Detection by Online Benchtop NMR Spectroscopy: Hydrogenation Reactions

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Introduction

Chemists strive to understand the underlying processes that govern the outcome of a reaction such that they can learn from, design, control, and optimize a chemical transformation. In order to gain understanding, there are a variety of options in the chemists' characterization toolbox – ranging from temperature, pressure and pH sensors to chemically specific techniques such as Infrared (IR), Raman, Ultraviolet-visible (UV-Vis) spectroscopy and Mass Spectrometry (MS). Despite its superiority in structure elucidation, Nuclear Magnetic Resonance (NMR) Spectroscopy is often underrepresented in this capacity. Since its commercialization in 1961, NMR spectrometers have remained large, expensive, both in capital costs and operating expenditures, and difficult to use without suitable expertise.

However, in the late 2000s, following the trend of other analytical technologies, the miniaturization of NMR spectrometers also began.[1] The development of:

(1) new NMR signal detectors (*i.e.*, microcoils, external-field configurations, and force-detectors); paired with

(2) the discovery of new rare earth metals (*i.e.*, samarium-cobalt (SmCo) and neodymium-iron-boron (NeFeB));

(3) suitable ways to manufacture magnets repeatedly and homogeneously; and

(4) new design principles.

has allowed for the development of a new class of NMR instrumentation: the benchtop NMR Spectrometer.

More powerful than a relaxometer, the permanent magnet based benchtop NMR spectrometer, is low-field (<100 MHz), high-resolution (<1.2 Hz peak width at half height) and compact such that it is amenable to in-laboratory, glovebox, fumehood or process line applications.[2] The performance facilitates a number of applications requiring chemical speciation – including reaction monitoring.

We have previously discussed the efficacy of benchtop NMR spectroscopy for at-line reaction monitoring,[3] but here we will discuss the hardware of the NMReady-flow kit necessary to convert an NMReady benchtop NMR spectrometer into a detector for analyzing online reactions.

The hardware consists of:

(1) a customized borosilicate glass flow cell designed to span the length of the hybrid Halbach magnet that generates the static magnetic field of the NMReady; and

(2) the necessary hardware to connect the glass flow cell with chromatography tubing.

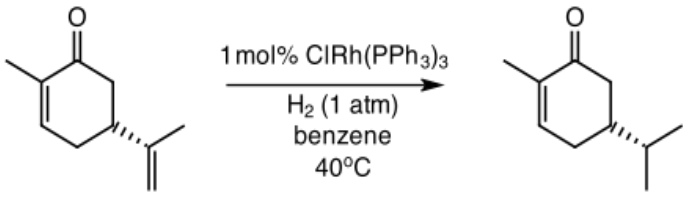
The flow cell was designed to be compatible with any NMReady-60e or -60PRO without probe modification. It minimizes volume in the flow cell, maintains a sealed loop and moves leaks to outside the magnet to ensure accidental spillage doesn't prevent the instrument from being used (figure 1).[4] There are many ways to acquire data, both manually and automatically. For simple reaction monitoring we offer a kinetics package and access to the Application Programmatic Interface (API) through JSON protocols, such that the entire liquid handling system can be controlled by the same interface.

Figure 1. Cartoon schematic of online flow loop and reaction monitoring system.

Results & Discussion

We performed a series of experiments to look at the efficacy of benchtop NMR as an online detector with a variety of reactions. Here we will discuss monitoring hydrogenation reactions performed in *proteo*-solvents without requiring the addition of any deuterium, with benchtop NMR. For these studies we are employing basic Schlenk techniques with a stir plate, a round bottom flask and a metering pump that can be operated in either stopped flow (0 mL/min) or continuous flow modes (0.1–4.0 mL/min). Depending on acquisition parameters, a scan can be acquired approximately every 4 seconds to allow for rapid signal averaging as required.

We have chosen typical Wilkinson Catalyst ([ClRh(PPh_3)$_3$] conditions to hydrogenate *(R)*-6,8-*p*-menthadie-2-one (*R*-(-)-carvone) and styrene with *tris*(triphenylphosphine rhodium (I) chloride.[5]



Scheme 1. Reaction schematic for *R-(-)*-carvone hydrogenation with [ClRh(PPh_3)$_3$].

