.[2] Other NMR techniques include the observation of deuterium isotope effects,[3] solution measurement of the chemical shift anisotropy,[4] dynamic NMR studies,[5] the studies of intermolecular NOE effects,[6] and very recently the observation of spin–spin coupling constants across the hydrogen bond in proteins.[7] We want to show here that diffusion-ordered spectroscopy (DOSY) can be another useful probe to qualitatively understand the relative strength of hydrogen bonding between a common ligand, and various other components present as a mixture in non-aqueous solutions.

In diffusion-ordered spectroscopy (DOSY),[8] which was introduced only a few years ago,[9] the results are displayed as 2D spectra with the NMR chemical shift on the horizontal axis and the derived diffusion coefficients on the vertical axis. Such DOSY plots are obtained by effective data inversion of the pulsed field gradient (PFG) spin echo NMR data obtained by incrementing the gradient strength. PFG NMR is a very effective tool to study the translational motion of molecules, and is used for studying molecular associations.[10] However, DOSY has the advantage

* Corresponding author.
† Present address: Indian Oil Corporation Limited, R&D Centre, Sector-13, Faridabad 121 007, Haryana, India.

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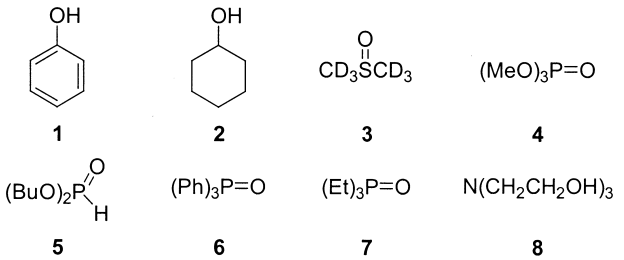
of immediately visualising the effects even in more complex mixtures. An important current development of the technique is the introduction of 3D-DOSY methods,[11] and heteronuclear detection of DOSY such as with $^{13}C$.[12]

The observation of molecular association forced by H-bonds by a change in molecular diffusion is only possible if the NMR time scales of both processes match. This can be shown for a mixture containing phenol (**1**) (MW = 94.1) and cyclohexanol (**2**) (MW = 100.2), and studying their interaction with an established H-bond acceptor, dimethyl sulphoxide (**3**) (Scheme 1).




Scheme 1.

Fig. 1a shows the $^1H$-detected DOSY plot for an equimolar mixture of phenol and cyclohexanol in $CDCl_3$ containing TMS as a reference. The normal one-dimensional spectrum of the mixture is shown as the projection. Both components have almost similar effective sizes, and as expected, cyclohexanol, being slightly heavier and having probably the more extended hydrodynamic surface due to its chair conformation, is associated with a lower diffusion coefficient when compared to phenol. The diffusion profile of the mixture is also a reflection of the molecular association between the two components, since they will be involved in H-bonding both among themselves and with each other. The addition of a third component with the ability to be involved in H-bonds acting as H-bond acceptor will break up this structure and the diffusion profile of the new mixture will thus reflect the interaction with the new component.

