Benchtop NMR spectroscopy

Putting NMR spectroscopy at the heart of the analytical chemistry lab

For many decades, access to Nuclear Magnetic Resonance (NMR) has been an intrinsic requirement for any analytical chemistry lab. The technique, particularly due to its ability to elucidate molecular structure and track reaction dynamics, is recognised throughout industry and academia as a powerful, non-destructive, non-invasive method and is taught in undergraduate chemistry curricula. But how is NMR now employed on the bench in almost any laboratory environment?

Access to NMR has often been difficult, with the requirement for substantial space, special facilities and expert users, limiting the usability of the technique in synthetic chemistry and industrial labs. However, the latest advances in benchtop NMR instrumentation, brings this technique out of the basement or centrally managed facility and into the heart of any laboratory. Benchtop NMR instruments are a smaller, cryogen-free version of traditional high field instruments that enable data collection even in the fume hood. Recently, we have added broadband capability to the field of benchtop NMR with X-Pulse. This new capability significantly expands the range of challenges solved by benchtop NMR across education, academia, and industry.

X-Pulse is the world's first broadband high-resolution benchtop NMR spectrometer. It is designed to be modular with an upgradeable user-removable probe as standard and includes workflow enhancing add-ons such as X-Auto, a 25 position autosampler, and wide range variable temperature accessories.

Industrial quality control

In industry, R&D scientists can utilise benchtop NMR at all stages of development. The flexibility and time efficiency of NMR makes it an essential tool for routine analysis. As the X-Pulse is portable, it can be put to work wherever it is needed. This can be as part of a reaction monitoring set-up near line to provide feedback on a process; as confirmational or corroborating analysis of product quality in test labs; or as a discovery tool in development.

One of the most common applications of NMR in industry is QA/QC. The sample preparation, which can be as easy as pipetting the sample into an NMR tube, and fast data acquisition, make it ideal for this purpose. This was demonstrated recently for fluorochemical reaction feedstocks in an application note that can be viewed here.

The quality of the supplied starting material directly impacts the quality of the final product. In the battery electrolyte example shown in figure 1, it led to a vast deviation from the expected performance of the final product. The remarkable nuclear and chemical specificity of NMR makes it possible to detect different components of the desired starting material and an impurity, which was found to be a breakdown product. This helps to understand how its resulting performance impacts lithium battery charging capacity, power output and lifespan.

The bottom (dark green) spectrum of the starting material the company was expecting to use whereas the top (light green) spectrum was the chemical they received from their supplier. Clearly, these two are different. Not only is there the desired starting material in the light green spectrum, but there is also a probable breakdown product. The chemical shifts (precise peak positions) fingerprinted the breakdown product as difluorophosphoric acid and additional presence of lithium fluoride identified that the electrolyte failure was caused by a hydrolysis reaction from traces of unwanted water.

As well as QA/QC applications, industrial R&D scientists can benefit from real-time feedback of their reactions. As a benchtop NMR instrument is small enough to fit in a fume hood, it can be placed right next to where the chemistry is happening to acquire real-time data on how the reaction is progressing.

Figure 2 shows the stacked spectra of a reduction of 3-Nitrobenzaldehyde which is a drug precursor and used in the synthesis of calcium channel blockers. Spectra were taken every 20 seconds as the reaction mixture was pumped continuously through the X-Pulse flow cell. The rapid disappearance of the signal at 10 ppm (aldehyde reactant) and the shifting signals in the aromatic region (7-9 ppm) indicate that the chemicals in the reaction have changed, and that the reaction proceeded rapidly to full completion after 200 seconds. Tracking the concentration curves of reactants and products over time enables the order and rate constant of the chemical reaction to be determined.