On a double manifold high vacuum line using standard Schlenck techniques, a 100 mL three-neck round bottom flask was charged with a stir bar, benzene (30 mL), and *R-(-)*-carvone (1.35 g, 9 mmol, 0.3 M). This was stirred vigorously while *tris*(triphenylphosphine rhodium (I) chloride (0.252 g, 3 mol%) was added against an argon flow. This solution was thoroughly evacuated and degassed, before H_2 (1 atm) was added. The solution was heated to 40 °C. Once at temperature the solution was circulated through the NMReady at 1.2 mL/min for 2 hours, with a ^{1}H NMR spectrum (59.96 MHz, 16 scans, 1.1 min) acquired every 5 minutes. The stacked plot is shown in figure 2.

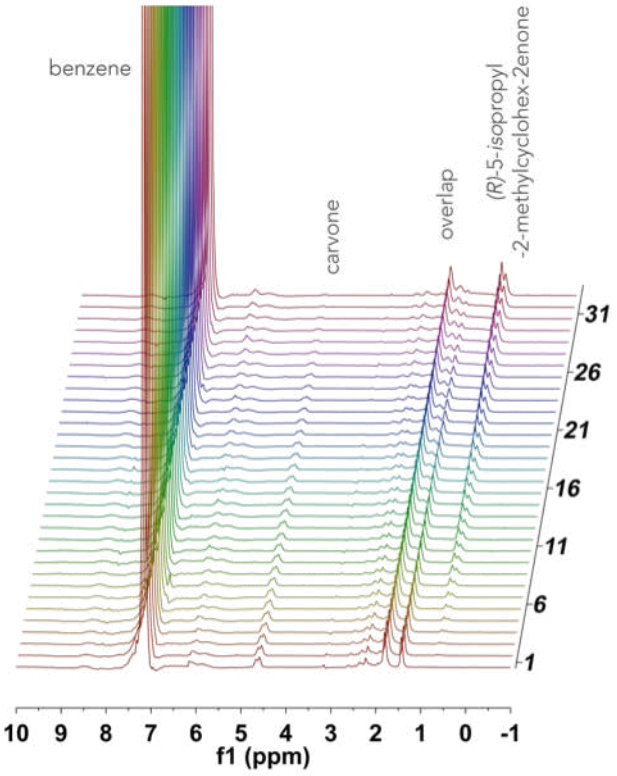


Figure 2. Stacked ^{1}H NMR spectra acquired over 2 hours for the hydrogenation of *R-(-)*-carvone.

The benzene solvent peak at 7.16 ppm dominates the spectrum, and the ^{1}H NMR spectra of the product and reactant are not completely resolved at 60 MHz. Due to the hindered ring flipping in the cyclohexene moiety, there are a number of diastereotopic protons that appear in the 1.5-2.5 ppm range. To quantify this reaction, we look for the well-resolved resonances: the terminal $=CH_2$ vinyl resonance at 5.76 ppm which disappears as *R-(-)*-carvone (figure 3a) is consumed and replaced by a doublet of the newly formed *iso*-propyl functionality (0.63 ppm) of 5-isopropyl-2-methylcyclo-hex-2-enone (figure 3b). The speciation plot is linear, suggesting saturation pseudo-zero order kinetics with this catalyst loading (figure 3c).

