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Polydimethylsiloxane: A General Matrix for High-Performance Chromatographic NMR Spectroscopy**

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Abstract: *The detection and structural characterization of the components of a mixture is a challenging task. Therefore, the development of a facile and general method that enables both the separation and the structural characterization of the components is desired. Diffusion-ordered NMR spectroscopy (DOSY) with the aid of a matrix is a promising tool for this purpose. However, because the currently existing matrices only separate limited components, the application of the DOSY technique is restricted. Herein we introduce a new versatile matrix, poly(dimethylsiloxane), which can fully separate many mixtures of different structural types by liquid-state NMR spectroscopy. With poly(dimethylsiloxane), liquid-state chromatographic NMR spectroscopy could become a general approach for the structural elucidation of mixtures of compounds.*

NMR spectroscopy is a powerful tool for the assignment of chemical structures. However, its application was limited in the field of mixture analysis until the development of diffusion-ordered NMR spectroscopy (DOSY). In DOSY spectra, different NMR signals are yielded in the diffusion dimension according to the diffusion coefficient (D) of various components of a mixture.[1] In general, D depends on many physical parameters, such as the mass, size, and shape of a molecule, the sample temperature, and the viscosity of the system under analysis. It is often described by the Stokes–Einstein equation:

$$D = \frac{kT}{6\pi\eta r_s} \quad (1)$$

in which k is the Boltzmann constant, T is the temperature, η is the viscosity of the liquid, and r_s is the (hydrodynamic) radius of the molecule. The DOSY technique has been dubbed chromatographic NMR (CNMR) spectroscopy, and the scope of application of this technique is becoming broader in the analytical field.[2] In CNMR spectroscopy, the critical precondition is that each species has a different coefficient D. This difference has been defined as diffusion resolution (ΔD),[3] by which the separation performance of CNMR spectroscopy can be evaluated.

CNMR spectroscopy can be employed to separate a mixture of components that are different from one another in terms of a certain molecular property. However, it often fails to resolve a mixture of species with a similar molecular mass, size, or shape. This defect mainly results from the pulsed field gradient of a NMR spectrometer and accordingly restricts the application of CNMR spectroscopy. A practical way to resolve this problem is to add a typical stationary phase used in HPLC, such as bare silica gel or octadecyl-silanized silica gel, to the NMR rotor as a matrix to enhance the spectral-separation capability of CNMR spectroscopy.[4] The matrix is regarded as a virtual stationary phase (VSP). In this method, the corresponding measurements have to be implemented in a solid-state NMR spectrometer or in a liquid-state NMR spectrometer equipped with a high-resolution magic angle spinning (HRMAS) probehead to improve the resolution of measurements. The line broadening and spectral overlap caused by the magnetic field inhomogeneity of a detection solution, however, may result in artifacts in DOSY spectra and reduce the diffusion resolution. Afterwards the method was modified by adding both CH_2I_2 and silica gel to the NMR tube with a deuterated solvent ($CDCl_3$) to provide narrow signals.[5] This modification was a significant step forward for the liquid-state CNMR technique despite some operational inconvenience.

Diverse matrices suitable for liquid-state CNMR measurements, such as surfactants, microemulsions, or lanthanide shift reagents, have been discovered over the past 10 years. For example, sodium dodecyl sulfate (SDS) has been used as a VSP to separate a few simple mixtures. Some signals of SDS, however, overlapped with those of the analytes.[6] Although such signal overlap can be avoided by using perdeuterated SDS, this matrix is not favored because of its high cost.[7] Another example can be found in the analysis of chiral molecules with micellar poly(sodium *N*-undecanoyl-L-leucyl-valinate) as a VSP; however, spectral overlap was again observed in DOSY spectra.[8] Moreover, although a number of microemulsions have been used for the analysis of commercial pharmaceuticals, the preparation of these VSPs is usually impractical.[9] The most recent matrix was the lanthanide shift reagent [Eu(fod)$_3$], which showed excellent separation of a mixture of *n*-hexane, *n*-hexanol, and *n*-heptanal; however, [Eu(fod)$_3$] is costly.[10]

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Alternatively, CNMR spectroscopy could become more practical by the addition of a polymer as a matrix to an NMR tube to separate a mixture of components. Poly(vinylpyrrolidone), for example, could separate a mixture of *p*-xylene, benzyl alcohol, and *p*-methylphenol well by liquid-state CNMR spectroscopy.[11] Furthermore, poly(ethylene glycol)[12] and other polymers that function as stationary phases for size-exclusion chromatography[13] are also novel resolving agents for CNMR spectroscopy. However, signal overlap is almost inevitable when these polymers are used as VSPs. High viscosity is another possible problem.