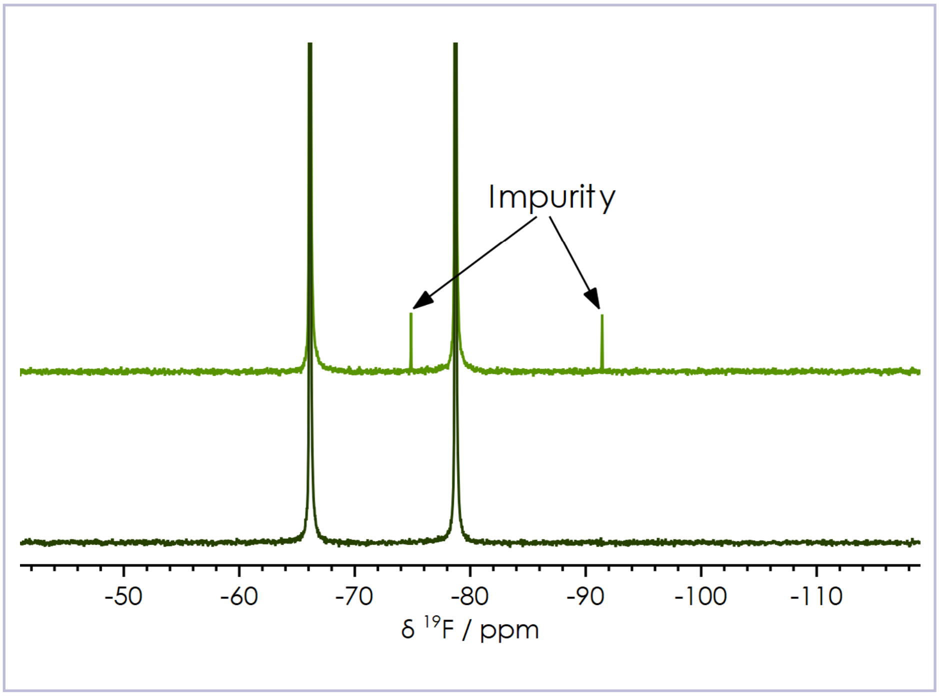


Figure 1: A comparison of two electrolyte components.

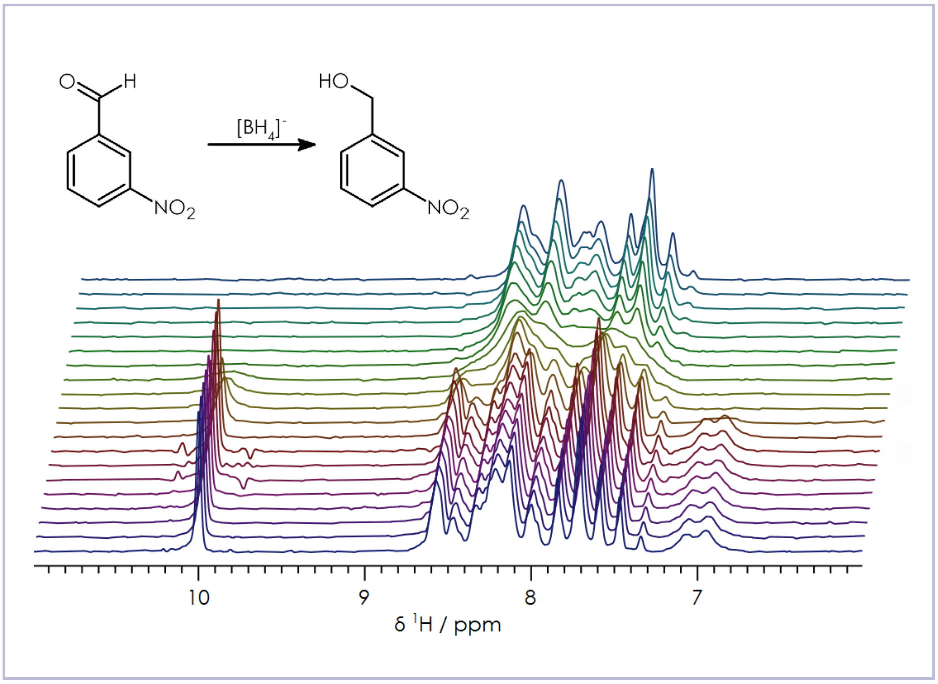


Figure 2: Time series NMR data of the reduction of 3-nitrobenzaldehyde.