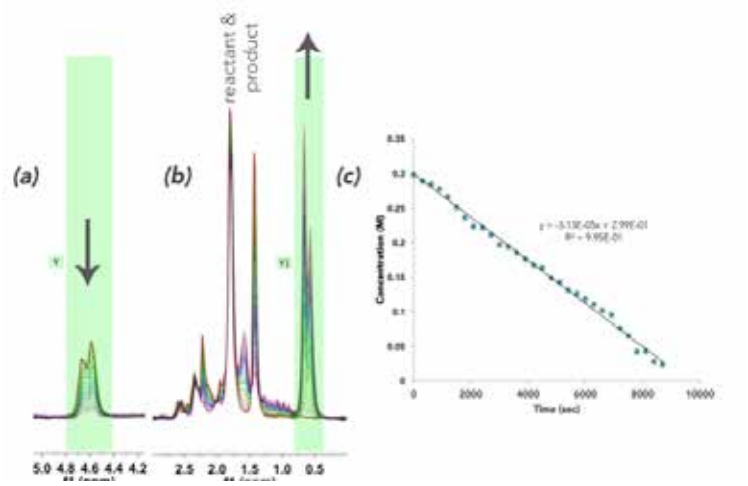
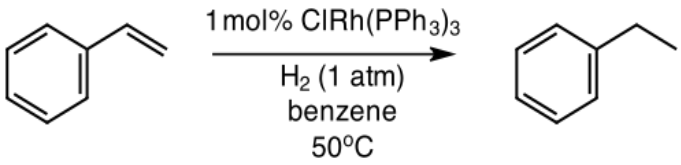


Figure 3. Superimposed spectra showing reaction progress by **(a)** *R-(-)*-carvone vinyl $=CH_2$ consumption; and **(b)** 5-isopropyl-2-methylcyclo-hex-2-enone *iso*-propyl methyl production; **(c)** Mnova time plot showing the change in the vinyl resonance integration over time.

To further examine the effects of dynamic range, we also explored styrene as a substrate under similar oxygen-free Wilkinson conditions (scheme 2). Styrene was chosen because the vinyl groups resonate far enough to the strong benzene signal (7.16 ppm) that it is possible to monitor their disappearance as the reaction progresses. This is illustrated in figure 4 showing a stacked plot of styrene, ethylbenzene and benzene in d_6-benzene.



Scheme 2. Reaction schematic for sytrene hydrogenation with $[ClRh(PPh_3)_3]$ to afford ethyl benzene.

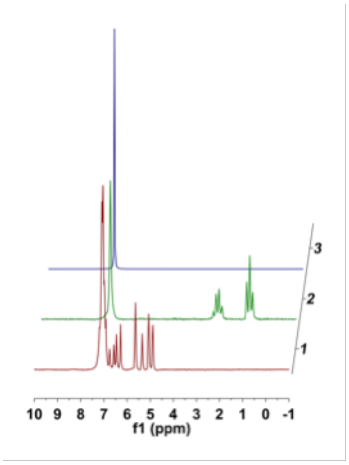


Figure 4. Illustrative ^{1}H NMR 8 scan spectra (40 sec) 5 v/v% in d_6-benzene showing proximity of styrene to solvent peak, and the vinyl styrene peak position relative to the hydrogenated ethyl group.

Styrene (1.25 g, 12 mmol, 0.4 M) was added to benzene (30 mL) in a three-neck round bottom flask. The solution was degassed and put under atmospheric hydrogen pressure before *tris*(triphenylphosphine) rhodium(I) chloride (0.222 g, 2 mol%) was added against positive pressure. The reaction was heated to 50 °C. Once at temperature, the solution was circulated through the NMReady at 2.2 mL/min for 2.5 hours, with a ^{1}H NMR spectrum (59.96 MHz, 8 scans, 32 sec) acquired every 5 minutes. The stacked plot is shown in figure 5.

