Applying Benchtop NMR Spectroscopy for Reaction Monitoring

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The latest analytical technology to move to the benchtop is Nuclear Magnetic Resonance Spectroscopy, NMR. High-end, high-cost instrumentation has dominated the NMR sector for many years, with both the initial purchase price and annual running costs putting the technique beyond the reach of almost all individual laboratories. Specialist is the word that would come to mind. A special room, with special supplies and, not least, a specialist to keep the instrument operating and acquire the data produced.

This might be compared to how mass spectrometry was twenty years ago, but look where it is today: buyers have a choice of many benchtop footprint instruments from multiple suppliers. The last twelve months has seen the world of NMR make similar strides, with the arrival of several new benchtop instruments and suppliers.

The synthetic organic chemist is the principal beneficiary from the advent of benchtop NMR spectrometers. Whether the user is in academia or in industry; in the chemical or pharmaceutical arenas, a key goal of any synthetic chemist is to be able to quickly and reliably identify exactly what has been made at each stage of the process. NMR is the ultimate technique for this. While mass spectrometry, IR and UV spectroscopies are widely used; organic chemists agree that NMR provides the most definitive information about the structure of an organic compound. In academia, benchtop NMR is now becoming established for both teaching and research, for example by the groups of Professor Magid Abou-Gharbia of the Temple University School of Pharmacy, and at Rochester Institute of Technology in the Magnetic Resonance Laboratory of Professor Joseph Hornak [1].

For organic chemists, proton (1H) and carbon-13 (13C) NMR form the backbone of routine molecular analysis, and the ability to be able to analyse compounds within the same laboratory as they were synthesised, without the need for cryogens or special facilities, allows for substantial improvements in efficiency compared to the centralised NMR functions that operated before the introduction of benchtop NMRs. The synthetic organic chemist has the ability to do 1 and 2D proton NMR with the new instrumentation that is available. An example of a benchtop NMR is shown in Figure 1. This technology allows for the broadening of the user base of NMR to allow specific groups of users such as; synthetic chemists, academics focused on organic chemistry education, pharmaceutical and medicinal chemists, chemical engineers, and researchers working on reactions using organic molecules.

Figure 1 Spinsolve Carbon – Benchtop NMR spectrometer

Users of benchtop systems have found them to be particularly convenient and robust to use. In laboratories where timeliness of results is imperative, ease of operation makes these instruments perfect for bench chemists and analysts who need immediate results. Being able to analyse samples and gather the data in a couple of minutes is far more effective use of time than sending samples away and waiting days for results.

A long-held aspiration of synthetic chemists and chemical engineers has been an NMR instrument that can both monitor reactions and be deployed in synthetic laboratories and pilot plants. Now it is possible to bring the NMR to the synthesis instead of having to bring the synthesis to the NMR [2]. The key ability to monitor reactions, by tracking reactants, products, intermediates, and by-products, and to determine end-points, is now available. Such work has been reported at the BAM Institute in Berlin where the Process Analytical Technology group works on the development and validation of online and at-line analytical methods.[2]

For our experiments, a Spinsolve high-resolution benchtop NMR spectrometer (Magritek, Wellington, New Zealand) was used. The experimental arrangement for on-line monitoring is given in Figure 2. A Dewar sleeve of 5 mm o.d. and 2.25 mm i.d. is mounted in the bore of the benchtop NMR to reduce the heat exchange between the flowing sample and the magnet. The reaction mixture is pumped through the bore of the magnet using 2 mm o.d. PTFE tubing. The pump can be operated in continuous mode or in stop flow mode to acquire spectra with a time resolution of about 15 seconds.

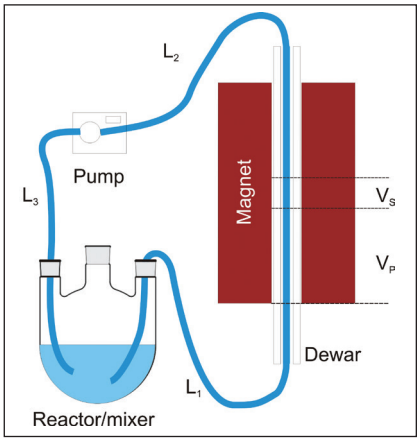


Figure 2 Schematic of online monitoring setup

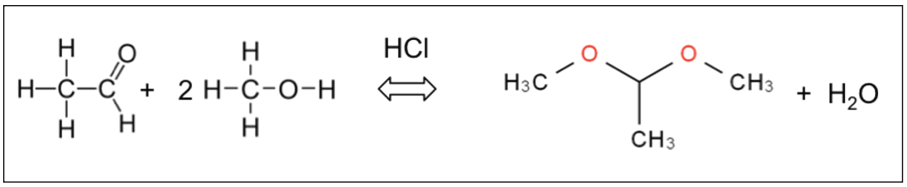


Figure 3 Acetalisation reaction

To illustrate the flexibility of the technology, the acetalisation of acetaldehyde was investigated, Figure 3. Acetalisation is a typical reaction in organic synthesis where an acetal is produced from an aldehyde and an alcohol. It is acid catalysed and eliminates water as by-product. Below the reaction equation is shown for acetaldehyde reacting with methanol to produce acetaldehyde dimethyl acetal, the reaction being carried out in DMSO.