By determining rate constants under different temperature conditions, the enthalpy, entropy, Gibbs free energy changes and other kinetic reaction parameters can be calculated. This supports optimizing reaction conditions, improving reaction efficiency, controlling the reaction process, and ultimately designing reactors.

Furthermore, by tracking reaction reactants, intermediates and final products, it may be possible to incorporate NMR into a feedback loop to automate the addition of reagents to the chemical reaction.

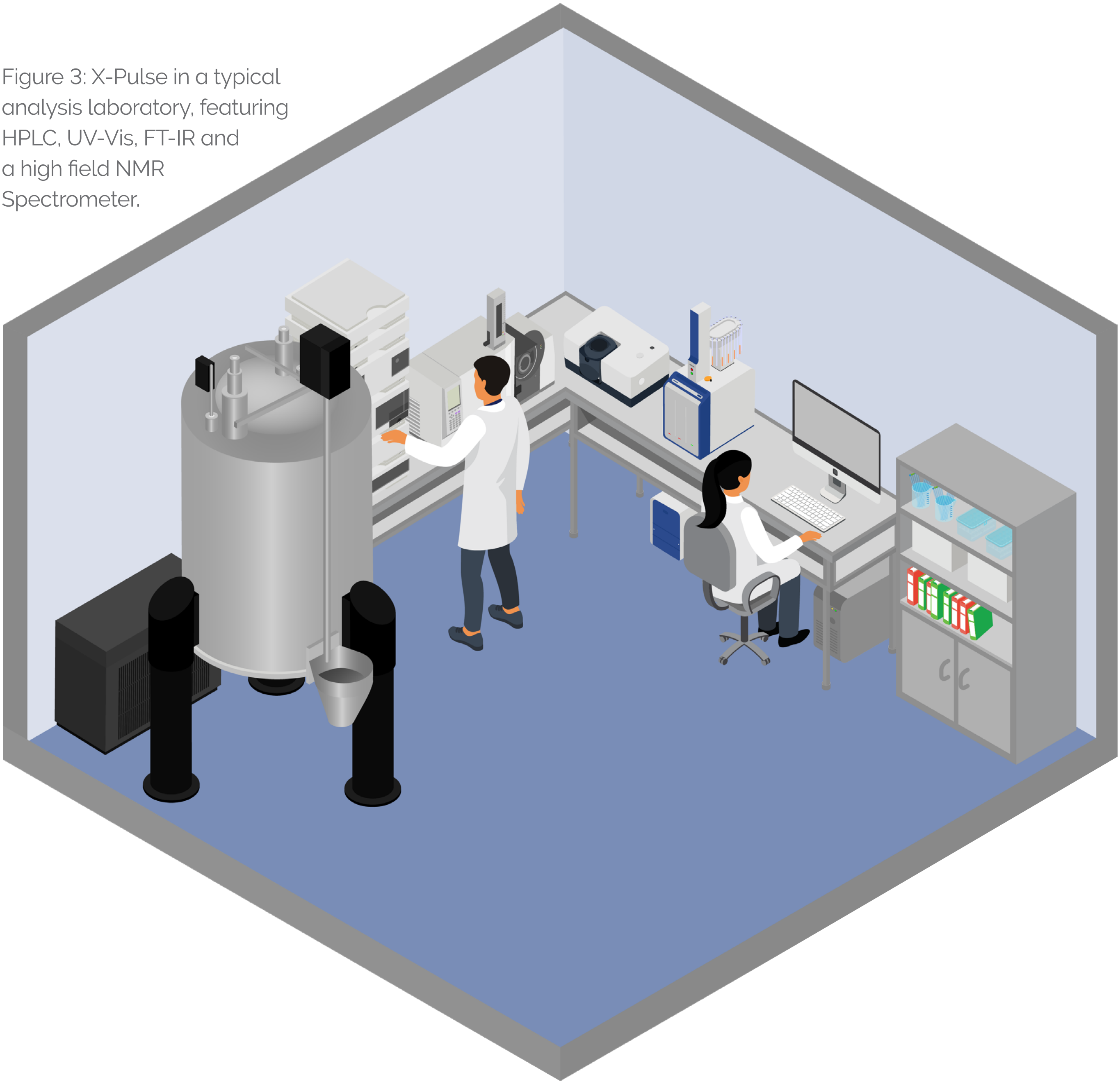


Figure 3: X-Pulse in a typical analysis laboratory, featuring HPLC, UV-Vis, FT-IR and a high field NMR Spectrometer.