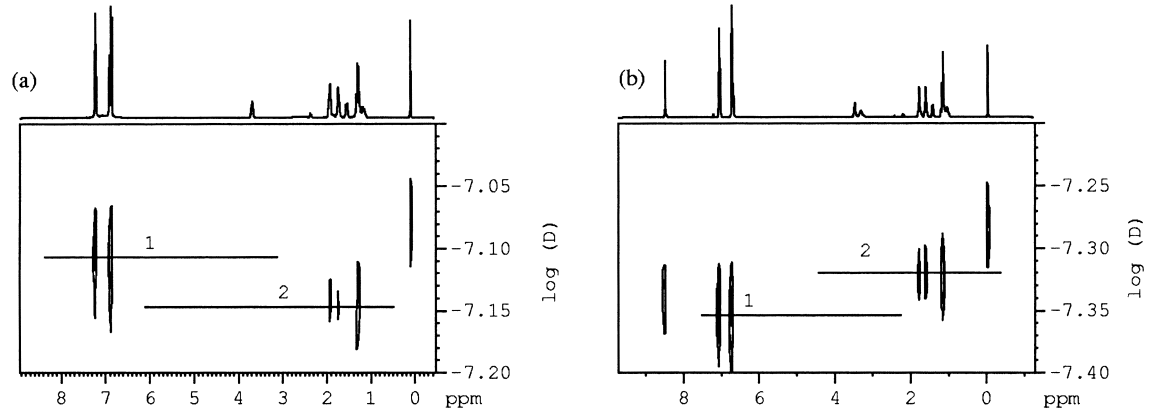



Figure 1. (a) The $^1H$-DOSY spectrum of a mixture containing phenol (**1**) and cyclohexanol (**2**) in $CDCl_3$ containing TMS as a reference; and (b) The $^1H$-DOSY spectrum of the same mixture containing DMSO-$d_6$ (**3**) as an additional component. The spectra were recorded on a Bruker DRX-400 instrument using the stimulated echo sequence incorporating bipolar gradients with an longitudinal eddy delay (BPPLED). The gradient strengths of 1 ms duration were incremented in 32 steps, with diffusion times of 50 ms

Fig. 1b shows the DOSY plot of the alcohol mixture, but containing 1 molar equivalent of DMSO-$d_6$ as an additional component. Both components are capable of forming hydrogen bonds with DMSO and by comparing the two plots (without and with DMSO) the effects of the interaction with the DMSO are readily visible. The addition of DMSO-$d_6$ as H-bond acceptor has resulted in the separation of the OH signals of the phenol and cyclohexanol. However, the DOSY plot reveals that the order of the appearance of diffusion contours of these components has reversed because of the addition of DMSO-$d_6$. The phenol, which was earlier moving faster (Fig. 1a), is now associated with a lower value of the diffusion coefficient, and moving slower compared to cyclohexanol. This means that compared to cyclohexanol, phenol is forming much stronger hydrogen bonds with DMSO. This is expected due to the much higher acidity of phenol compared to cyclohexanol. The phenol and DMSO are spending sufficient time together as an associated molecular system, which results in an effective increase in the size of phenol, and hence decrease in its diffusion coefficient. Preliminary results using the value of the diffusion coefficient of TMS as an internal standard indicate that it is possible to obtain information about the relative size modification of the components upon the addition of DMSO, and this is currently under investigation.

A similar effect has been observed for a more complicated mixture of phosphorus components using a $^{31}$P-detected DOSY experiment. Fig. 2a shows the $^{31}$P-DOSY spectrum of an equimolar mixture containing four phosphorus components, namely trimethyl phosphate (**4**) (TMP, MW = 140.1), dibutylphosphite (**5**) (DBP, MW = 194.2), triphenylphosphine oxide (**6**) (TPPO, MW = 278.3) and triethylphosphine oxide (**7**) (TEPO, MW = 134.2). The normal $^{31}$P NMR spectrum of the mixture is shown as the 1D projection along with the assignment. The component DBP shows a doublet due to P–H coupling. The spectrum in the diffusion dimension also shows resolved contours due to all the four components filtered out based on their respective diffusion coefficients. The fastest of the four components is TMP, which has been found to be associated with the highest value of the diffusion coefficient. However, in spite of its lower molecular weight, the TEPO is associated with a lower diffusion coefficient compared to TMP, and this is probably due to the more extended structure of TEPO.

