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Enhanced Resolution in MAS NMR for Combinatorial Chemistry

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Abstract: We have demonstrated the ability to obtain high resolution NMR spectra from samples on resin using J-resolved 2D NMR. Projection of the non-tilted spectrum onto the chemical shift dimension provides enhanced resolution and virtually complete disappearance of the polymer resonances. © 1997 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] The difficulty in monitoring reactions on resin is well recognized and thus analytical tools used for solution synthesis have been adapted for resin beads.[2] Recently we and others demonstrated that MAS NMR is a useful technique by which "solution" quality NMR data for resin supported molecules can be obtained.[1,3] We have obtained ^{13}C NMR data in this manner and have successfully distinguished diastereomers on a resin and obtained quantitative data on the product yields.[4] The main problem for NMR analysis of on-resin products, with the exception of TentaGel, is that the ^{1}H NMR spectra are generally broad and featureless.[5] The additional complication of polymer peaks can be attenuated by using a spin echo sequence but the residual peaks can be problematic.[6] The loss of coupling information relegates the interpretation to chemical shift information criteria only, making peak assignment difficult. Coupling information can be reintroduced by performing a 2D J-resolved experiment.[7] Typically the 2-D J-resolved spectrum is "tilted" by rotating the data to align the chemical shift axis so that upon projection of the data a "proton- decoupled" proton NMR spectrum can be obtained. However, for on-resin samples we wish retain the J-coupling information on the chemical shift axis and a projection of the untilted spectrum is found to be more useful. This untilted projection can yield 1D proton NMR spectra of resin bound molecules that are of very high quality and useful for monitoring combinatorial chemistry reactions.

Shown in Figure 1 is the spin-echo MAS NMR spectrum for DMF-swollen crude product of isoleucine on Wang resin obtained by FMOC deprotection. The quality of the NMR spectrum is typical of this derivatized 1% cross linked polystyrene resin.

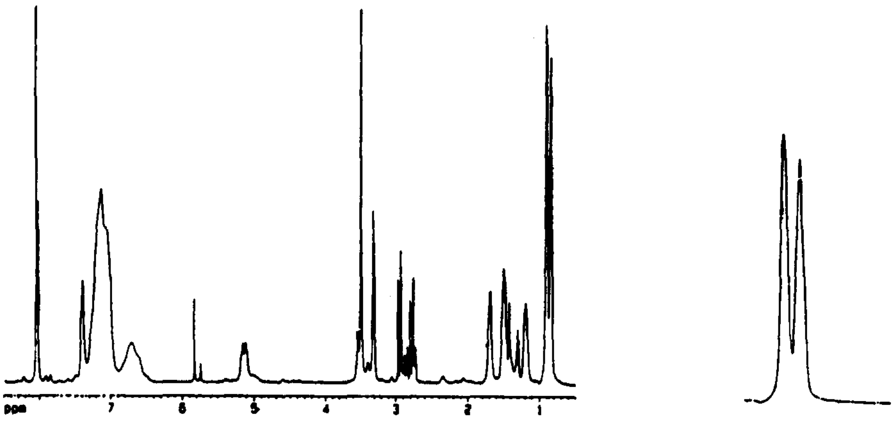

Figure 1. Spin echo MAS 1H NMR spectrum for DMF -swollen isoleucine on Wang resin. Inset are the two methyl resonances at δ = 0.95 and 0.89.

In contrast, shown in Figure 2 is the spectrum obtained for the same compound by projection onto the chemical shift axis of the untilted 2-D J-resolved data. The resonance patterns for the two methyl groups of isoleucine, inset Figures 1 and 2, serve as a comparison of the difference in the resolution.

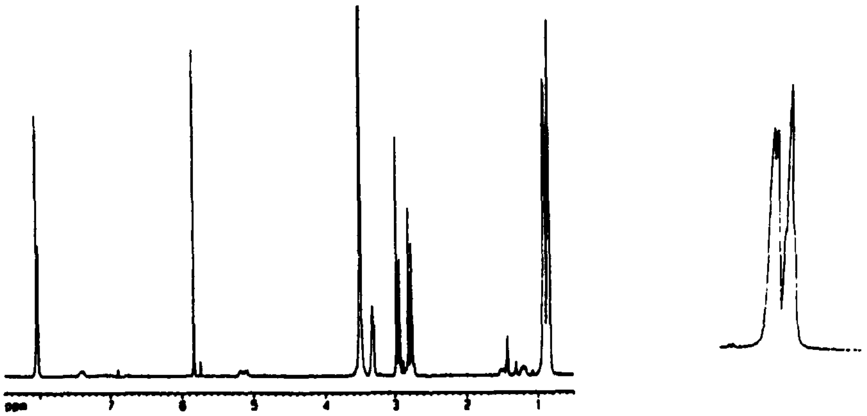

Figure 2. Projection of the homonuclear 2D J-resolved MAS of DMF swelled isoleucine on Wang resin. Inset are the methyl resonances at δ = 0.95 and 0.89.