Generating return on investment

For industry, the benefits of benchtop NMR are clear: shorter preparation times, automation capabilities, fewer staff specialists, and a reduced space demand. These mean that the time efficiencies and cost savings versus a high field instrument can be made from day one. High field instruments demand significant initial capital investment and often require a dedicated room to operate in. This can be an inefficient use of space. Benchtop NMR solves this issue with its much smaller footprint enabling it to fit right beside existing instruments in an analysis lab (see figure 3). As benchtop NMR is cryogen-free, it is much cheaper to run than traditional high field instruments. Our analysis showed that one can conservatively save over $9,000 per year in running cost just from the cryogens alone.

As well as the on-going, and ever rising, cost of cryogens there is also the peripheral logistics of buying and installing a high field system to consider:

- Can one establish a reliable and continuous supply of liquid helium and liquid nitrogen?
- How will they be stored safely on site?
- Is there someone on site that is qualified to handle them in a safe manner?

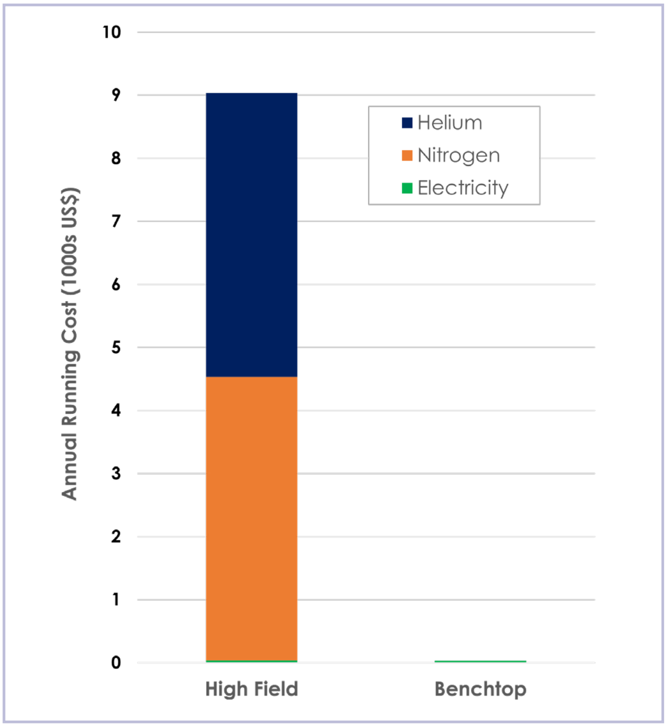
Any business looking to invest in high field NMR needs to answer these questions. As benchtop NMR utilises a cryogen-free permanent magnet, these questions and associated costs simply do not exist. This enables one to extract a return from that initial investment much more quickly.

Flexibility of benchtop NMR

As benchtop NMR is mobile, the instrument can be physically placed inside any lab and transported between labs, paving the way for equipment sharing between groups in a department to make NMR analysis cheaper. As X-Pulse is a broadband spectrometer, the flexibility to rapidly tune between the nuclei of interest in each individual sample further enables sharing across a wide range of applications whilst also future-proofing research or development capabilities.

Figure 5 below shows a selection of the 31 nuclei that it is possible to monitor using X-Pulse. Hence, complex mixtures can be investigated in a non-invasive and non-destructive way. This allows for future changes in research focus whilst simultaneously providing the potential for X-Pulse to be based in a multi-user facility. This critical functionality has facilitated specific applications in battery development research. Quantifying the many different chemical species in electrolytes with multiple nuclei of interest accelerate new formulation development, elucidates degradation mechanisms and improves quality control.

