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Covalent or trapped? PFG diffusion MAS NMR for combinatorial chemistry

Michael J. Shapiro,[a,*] Jefferson Chin,[a] Aidi Chen,[a] James R. Wareing,[b] Qing Tang,[b] Ruben A. Tommasi[c] and Hanumantha R. Marepalli[c]

[a]*Department of Analytics, Novartis Institute for Biomedical Research, 556 Morris Ave. Summit NJ 07901 USA*

[b]*Department of Metabolic and Cardiovascular Diseases, Novartis Institute for Biomedical Research, 556 Morris Ave. Summit NJ 07901 USA*

[c]*Department of Arthritis and Bone Metabolism, Novartis Institute for Biomedical Research, 556 Morris Ave. Summit NJ 07901 USA*

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Abstract

We have demonstrated the ability to distinguish covalently bound compounds from compounds 'trapped' within the resin matrix in high resolution NMR spectra using PFG diffusion NMR. In addition, the signals of the solvent used to swell the resin are also eliminated from the spectrum. PFG diffusion COSY data was used to confirm the structure of the on-resin product. © 1999 Elsevier Science Ltd. All rights reserved.

The ability to obtain high quality NMR data on resin bound molecules derived from combinatorial chemistry has been demonstrated by the use of Magic Angle Spinning (MAS) NMR.[1] We and others have demonstrated that MAS NMR is a useful technique by which 'solution' quality NMR data for resin supported molecules can be obtained.[2] A problem for ^{1}H NMR analysis of on-resin products is the complicated spectrum which contains not only resonances from the compound on resin and polymer, but also signals from solvent and trapped impurities. These impurities often have similar or overlapping chemical shifts with the compound of interest, making the analysis difficult. While the additional complication of polymer peaks can be attenuated by using a spin echo sequence[3] or 2D J-resolved data,[4] the residual peaks can be problematic.

The advent of the gradient MAS probe has increased the ability to utilize diffusion NMR as a technique.[5] Pulsed Field Gradient (PFG) diffusion NMR has been used effectively to suppress water signals from the NMR spectrum in protein studies.[6] Due to its convenient and non-destructive nature, PFG diffusion NMR has become a popular tool in resolving complex mixtures. When a diffusion filter is applied to filter away fast diffusing components, only slow moving covalently-bound compounds and

* Corresponding author.

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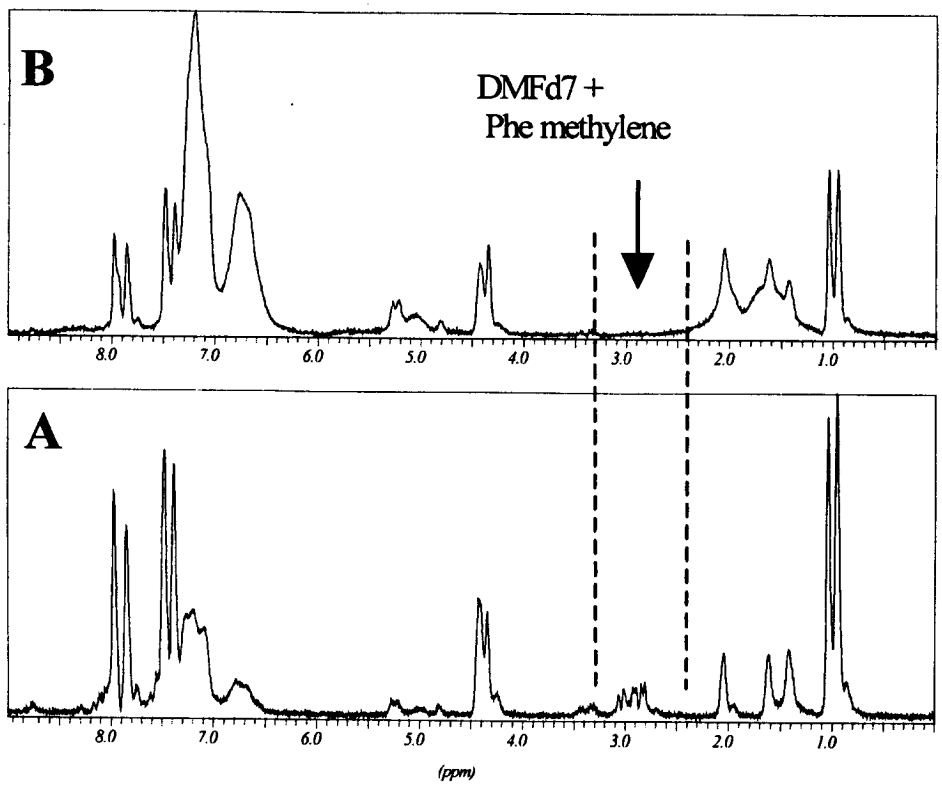