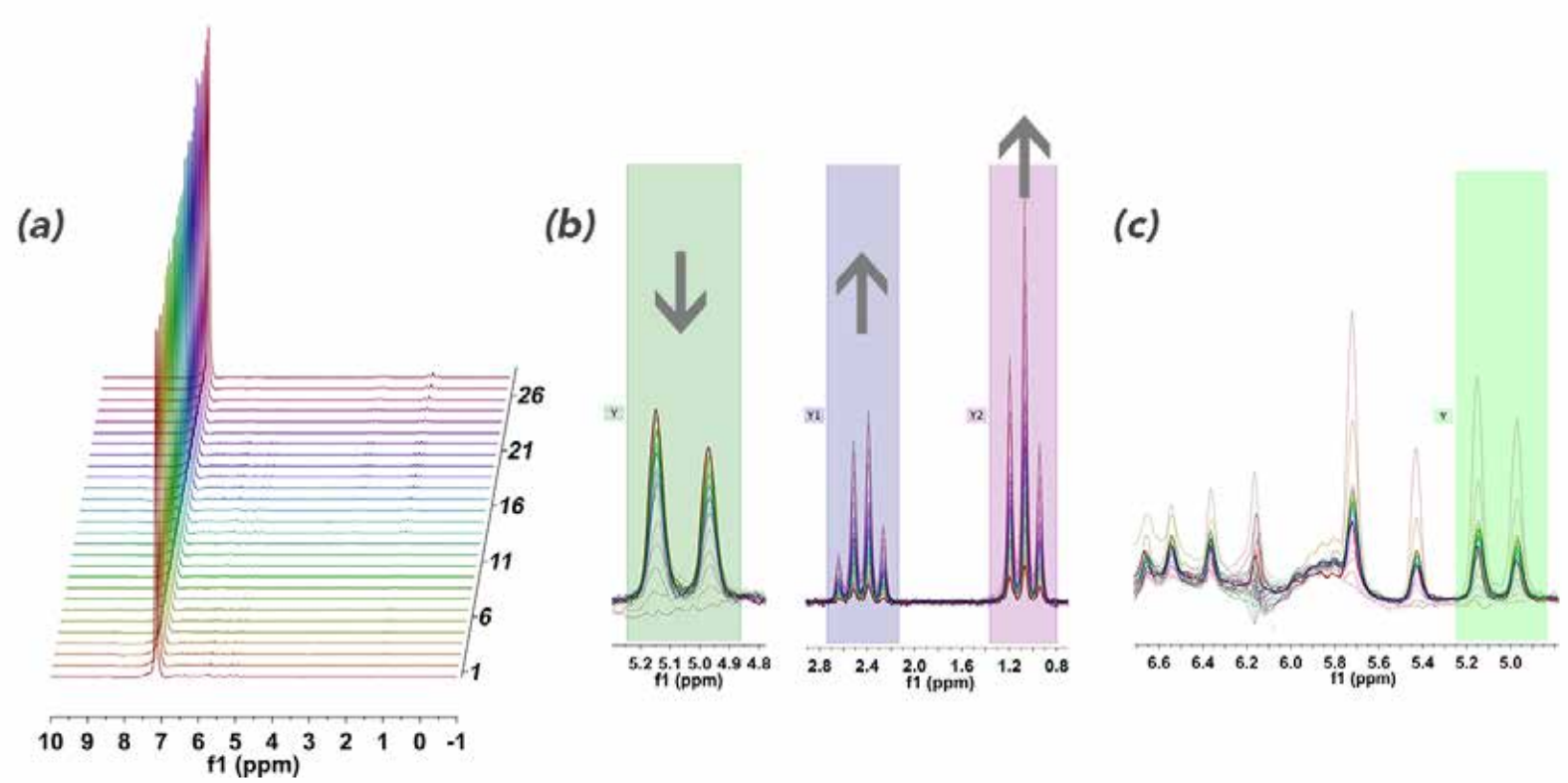


Figure 5. (a) Stacked ^{1}H NMR plot of styrene reaction monitoring in benzene; **(b)** zoomed in regions of 5.0 ppm showing consumption of styrene and corresponding emergence of the ethyl group at 0.5 - 3.0 ppm; **(c)** zoomed in of styrene vinyl region to show baseline distortion from strong benzene resonances.

Despite some distortions near the strong benzene peak that limit the accuracy of the downfield integrals (figure 5c), we can easily extract the necessary information as we move further up-field.

Conclusions

In conclusion, we have used the flow cell to successfully monitor the extent of hydrogenation reactions, maintaining a sealed loop and without the addition of deuterated solvents. If you are interested in self-optimization of fine chemical synthesis using ^{19}F NMR,[4] interested in neat solutions,[6] or would like additional information, please don't hesitate to contact at us.

References

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www.nanalysis.com/nmready-blog/2017/3/28/process-nmr-future-key-elements-in-the-world-of-process-analytical-technology-pat

"Continuous-flow synthesis of fluorine-containing fine chemicals with integrated benchtop NMR analysis" *React. Chem. Eng.* 2017, *ASAP*

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