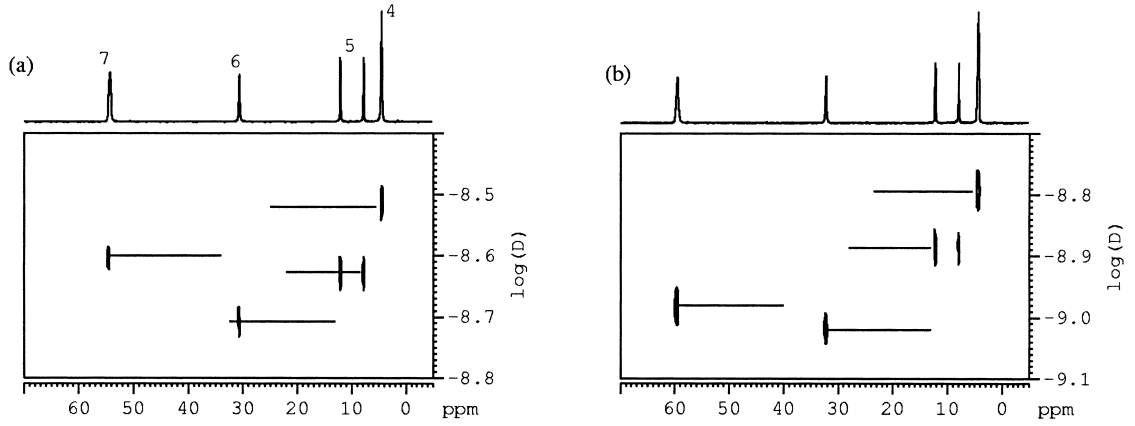



Figure 2. (a) The $^{31}$P-DOSY spectrum of a mixture containing 4 phosphorous components viz. trimethyl phosphate (**4**), dibutyl phosphite (**5**), triphenylphosphine oxide (**6**), and triethylphosphine oxide (**7**); and (b) The $^{31}$P-DOSY spectrum of the same mixture containing triethanol amine (**8**) as an additional component. The BPPLED sequence was used with gradient strengths of 2 ms duration incremented in 32 steps, with diffusion times of 200 ms for spectrum (a), and 500 ms for spectrum (b)

In Fig. 2b the $^{31}$P-DOSY spectrum of the same mixture is shown, but containing 1 equivalent of triethanol amine (**8**) (MW = 152; TEA) as an additional component and H-bond donor. The normal $^{31}$P NMR spectrum in the projection shows a small downfield shift in the resonances of TEPO and TPPO, due to their interactions with TEA. However, a change in the chemical shift does not provide a sufficient indication about the strength of interaction between the components, which could be due to other effects influencing the chemical shift. The DOSY plots provide a better insight about the strength of such interactions which are clearly manifested in the diffusion dimension. There is a decrease in the value of diffusion coefficient of all the components due to increase of viscosity resulted due to addition of viscous TEA. However, the order of the components in the diffusion dimension has also changed, where the diffusion coefficient of TEPO has decreased considerably compared with the components TMP and DBP. This decrease in the diffusion coefficient of TEPO is attributed to its complexation with TEA through hydrogen bonds, resulting in an overall increase in the effective size. Though all molecules used here are also expected to form hydrogen bonds with TEA, the interaction between TEPO and TEA is, according to the DOSY results, the strongest. The relative diffusion behaviour displayed in Fig. 2b is as expected from chemical reasoning. The ability of the double bonded oxygen in the four phosphorus compounds to accept a hydrogen bond should be highest in TEPO where pure aliphatic residues are at the other side of the phosphorus atom. In an additional experiment (data not shown) we have used a similar component mixture with TBPO (tributylphosphine oxide), TPPO, HMPA (hexamethylphosphoramide) and TMP. In this case, one of the weakly interacting species (DBPO) was replaced by HMPA, and it was expected that this more basic compound would now form the strongest interacting species with TEA. After the addition of the TEA there was indeed a relatively large decrease of the diffusion coefficient of HMPA when compared to TBPO reflecting the stronger ability of HMPA to form hydrogen bonds with TEA, although in the chemical shift dimension TBPO remains the component with the largest downfield shift.

In conclusion, we have shown that DOSY can be utilised to obtain information about the relative strength of H-bonds, and about those components that show stronger binding affinities to a particular ligand in a pool of several candidate molecules, which may be either weakly or not interacting at all.

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## References

1. Konrat, R.; Trollinger, M.; Kontaxis, G.; Kräutler, B. *Monatshefte f. Chemie* **1999**, *130*, 961.
2. Sandstroem, C.; Baumann, H.; Kenne, L. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2385.
3. Hansen, P. E.; Simon, S. *Magn. Reson. Chem.* **1997**, *35*, 520.
4. Tjandra, N.; Bax, A. *J. Am. Chem. Soc.* **1997**, *119*, 8076.
5. Haushalter, K. A.; Lau, J.; Roberts, J. D. *J. Am. Chem. Soc.* **1996**, *118*, 8891.

6. Seba, H. B.; Ancian, B. *Chem. Commun.* **1990**, 996.
7. Cordier, F.; Grzesiek, S. *J. Am. Chem. Soc.* **1999**, *121*, 1601.
8. Johnson, C. S. *Progr. NMR Spectrosc.* **1999**, *34*, 203.
9. Morris, K. F.; Johnson, C. S. *J. Am. Chem. Soc.* **1992**, *114*, 3139; *115*, 4291.
10. Stilbs, P. *Progr. NMR Spectrosc.* **1987**, *19*, 1.
11. Barjat, H.; Morris, G. A.; Swanson, A. G. *J. Magn. Reson.* **1998**, *131*, 131.
12. Kapur, G. S.; Findeisen, M.; Berger, S. *Fuel* **2000**, *79*, 1347.