Figure 1. (B) MAS ^{1}H NMR spectrum after PFG diffusion NMR for $DMFd_7$-swollen Fmoc-isoleucine on Wang resin to which a solution of phenylalanine has been added. (A) Identical sample using spin–echo MAS ^{1}H NMR spectrum without PFG. Dashed lines indicate the chemical shift region for the methylene protons of Phe and the methyl groups from DMF

resin resonances are left in the spectrum. When applied to ligand receptor interactions this methodology has been termed 'affinity NMR'.[7]

Shown in Fig. 1A is the spin–echo MAS NMR spectrum for DMFd7-swollen Wang resin beads containing covalently attached isoleucine to which has been added a small quantity of dissolved phenylalanine. The quality of the NMR spectrum is typical of 1% cross linked polystyrene resin. The ability to suppress the non-covalently bound molecules by using diffusion PFG is shown in Fig. 1B where it can be seen that all of the non-covalently bound phenylalanine as well as DMF related resonances have disappeared from the spectrum.[8,9]

Powerful 2D experiments can be applied to readily assign product peaks using the PFG diffusion 2D COSY or TOCSY (Fig. 2). The increased spectral quality, and therefore the ease of interpretation of the spectrum, can be readily seen for the on-resin products we have studied. By taking advantage of the differential diffusion of the resin-bound molecules, we are able to suppress by-product signals of the synthesis trapped in the resin matrix. In our laboratory, we have also applied this technique to pins where washing free the unreacted reagents can be troublesome.[10]

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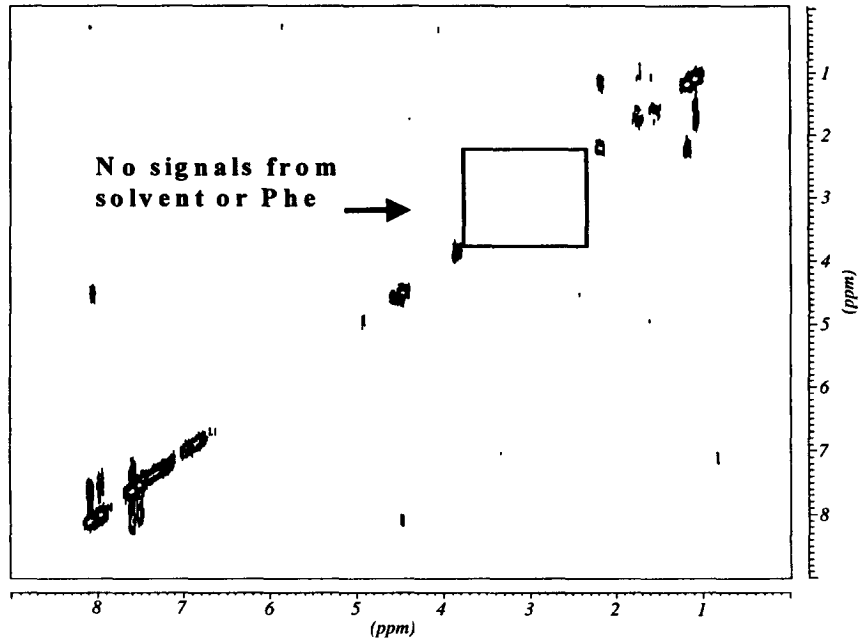

Figure 2. 2D COSY using PFG diffusion for Fmoc-isoleucine Wang swollen in $DMFd_7$ with added phenylalanine

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9. All NMR data were collected on a Bruker DMX-500 NMR system equipped with a high resolution gradient 4 mm MAS probe with a spinning speed of 4000 Hz. 1–2 mg of resin containing compound was swelled in $DMFd_7$ to which benzyol-Phe was added. All 1D NMR data were obtained using the bpp-LED pulse sequence. The gradient strength was about 35 G/cm for 2 ms. The COSY spectrum shown was obtained using pulse sequences described in Ref. 7.
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