Figure 4: Comparative running costs for a typical high field vs. a benchtop NMR instrument.



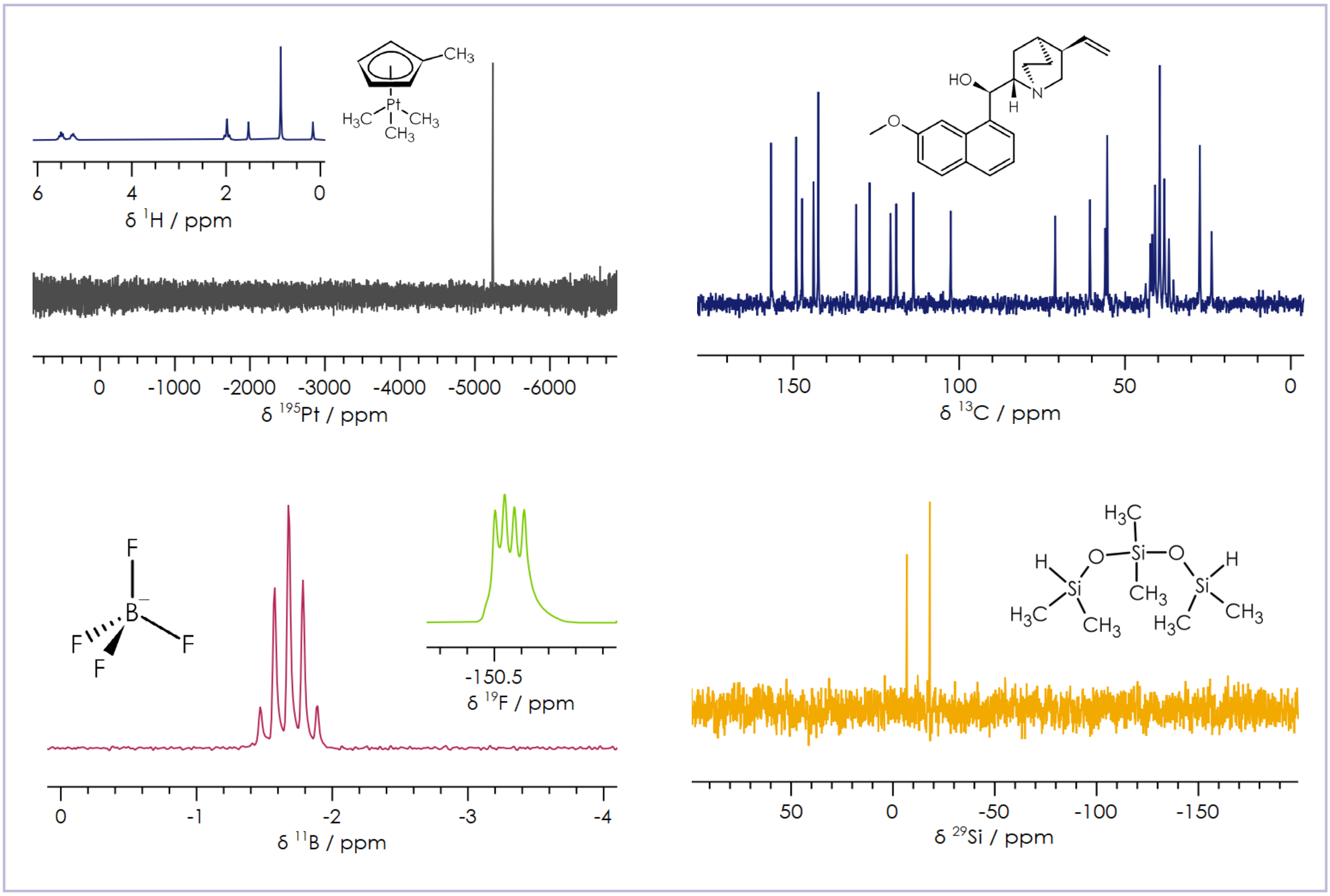
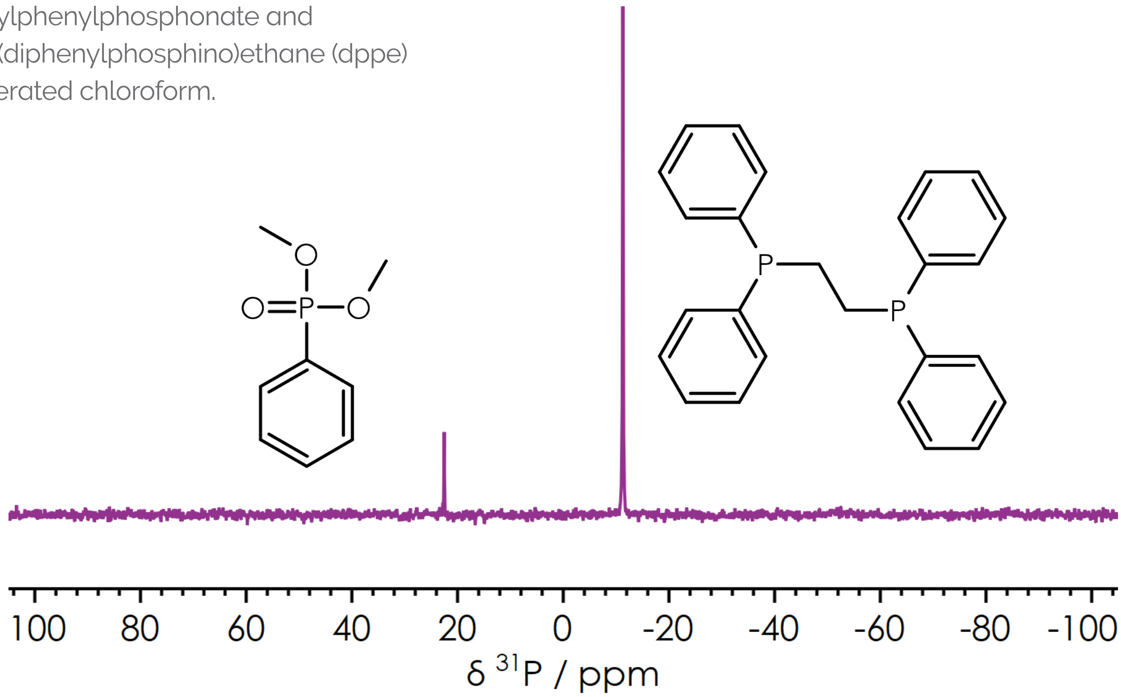