The spectrum of the initial mixture (green) shows the signal of acetaldehyde (carbonyl at 9.7 ppm and methyl at 2.25 ppm). At the end of the reaction (brown) the signals of acetaldehyde dimethyl acetal (CH at 4.8 ppm, CH3 at 1.4 ppm, and -O-CH3 at 3.5 ppm) and water at 4.7 ppm can be seen, Figure 4. There is a signal from DMSO at 2.7 ppm, but this does not interfere with the signal of either the reactants or the products. There is no need to use deuterated DMSO.

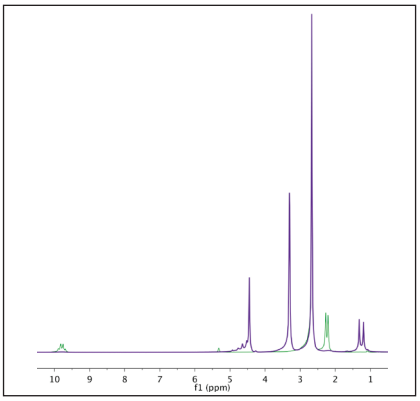


Figure 4 Spectrum obtained before (green line) and after the completion (brown line) of the acetalisation reaction

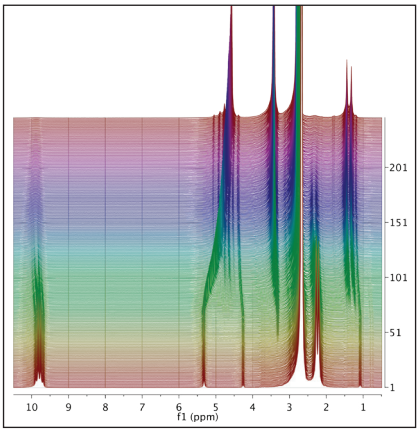


Figure 5 Waterfall plot of acetalisation reaction

The reaction was carried out in a flask where 20 ml of acetaldehyde was dissolved in 30 ml of DMSO (to avoid evaporation) and 0.5 ml of hydrochloric acid (catalyst). 35 ml of methanol were added in drops to the reactor at a rate of about 1 ml/ min. The reaction was monitored for one hour with spectra acquired every 15 seconds, as shown in the waterfall plot, Figure 5. By integrating the regions marked in green and purple the total mass of aldehyde (green) and acetaldehyde dimethyl acetal in the reactor can be easily determined, Figure 6.

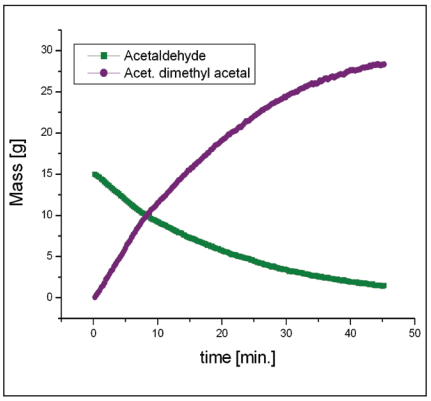


Figure 6 Time plot to show decay of reactant and increase of product

For a second example, the reduction of acetophenone (AP) to 1-phenylethanol (PE) via the transfer hydrogenation with isopropanol was monitored. The experiments started with only isopropanol in the reactor. After turning the pump on, 2% of AP was added to the reactor with the NMR spectrometer set to acquire NMR spectra at regular ten second intervals. The main peaks in Figure 7 (a) correspond to the three different chemical groups of isopropanol and the AP signals (blue) can be seen only after zooming in the spectrum by more than one order of magnitude, Figure 7 (b). Then the iridium catalyst was added to the solu¬tion and the reaction was monitored for some hours. The final spectrum is shown in Figure 7 (c). It can be seen in Figure 7 that the signals from AP have been replaced by the peaks of acetone (red) and 1-phenylethanol (green).

