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Notes

2D SECSY NMR for Combinatorial Chemistry. High-Resolution MAS Spectra for Resin-Bound Molecules

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The difficulty of monitoring solid-phase reactions is well recognized, and thus analytical tools used for solution synthesis have been adapted for resin beads.[1] 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, a useful technique which provides good quality NMR data for resin-supported molecules.[2] A problem for ^{1}H NMR analysis of products on resins other than TentaGel is that the spectra are often broad and featureless.[3] The loss of coupling information relegates the interpretation to chemical shift information criteria only, making peak assignment difficult. We have shown that coupling information can be reintroduced by performing a 2D *J*-resolved experiment.[4] The on-resin *J*-coupling information can be retained on the chemical shift axis by projection of the untilted spectrum. This untilted projection can often yield 1D proton NMR spectra of resin-bound molecules that are of high quality and useful for monitoring combinatorial chemistry reactions. A more detailed measure of the couplings can be evaluated from the full 2D *J*-resolved spectrum in the normal manner.

It would be advantageous if we could retain the enhanced resolution afforded by the projection of the 2D *J*-resolved data and also obtain spin system connectivities. While COSY and TOCSY data allow for the connectivities to be obtained, the projection onto the chemical shift axis does not lead to enhanced resolution.

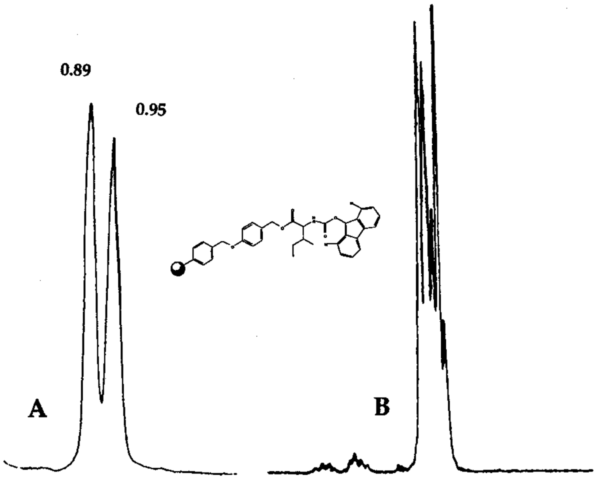

Figure 1. (A) Spin−echo and (B) projection of the SECSY data MAS ^{1}H NMR spectrum for DMF-swollen FMOC-isoleucine on Wang resin **1**.

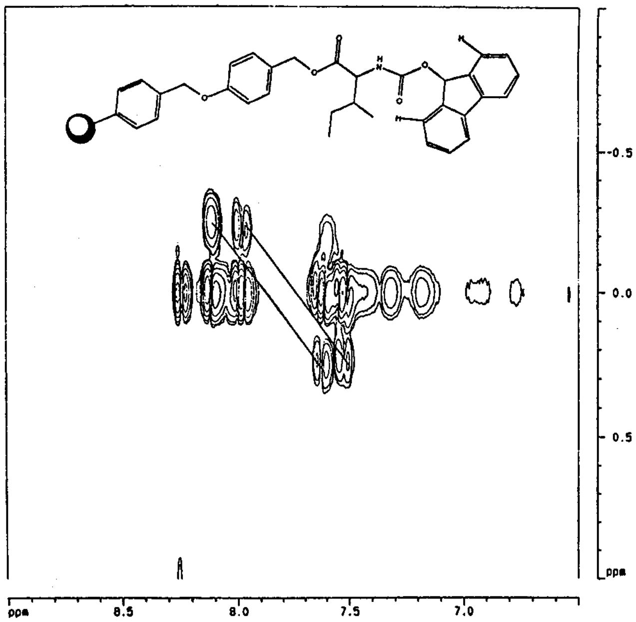

Figure 2. Aromatic portion for MAS SECSY ^{1}H NMR spectrum for FMOC-isoleucine on Wang resin. Diastereotopic protons for the fluorenyl ring are indicated with an arrow.

We have found that if spin−echo correlated spectroscopy (SECSY)[5] is used, then both spin connectivities andenhanced resolution can be obtained. SECSY data contains the same information as a COSY spectrum, but the appearance of the spectrum is different. The diagonal lies along the F1 = 0, and the off-diagonal peaks occur

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(1) (a) Fitch, W. L.; Detre, G.; Holmes, C. P.; Shoolery, J. N.; Keifer, P. A. *J. Org. Chem.* **1994**, *59*, 7995−7996. (b) Anderson, R. C.; Jarema, M. A.; Shapiro, M. J.; Stokes, J. P.; Ziliox, M. J. *Org. Chem.* **1995**, *60*, 2560−2651. (c) Yan, B.; Kumaravel, G.; Anjaria, H.; Wu, A.; Petter, R.; Jewell, C. F., Jr.; Wareing, J. R. *J. Org. Chem.* **1995**, *60*, 5736−5738.