Figure 5: A selection of the many nuclei X-Pulse is capable of detecting.

Figure 6: A ^{31}P spectrum of dimethylphenylphosphonate and 1,2-Bis(diphenylphosphino)ethane (dppe) in deuterated chloroform.



Phosphorus NMR is used in coordination chemistry, catalysis, and for qualifying pharmaceuticals and dietary supplements. In figure 6 a spectrum of a mixture containing dimethylphenylphosphonate and 1,2-Bis(diphenylphosphino)ethane is shown. Both molecules contain aromatic rings, and would therefore be difficult to separate using proton NMR. Both phosphorous nuclei are in similar environments, so one might expect them to have similar chemical shift, however, even at low field the spectral dispersion is good enough to easily distinguish them. This shows how NMR can be used to distinguish between structurally similar molecules.

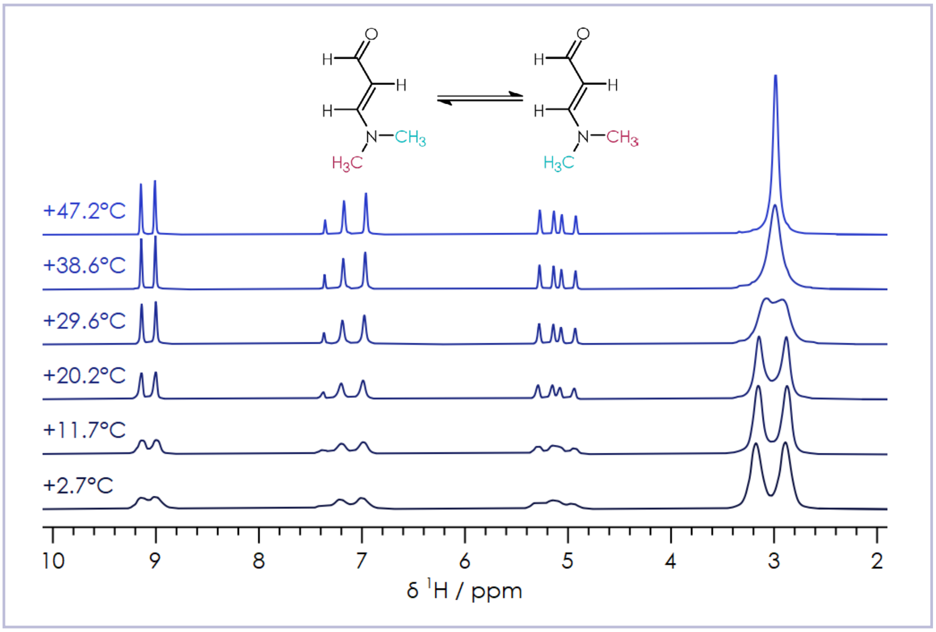
Education: from teaching to novel research

Synthetic chemistry education benefits from early hands-on NMR exposure to deepen understanding of the analytical technique. Having benchtop NMR in the lab speeds up acquisition, so students can be analysing what they have synthesised minutes after having made it. To prepare students for a future in chemistry it is essential that they are well versed in NMR, which is employed widely throughout the chemical research world and industry. For education, NMR can now be a much more hands-on experience. To learn structural elucidation, often students are handed paper copies of spectra which have been at least partially processed for them, sometimes with challenging-to-read axes. They perform the analysis with the knowledge that all the information they require to determine the structure has been provided to them. This process is not a reality in a research environment where researchers interact with the data electronically, and where they may need to identify and run more complex spectra to complete their analysis. Using benchtop NMR, even these more complex spectra are readily available in the lab. Two-dimensional (2D) experiments are now commonplace in most instruments and the most used ones come as standard on the X-Pulse. The extra dimension of data provided by these experiments accelerates structure determination of small molecules. You can read more about structure elucidation using X-Pulse here.

In the example of variable temperature as shown in figure 7, students can watch the progression of dynamic changes in molecular structure using NMR to reinforce learning concepts from both molecular structure and NMR. Here, the NMR spectra show that as the sample temperature increases, the two methyl group signals coalesce into a single signal. At the molecular level, increasing the sample temperature increases the rotational energy of the molecule which speeds up the rotation of the methyl groups until they are spinning so fast that they become equivalent. With a benchtop instrument, NMR experiments can now follow a more similar pattern with prediction, experiment, and result happening in the same session.

The benefits within a higher education environment also extend beyond the teaching lab into the research lab. With benchtop NMR, analysis can be run in minutes to determine the success of a reaction – no more running down to the user facility or even sending samples to external companies for routine analysis. If your samples do require higher fields, then benchtop NMR can become an invaluable pre-screening tool to determine if the product or sample you are looking at really does warrant the time and money required for high field evaluation.

Figure 7: Stacked spectra of 3-Dimethylaminoacroleinat various temperatures.



This pre-screening functionality can be useful to NMR facility managers too. As well as taking up much less space than a traditional high field set-up, benchtop NMR can also free up the more expensive-to-run magnets to be used in a more efficient way.

Conclusion

In summary, cryogen-free benchtop NMR has become an essential tool in any analytical chemistry laboratory. It removes the high upfront, and ever-increasing running costs of traditional high field NMR providing a simple to use portable solution. With the arrival of the true broadband X-Pulse NMR system, incorporating comprehensive flow and temperature control, a single instrument now addresses needs from student teaching, right through to high end R&D and industrial quality control.

For more information about X-Pulse, please contact us: **magres@oxinst.com** or visit: **nmr.oxinst.com**