Magic Angle Spinning NMR for Reaction Monitoring and Structure Determination of Molecules Attached to Multipin Crowns

Jefferson Chin,[†] Brad Fell,[‡] Michael J. Shapiro,*[,†] John Tomesch,[‡] James R. Wareing,[‡] and Andrew M. Bray[§]

Preclinical Research, Sandoz Research Institute, Sandoz Pharmaceuticals Corporation Departments of Central Technologies and Combinatorial Chemistry, 59 Route 10, East Hanover, New Jersey 07936 and Chiron Mimotopes Pty Ltd, Victoria 3168, Australia

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The first example of magic angle spinning NMR on crowns has been demonstrated. The ability to monitor a reaction on a crown and to confirm the structure of the reaction product directly on the crown without resorting to chemical cleavage should greatly enhance the utility of this convenient format for combinatorial chemistry.

Combinatorial chemistry has developed using resin beads as a primary format for the synthesis of nonpeptide targets. An alternate format is the Multipin crown system where resin is grafted onto a base polymer unit called a "crown", and arrays of these units are held on the ends of pins in a system for parallel synthesis.[1] The difficulty in monitoring reactions on resin is well recognized, and analytical tools used for solution synthesis have been adapted for resin beads.[2] The ability to obtain information on chemical synthesis in a nondestructive way from crowns has been limited to a single application of FTIR using a special accessory.[3] FTIR as a general tool is hampered by the abundance of interfering peaks that arise from the base plastic, the grafted resin, as well as from the linker molecule. We decided to extend our resin studies using magic angle spinning **(**MAS) NMR to investigate if useful information could be obtained from crowns.[2c−e] Furthermore, we hoped to demonstrate that the same crown can be monitored nondestructively through several reaction steps, thereby aiding the development of new reactions as well as monitoring the synthesis of combinatorial libraries directly. We present here the results obtained from MAS NMR on solvent-swelled crowns.

The initial NMR studies were performed on compound **1** in Scheme 1.

Data were obtained from a high resolution MAS probe in the usual manner.[4] The resulting spectrum from MAS still contains very broad lines due to the grafted resin and base polymer. Proper choice of spin lock time in the CPMG pulse sequence allows the removal of the broader resonances due to the plastic as well as the signals from the slower moving components of the resin.[5] The MAS proton NMR spectrum of aldehyde **1** obtained using a 60 ms spin lock is shown in Figure 1A. The aldehyde peak is clearly present at $\delta = 10.17$. The crown was removed from the rotor and the Wittig reaction shown in Scheme 1 was performed. The MAS spectrum shows

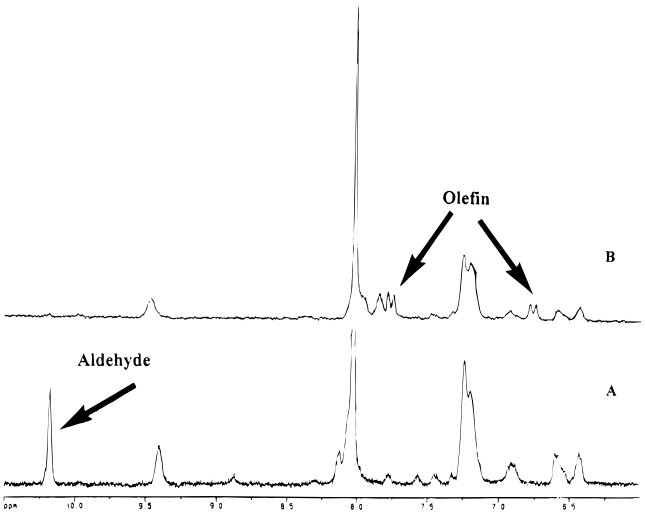

Figure 1. (A) 400 MHz Proton MAS NMR spectrum of a crown with aldehyde **1** attached to the graft polymer[7] and (B) with olefin **2** attached, swelled in DMF-d_7 using a spin echo sequence with a 60 ms echo.