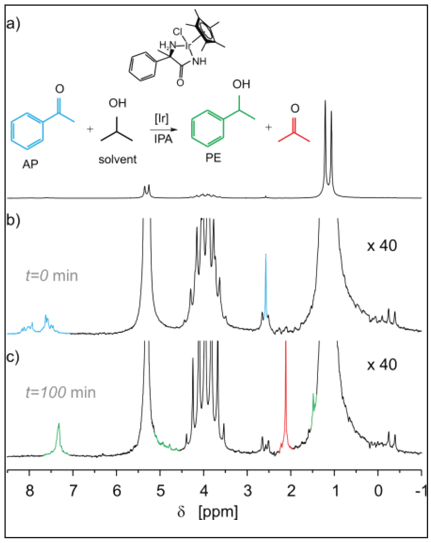
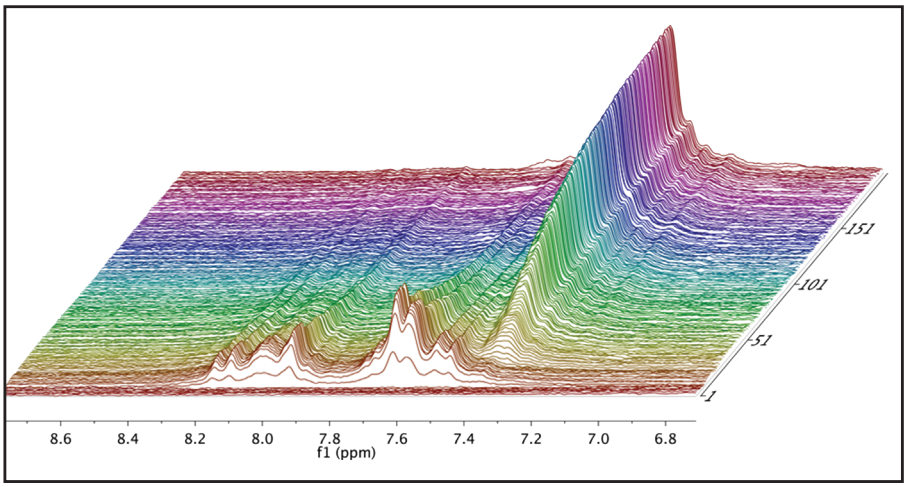


Figure 7 Spectra showing the three-stage transfer hydrogenation process

Zoom of the aromatic region of the spectrum: The large solvent peaks do not affect this region and the signals can be integrated to measure the concentration of both AP (from 7.85 to 8.3 ppm) and PE (from 7.1 to 7.45 ppm), Figure 8.

Figure 8 Waterfall plot showing change in concentration of reactants



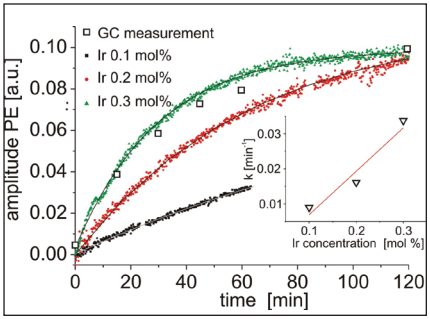


Figure 9 Concentration plot comparing GC and NMR data

The concentration of PE as a function of time was measured for three different concentrations of catalyst. The results are compared with GC and show excellent agreement, Figure 9.

So, in conclusion, benchtop NMR has been shown to be an ideal, convenient tool for reaction monitoring in the laboratory environment. The advent of benchtop NMR instrumentation addresses a long-recognised need in the field of reaction monitoring. Whilst there have been examples of the use of high-field NMR for reaction monitoring, the challenging environmental and technical requirements of high-field instruments have prevented widespread use of the technique on-line. The substantially greater cost of a 300 or higher MHz instrument, and the substantial ancillary services required (a dedicated room or area, liquid Helium and liquid Nitrogen supplies, compressed air supply, continuous oxygen-level monitoring, etc.), together with much higher running costs (usually including a NMR spectroscopy specialist) have been a significant deterrent. The convenience of being able to take a benchtop NMR to the reaction greatly simplifies experimental setup, and makes NMR reaction monitoring a practical and affordable approach in a wide range of applications and environments. Operation in a normal synthetic chemistry lab, in or next to a fume hood, or in a pilot plant, is now easily achievable.

Performing reaction monitoring with a high field system is a major challenge. Previous systems integrating in-line NMR spectroscopy had been limited to bypass configurations, flow cells in high-field magnets or applied microfluidics. The advent of a benchtop spectrometer has allowed for Cronin et al. to use a bench top NMR in flow mode. The research group at the University of Glasgow headed by Professor Cronin takes advantage of the high performance of a compact permanent moderate-field (43 MHz) instrument, which nevertheless achieves excellent spectral resolution of better than 1 Hz. As he reported in a recent paper in the Royal Society of Chemistry journal, Chemical Science [3], "Despite the low field of the magnet, the system has remarkable sensitivity and stability." The group now use their benchtop system in the 'flow' mode which is important for their work as it allows the study of reaction dynamics. Now, they can run entire reactions (with no need for deuterated solvent) or look at things in real time; also they can adjust reaction outcomes as a function of NMR, making this a very flexible system.

All in all, this means benchtop NMR spectroscopy is on its way to becoming well established in teaching, academic research as well as in industrial laboratory environments. It will continue to grow as a technique creating new opportunities for timely and cost-effective NMR analysis.

Acknowledgement

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References:

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3 'A self optimising synthetic organic reactor system using real-time in-line NMR spectroscopy': Victor Sans, Luzian Porwol, Vincenza Dragone and Leroy Cronin, DOI: 10.1039/c4sc03075c. (This is an open access publication).