

Application of a 60 MHz Permanent Magnet NMR System to Online NMR Reaction Development in the Pharmaceutical Industry

David A. Foley,¹ Mark T. Zell,¹ Brian L. Marquez, John C. Edwards² and Paul J. Giammatteo.²

¹ Worldwide Global Research & Development, Center for Discovery & Development Sciences, Pfizer Inc, Groton, Connecticut

² Process NMR Associates, Danbury, Connecticut

INTRODUCTION TO ONLINE NMR

Online NMR is routinely employed as a reaction monitoring tool in the process development area at Pfizer. Investigation of organic reaction processes by online NMR at 400 MHz provides detailed process understanding for development chemists.

Here we outline the details of expansion of this reaction monitoring platform to include a 60 MHz NMR portable NMR. The utilization of a compact and portable 60 MHz instrument provides increased flexibility and cost benefits over traditional cryogenically-cooled superconducting magnets. These advantages allow the analysis to be performed at the location where the chemistry is being conducted, rather than bringing the chemistry to the lab space specifically designed for online NMR.

WHAT INFORMATION CAN ONLINE NMR PROVIDE?

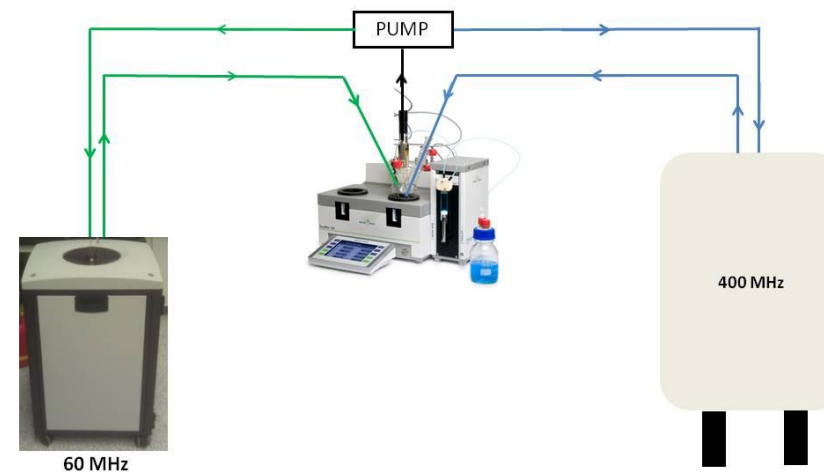
- **INFORMATION RICH DATA FROM A SINGLE EXPERIMENT** – Online NMR is a powerful analytical tool that enables a plethora of information to be gathered from a single experiment. It provides a real-time, detailed picture of what is occurring in the process.
- **CONTINUOUS ONLINE SAMPLING**¹ – Stream of reaction mixture removed from vessel and returned following analysis. No sample preparation or isolation allows detection of labile species in solution.
- **PROTONATED SOLVENTS & REAGENTS** – Solvent suppression eliminates the necessity for expensive deuterated solvents or isotopic enhancement.
- **REACTION KINETICS** – Quantitative nature of the technique furnishes reliable kinetic data.
- **REACTION CHARACTERIZATION** – Structural information of individual components in the mixture is obtained at 400 MHz which aids assignment at 60 MHz.
- **REACTION OPTIMIZATION** – Real-time analysis permits “on the fly” adjustments to reaction conditions.
- **MECHANISTIC INSIGHT** – Combination of reaction profile and intermediate identification sheds new light on reaction mechanisms.

EQUIPMENT SET-UP

Reaction Processes were monitored simultaneously using an AI-60-RMS NMR Reaction Monitoring System (60 MHz) and Bruker 400 MHz Avance III. NMR spectra were recorded at regular intervals over the course of the reaction.

Experimental conditions:

- Typical reaction concentration: 0.2 mol/L.
- Flow rate: 4 mL/min
- Transfer time from reaction vessel to detection: <1 min.

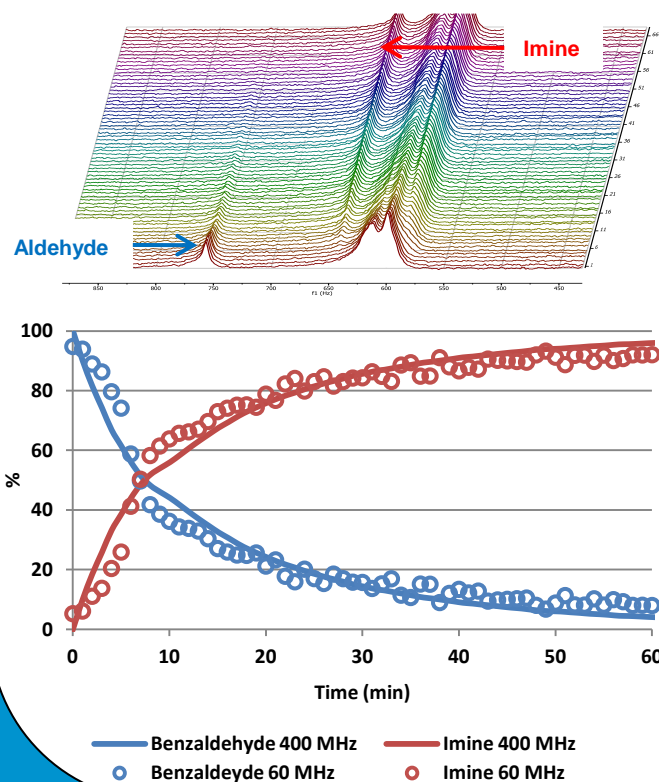
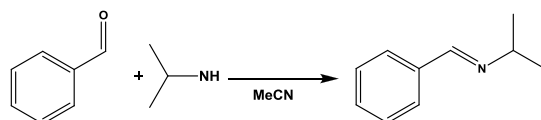