[†] Central Technologies, Sandoz Pharmaceuticals.
[‡] Combinatorial Chemistry, Sandoz Pharmaceuticals.
[§] Chiron Mimotopes Pty Ltd.
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(1) Synthesis system from Chiron Mimotopes, see Valerio, R. M.; Bray, A. M.; Campbell, R. A.; Dipasquale, A.; Margellis, C.; Rodda, S. J.; Geysen, H. M.; Maeji, N. J. *Int. J. Pept. Protein Res.* **1993**, *42*, 1.

(2) (a) Yan, B.; Kumaravel, G.; Anjaria, H.; Wu, A.; Petter, R. C.; Jewell, C. F., Jr.; Wareing, J. R. *J. Org. Chem.* **1995**, *60*, 5736. (b) Yan, B.; Kumaravel G. *Tetrahedron*, **1996**, *52*, 843. (c) Anderson, R. C.; Jarema, M. A.; Shapiro, M. J.; Stokes, J. P.; Ziliox, M. *J. Org. Chem.* **1995**, *60*, 2650. (d) Anderson, R. C.; Stokes, J. P.; Shapiro, M. J. *Tetrahedron Lett.* **1995**, *36*, 5311−5314. (e) Shapiro, M. J.; Kumaravel, G.; Petter, R. C.; Beveridge, R. *Tetrahedron Lett.* **1996**, *37*, 4671−4674.

(3) Using a "SplitPea" accessory; see Gremlich, H. U.; Berets, S. L. *Appl. Spectrosc.* **1996**, *50*, 532.

(4) All MAS data was collected on a Bruker DMX-400 wide-bore NMR in a high-resolution 7 mm Bruker MAS probe with a spinning speed of 2.5 KHz. The whole crown was placed into the Bruker liquid capable rotor and covered with DMF-d_7. Proton NMR spectra were obtained using MAS with a sweep width of 2 KHz using digital filtering. Spectra on cleaved substrates was obtained on a Bruker DMX-500. MAS 2D COSY spectrum of the crowns was obtained using the standard Bruker high resolution pulse sequence without modification. The data were collected for 32 scans for each of 128 t_1 increments with a recycle delay of 1 s, a spectral width of 5 KHz in F1 and F2, and an acquisition time of 0.2 s. Data were processed with an unshifted sine-bell in both dimensions.

(5) Hahn, E. L. *Phys. Rev.* **1950**, *80*, 580.

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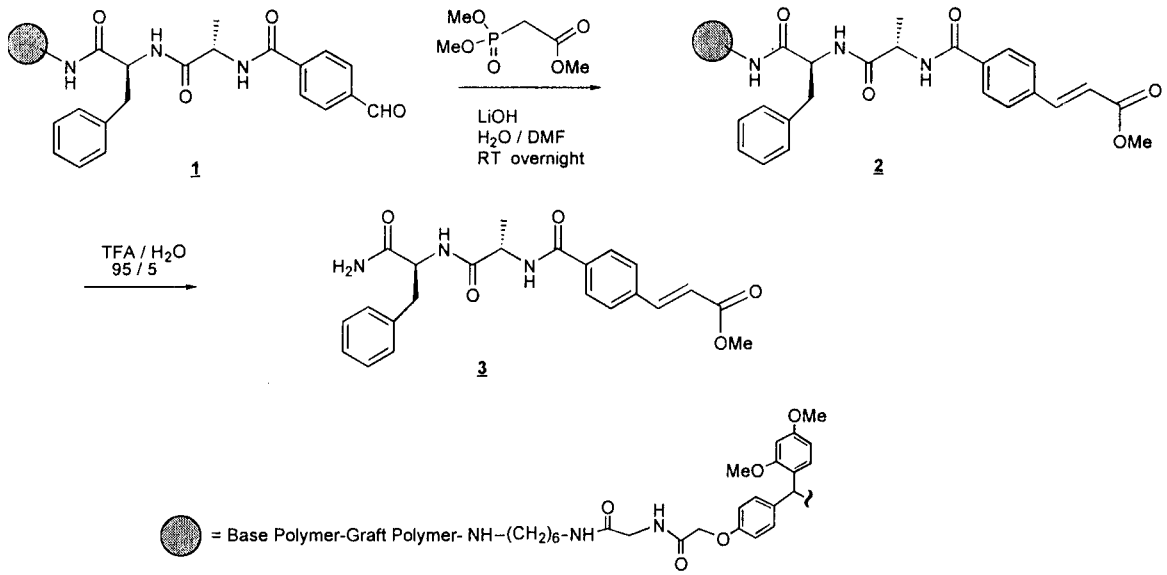
Scheme 1