(2) (a) Anderson, R. C.; Shapiro, M. J.; Stokes, J. P. *Tetrahedron Lett.* **1995**, *36*, 5311−5314. (b) Shapiro, M. J.; Kumaravil, G.; Petter, R. C.; Beveridge, R. *Tetrahedron Lett.* **1996**, *37*, 4671−4674.

(3) Keifer, P. *J. Org. Chem.* **1996**, *61*, 1558−1559.

(4) (a) Shapiro, M. J.; Chin, J.; Marti, R. E.; Jarosinski, M. A. *Tetrahedron Lett.*, in press. (b) Aue, W. P.; Bartholdi, E.; Ernst, R. R. *J. Chem Phys.* **1976**, *64*, 2229.

(5) Nagayama, K.; Wuthrich, K.; Ernst, R. R. *Biochem. Biophys. Res. Commun.* **1979**, *90*, 395.

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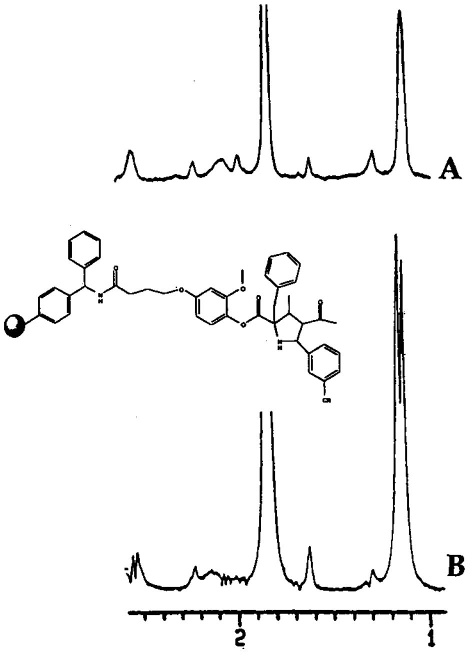
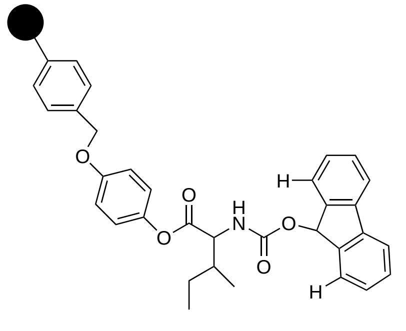


Figure 3. (A) Spin−echo and (B) projection of the SECSY MAS ^{1}H NMR spectrum for DMF-swollen pyrrolidine **2** on resin.

in pairs along lines that make an angle of 135° with the diagonal.[6] This complication in the data leads to a more difficult interpretation than COSY data and may explain why SECSY is not a more commonly used 2D NMR experiment. However, we demonstrate here that this experiment is more useful than COSY for NMR analysis of resin bound compounds.

The MAS SECSY data shown for FMOC isoleucine on Wang resin **1** in Figures 1 and 2 illustrates the apparent increase in resolution as well as the ability to make spin−spin connectivities. We chose Wang resin as it often gives rise to the broadest MAS ^{1}H NMR spectra.[2]



1

We can now readily assign the methyl resonances as we can observe the doublet at $\delta = 0.95$ and easily make out the triplet resonance at $d = 0.89$. The coupling constants measured are not useful for detailed structure determination since they appear to be approximately twice their expected value as a consequence of the line widths observed and the processing.[7] In the aromatic region of the spectrum, the resolution is so good that diastereotopic protons in the fluorenyl moiety can be observed both in the 1D and 2D data.