PORTABLE ONLINE NMR

- **MOBILE ANALYSIS** – The size, mobility and standard utility requirements facilitates analysis at the site of chemistry, at the fume-hood, kilo lab or manufacturing.
- **REACTION MONITORING** – Capable of monitoring multiple species in solution in real-time.

RESULTS

IMINE FORMATION

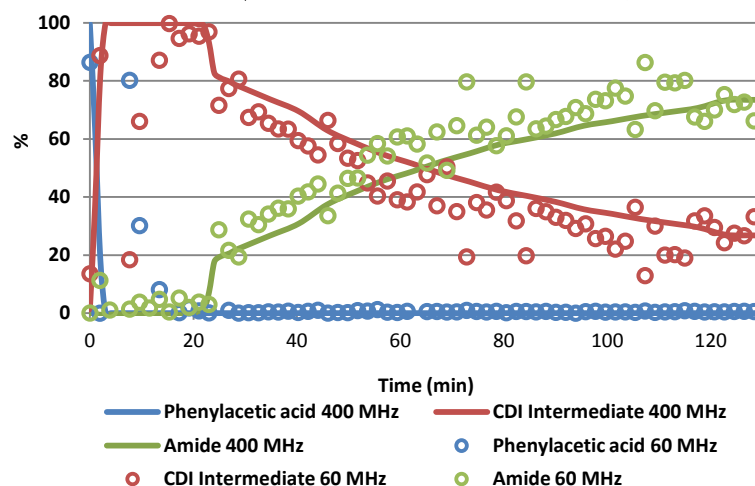
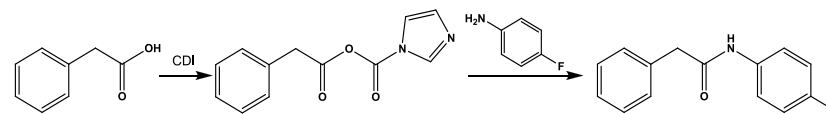


60 MHz NMR was used to monitor three of reaction processes; imine formation, CDI mediated amide coupling and transesterification.

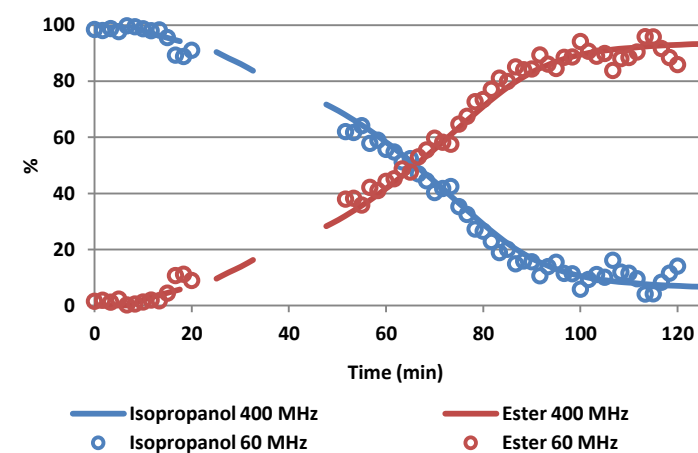
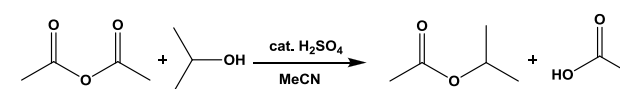
Each reaction was monitored at regular intervals by both 400 and 60 MHz NMR and the data was overlaid to compare the data at the two different field strengths.

The NMR data generated from these three reactions demonstrate the application of low field NMR as a PAT tool for reaction monitoring.

CDI COUPLING



TRANSESTERIFICATION



ACKNOWLEDGMENTS

The authors would like to thank Cosa Xentaur, and Aspect Italia, for development of the 60 MHz online NMR system and MestreLab Research for development of NMR reaction monitoring software.

REFERENCES

1. D. A. Foley, M. T. Zell, B. L. Marquez, and A. Kaerner, *Pharm. Tech.* S19-S21 (2011).