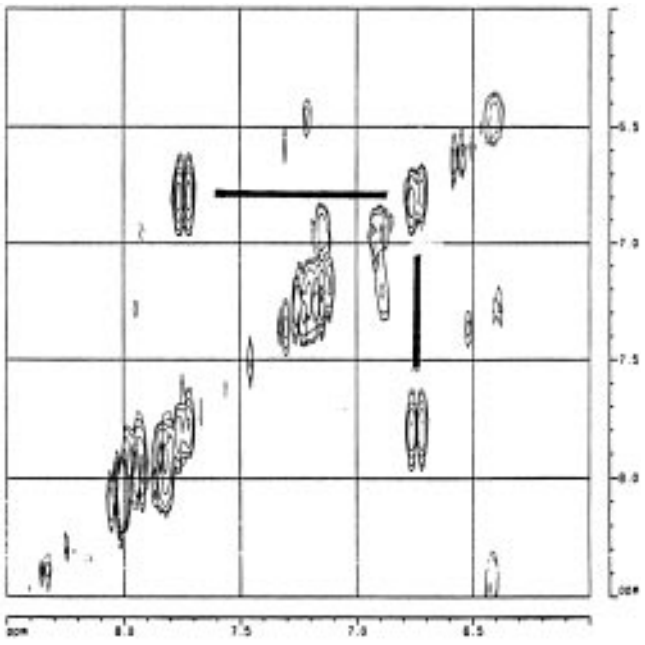


Figure 2. 400 MHz MAS COSY NMR spectrum on crown for the olefinic region of compound **2** swelled in DMF-d_7.

the complete disappearance of the aldehyde peak and the appearance of the olefin moiety $\delta = 6.78$ and 7.72 for **2**, as shown in Figure 1B. The olefin was found to be trans as determined from the measured coupling constant of 16 Hz. Confirmation of the olefinic peaks was obtained by a COSY experiment shown in Figure 2.[6] Both the aldehyde and the olefin were confirmed by cleavage from the crown followed by high resolution solution NMR. In addition, MAS NMR on the crown following cleavage showed complete absence of peaks related to the target compound, confirming that the observed spectrum was the result of the cleaved compound. Compound **3** was also prepared on resin beads and cleaved to give an authentic sample for comparison.

In conclusion, we have demonstrated the first example of MAS NMR on crowns. We have shown the ability to monitor a reaction on crown and to confirm the structure of the reaction product directly on the crown without resorting to chemical cleavage. This method allows the same crown to be sequentially followed by NMR and returned to the reaction conditions until the desired transformation is complete. The use of MAS NMR to monitor crown chemistry will greatly enhance the utility of this convenient format for combinatorial chemistry.

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(6) Aue, W. P.; Bartholdi, E.; Ernst, R. R. *J Chem. Phys.* **1976**, *64*, 2229.

(7) The graft polymer is methacrylic acid−dimethylacrylamide copolymer, see Maeji, N. J.; Valerio, R. M.; Bray, A. M.; Campbell, R. A.; Geysen, H. M. *React. Polym.* **1994**, *22*, 203−212.