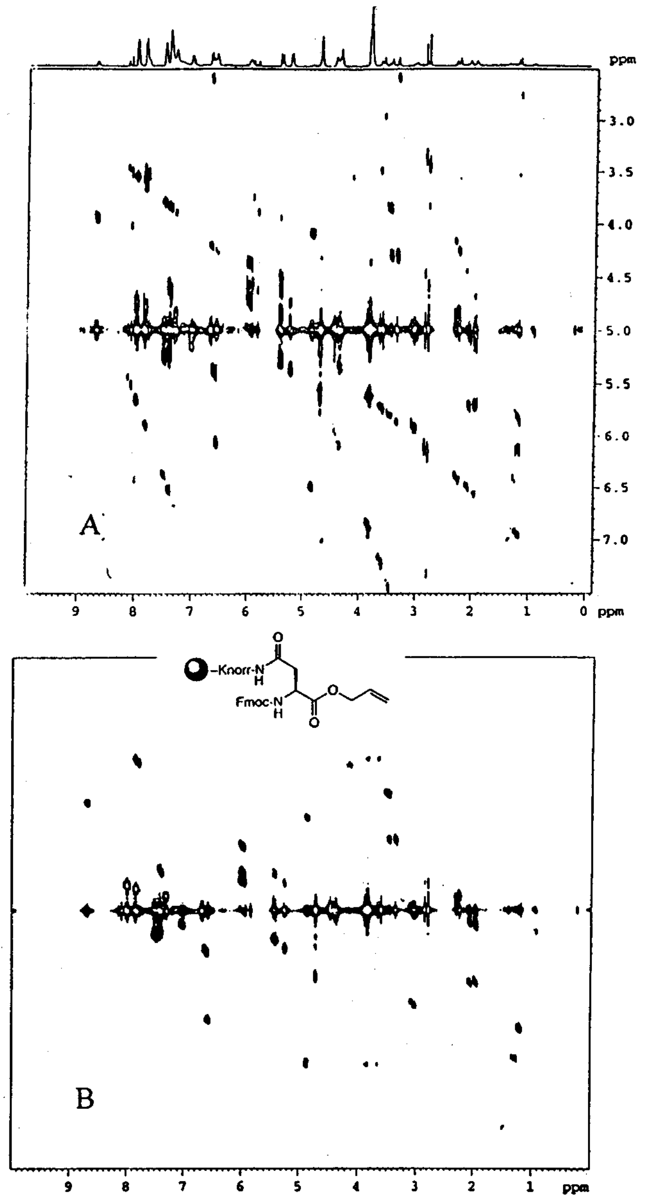
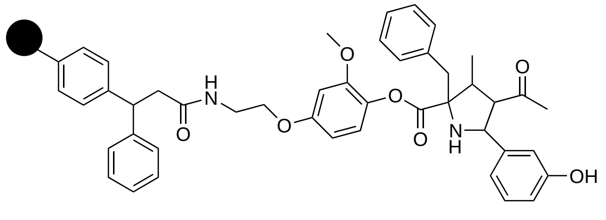


Figure 4. MAS SECSY ^{1}H NMR spectrum obtained using a 4 mm high-resolution MAS probe (A) without gradients and (B) with gradients.

The increased resolution and spectral quality can also be seen for other compounds we have studied on-resin such as the tetrasubstituted pyrrolidine **2** shown in Figure 3.



2

In this case, the methyl doublet at $\delta = 1.15$ is readily observed and confirms the structure as opposed to the

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[6] The diagonal peaks lie along the F2 at F1 = 0 axis and represent the chemical shift as in a COSY spectrum. The F1 axis represents one-half of the chemical shift difference between the coupled spins.

[7] Kim, Y.; Prestegard, J. H. *J. Magn. Reson.* **1989**, *84*, 9.

spin–echo data[8] where the methyl group remains a broad signal and might lead to an ambiguous assignment. Similar high-quality data has also been obtained with Rink and SCAL linkers.

A major problem associated with 2D NMR data obtained using MAS is that artifacts and T_1 noise are abundant, leading to potential confusion in data interpretation. With the advent of a gradient MAS probe, this problem can be alleviated.[9] The SECSY data seen in Figure 4 serves as an illustration of the improvement obtainable using the gradient MAS probe.

The SECSY experiment is a very useful addition to the interpretation of MAS NMR data of on-resin products. By projection of the SECSY data on to the chemical shift axis (F2), high-resolution MAS ^{1}H NMR data should be obtainable.[10]

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[8] Hahn, E. L. *Phys. Rev.* **1950**, *80*, 580.

[9] Mass, W. E.; Laukien, F. H.; Cory, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 13085–13086.

[10] All NMR data were collected on a Bruker DMX-400 NMR system equipped with a high-resolution 7 mm MAS probe with a spinning speed of 2300 Hz except for the gradient MAS SECSY spectrum which was collected with a 4 mm MAS probe. Then 3–5 mg of resin-containing compound was swelled with an appropriate solvent. All data was obtained using standard solution pulse programs. The spin–echo data was collected using a 70 ms echo, and the 2D SECSY data was obtained with a 4K by 128W data matrix zero-filled to 256W. The sweep width of F1 was one-half that of F2. Typically 32–128 transients were obtained for each increment and the data was processed in the magnitude mode with an unshifted sine window function in both dimensions.