The development of CNMR spectroscopy based on a matrix is still at an early stage, since the existing VSPs are not versatile for structurally diverse analytes. Therefore, it is necessary to develop new general VSPs for broader application of the CNMR technique. A general matrix should preferably be simple in its structure, to avoid a possible overlap of the signals of analytes and the VSP. Furthermore, the addition of a VSP should not cause high viscosity of the sample solution, or else extensive line broadening of analyte signals is observed. Finally, the VSP should be economically affordable.

Herein we introduce a candidate that bears the features of an excellent VSP. This new matrix is poly(dimethylsiloxane) (PDMS), which has been widely used in the field of analytical chemistry.[14] PDMS is very simple in its structure, and only shows a single signal at a higher field in the NMR spectrum just as tetramethylsilane (TMS). The signal of PDMS overlaps with those of hardly any other compounds. The oxygen atoms of PDMS possess lone-pair electrons that can interact with the functional groups in analytes. The difference in the interaction strengths may lead to various diffusion coefficients, and as a result, the analyzed components can be separated in the DOSY spectrum. Notably, the addition of PDMS does not significantly increase the viscosity of a solution in comparison with that of the pure solvent. Furthermore, PDMS is inexpensive. Most importantly, PDMS demonstrates a remarkable capability to separate many mixtures of similar species. Overall, PDMS holds great potential for becoming a general VSP for CNMR spectroscopy.

In this study, PDMS was used to enhance the diffusion resolutions of six model mixtures consisting of components with a similar molecular mass, size, or shape. Figure 1 displays ^{1}H DOSY spectra of the first mixture consisting of 1,2-propanediol, *n*-propanol, and propylene oxide. The measurements were performed in $CDCl_3$ in the absence or presence of PDMS. In the absence of PDMS, the three components exhibited almost the same *D* value and were not separated in the diffusion dimension (Figure 1 a). In comparison, the three components were well-resolved in the presence of PDMS and could be readily assigned in the DOSY spectrum (Figure 1 b). The upper line corresponds to 1,2-propanediol because it bonds more tightly to PDMS through its two hydroxy groups, thus resulting in the slowest diffusion. *n*-Propanol diffuses faster than 1,2-propanediol owing to the weaker interaction between the single hydroxy group in *n*-propanol and PDMS. Similarly, propylene oxide diffuses fastest, since the interaction between PDMS and propylene oxide should be weakest. Thus, the middle line refers to *n*-propanol, and the bottom line matches propylene oxide (see Figure S2 in the Supporting Information for the spectral assignment). With regard to separation by CNMR spectroscopy, the binding force depending on the polar groups of analytes is the principal factor for resolution. The signal yielded by PDMS was adjacent to the TMS signal and did not interfere with the signals of investigated components (Figure 1 b).

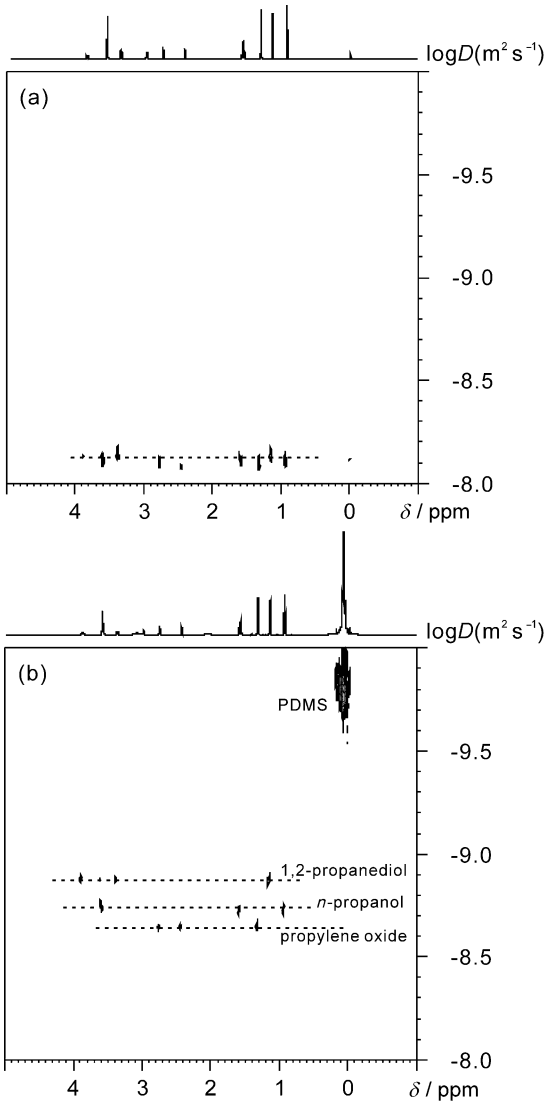

Figure 1. ^{1}H DOSY spectra (600 MHz) of a mixture of 1,2-propanediol (8 mg), *n*-propanol (8 mg), and propylene oxide (8 mg) in $CDCl_3$ (0.6 mL) before (a) and after (b) the addition of PDMS (80 mg); sample temperature: 298 K. In spectrum (b), the *D* coefficient of each component is indicated by a dotted line.