We can now readily assign the methyl resonances as we can easily observe the doublet at $\delta = 0.95$ and start to make out the triplet nature of the resonance at $\delta = 0.89$.

The increased resolution and spectral quality can be seen for on-resin products we have studied. This is further exemplified for Alloc-Asp derivatized oxazolidinone attached via its side chain carboxyl to SCAL linked aminomethyl polystyrene as seen in Figure 3.[8]

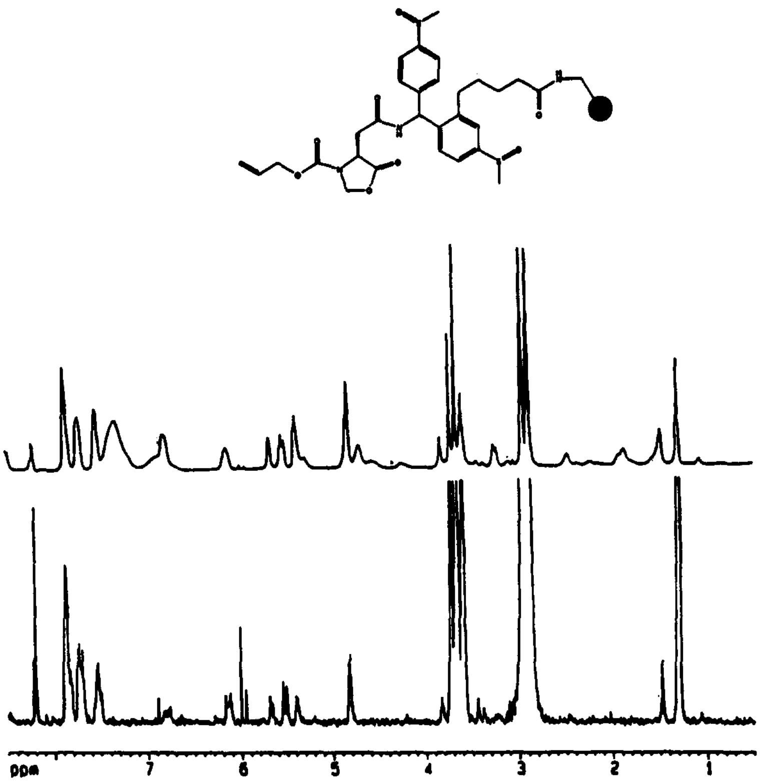

Figure 3. Comparison of MAS NMR spectrum obtained via a) spin-echo conditions and b) untilted 2D J-resolved projection.

In the J-resolved projection, the aromatic rings of the SCAL are clearly present while the polymer resonances have "dropped out" of the spectrum. In addition the coupling constants in the alloc group are readily measured. Identical data has also been obtained for a number of other resin tethers.

If a more detailed measure of the couplings is desired, then the full 2D J-resolved spectrum can be evaluated in the normal manner as exemplified in Figure 4.

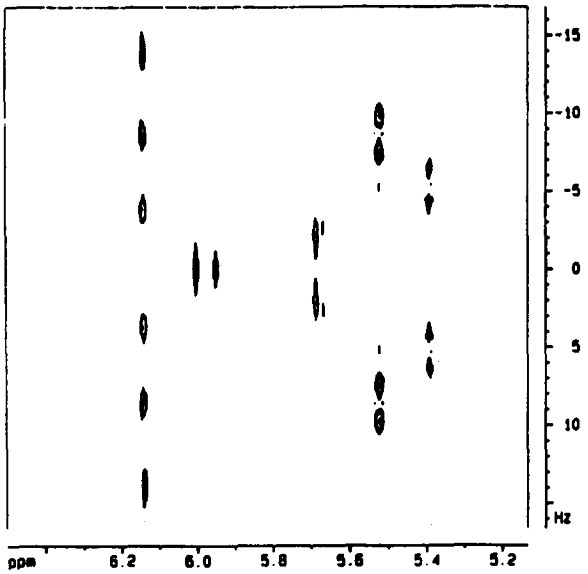

Figure 4. Portion of the 2D J-resolved Spectrum for Alloc-Asp derivatized oxazolidinone.

As with any spin echo sequence, the major drawback is that quantitation of signal intensity is usually not possible. This issue aside, the untilted 2D J-resolved projection, is a very useful addition to the interpretation of MAS NMR data of on-resin products and removes the necessity to use TentaGel as the tether in order to get high resolution MAS ^{1}H NMR data.

References and Notes

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9. All NMR data were collected on a Bruker DRX-500 NMR system equipped with a high resolution 4mm MAS probe with a spinning speed of 3500KHz. 3-5 mg of resin containing compound was swelled with an appropriate solvent . All data wasobtained using standard solution pulse programs. The spin echo data was collected using a 70ms echo and the 2D J-resolved data was obtained with a 4K by 32 data matrix optimized for 50 Hz coupling in F1. Typically 32-64 transients were obtained for each increment and the data was processed in the magnitude mode with an unshifted sine window function in both dimensions.

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