To evaluate the generality of PDMS, we recorded the CNMR spectra of an additional four mixtures of different compounds. Specifically, the second mixture consisted of anthracene, naphthalene, and benzene; the third mixture consisted of 1,5-dibromopentane, 1-bromopentane, and *n*-pentane; the fourth mixture consisted of acetic acid, ethanol, and acetonitrile; and the fifth mixture consisted of formic acid, ethanol, and methanol. Again, all these structurally relevant compounds were separated extremely well in each

mixture by PDMS in the CNMR spectra (see Figures S3–S6). These results indicate that PDMS is a general VSP for CNMR spectroscopy.

Finally, to investigate the potential of CNMR spectroscopy with a PDMS matrix in practical applications, we designed a sixth mixture to mimic a Suzuki reaction[15]: phenylboronic acid (reactant), iodobenzene (reactant), and biphenyl (product). As expected, the components were not separated in the absence of PDMS (Figure 2a). By contrast, the components diffused slowly in the presence of PDMS, and the diffusion resolution of the components increased (Figure 2b). According to the interaction strength between the polar groups in PDMS and the components of the mixture, the upper line is designated as phenylboronic acid, the middle line corresponds to biphenyl, and the bottom line is assigned to iodobenzene (see Figure S7 for the spectral assignment). Theoretically, the two hydroxy groups in the acid bond more tightly to PDMS; hence, this compound diffuses more slowly. The components with lower molecular polarity bond weakly to PDMS and therefore diffuse faster. In analogy with the observations in the measurement of the first mixture, the conclusion can be drawn that the binding force between the polymer and the components dominates the separation performance, although these two mixtures were different in their molecular structures. The separation outcome of phenylboronic acid, biphenyl, and iodobenzene demonstrates that CNMR spectroscopy with a PDMS matrix is an applicable technique for monitoring the process of various coupling reactions, such as the Suzuki reaction,[15] Heck reaction,[16] and Sonogashira reaction.[17]

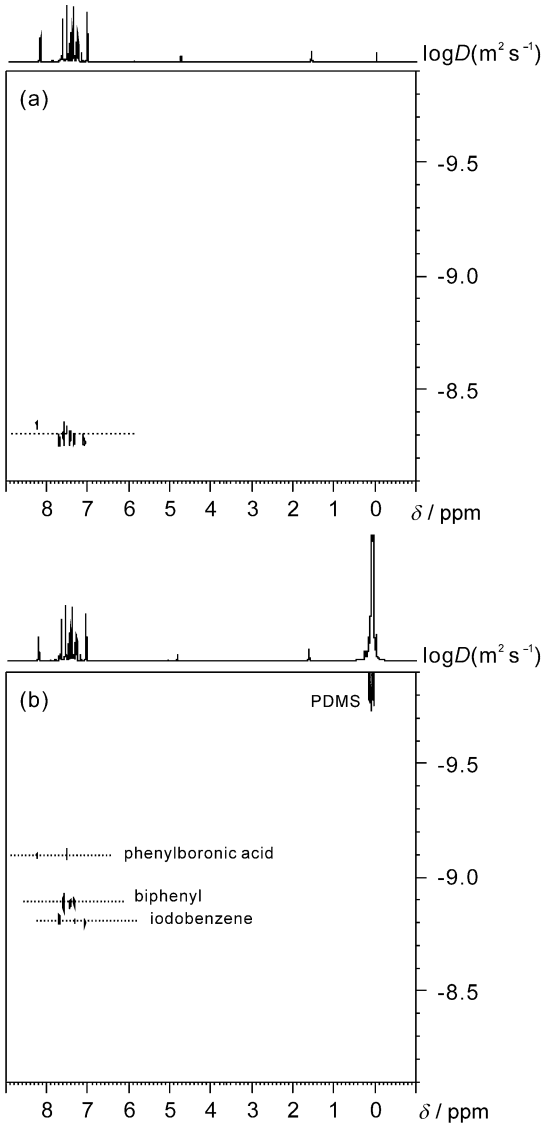

Figure 2. ^{1}H DOSY spectra (600 MHz) of a mixture of phenylboronic acid (10 mg), biphenyl (10 mg), and iodobenzene (10 μL) in $CDCl_3$ (0.6 mL) before (a) and after (b) the addition of PDMS (80 mg); sample temperature: 298 K. In spectrum (b), the *D* coefficient of each component is indicated by a dotted line.

In the field of chemistry, mixture analysis is a complex and strenuous task. PDMS may provide excellent diffusion resolution for similar components in various mixtures, thus serving as an effective general VSP. We envision that CNMR spectroscopy with the aid of PDMS will become a powerful tool for mixture analysis. The separation performance will be further improved by optimization, such as changing the deuterated solvent and/or altering the sample temperature for the CNMR measurement. Such investigations are currently ongoing in our laboratories.

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