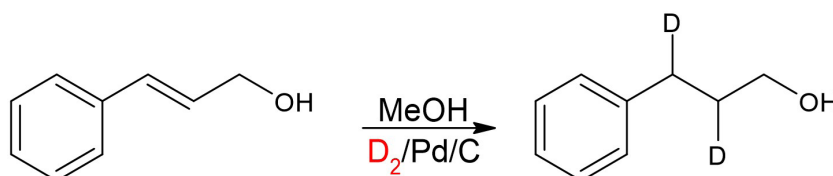# Monitoring the deuteration of cinnamyl alcohol in a flow reactor with a Spinsolve Benchtop NMR

Introduction

In previous blog posts, we have reported on the potential of using a Spinsolve benchtop NMR spectrometer to monitor on-line different hydrogenations conducted on an H-Cube® Pro flow reactor. here. As a follow-up, in this application note, we demonstrate how straightforward it is to perform deuteration reactions employing the H-Cube Pro® flow reactor. This can be achieved by simply replacing the water used to produce H_2 (electrolysis) with heavy water. In this application note, we connected a Spinsolve 80 MHz ULTRA benchtop NMR spectrometer from Magritek at the outlet of an H-Cube® Pro flow reactor from ThalesNano©. The Spinsolve ULTRA model allowed us to capture high-resolution spectra of the different products even though they are dissolved in protonated solvents. The H-Cube® Pro offers the flexibility to optimize a reaction in flow, allowing adjustments to temperature, pressure, and hydrogen amount, while also efficiently reducing catalyst loading. In our previous study, we optimized the reaction conditions for the hydrogenation of the double bond of cinnamyl alcohol. In this work, we replaced the water within the tank with heavy water. Consequently, we aimed to illustrate that an optimization of the deuteration of the double bond can be simply achieved through the combination of a Spinsolve benchtop NMR spectrometer and an H-Cube® Pro.
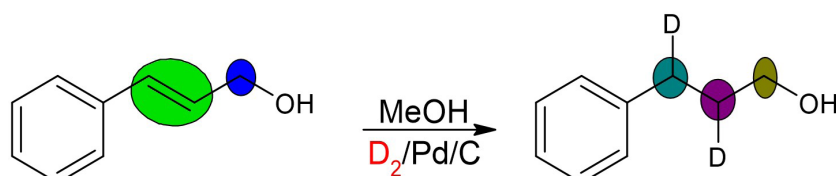

Scheme 1: Deuteration of the double bond of Cinnamyl alcohol.

Experimental Setup

For continuous flow monitoring, we employed the Reaction Monitoring Kit 2 (RMK2) set up on a Spinsolve Ultra 80 MHz Multi-X Benchtop NMR spectrometer. This kit features a glass flow cell positioned from top to bottom in the bore of the spectrometer, allowing the reaction mixture to pass through the magnet in continuous flow. Within the software, we operated in continuous flow mode using a ^{1}H-NMR protocol with WET solvent suppression. In this study, the output of the H-Cube® Pro was connected to a Zaiput "SEP-10" gas-liquid phase separator to separate bubbles from the D_2 gas remaining in the reaction mixture. Subsequently, the output flowed directly into the flow cell from bottom to top. The initial material consisted of a solution of Cinnamyl alcohol in methanol at a concentration of 0.5 Molar (11.751 g / 87.58 mmol in 200 ml). The reactor was equipped with a 10% Pd/C cartridge from ThalesNano©. The reaction mixture was monitored every 1-3 minutes by acquiring a 1D ^{1}H WET NMR sequence with 2 scans and a 10 second repetition time. The WET sequence was configured to suppress the two methanol signals at 3.3 ppm and 4.9 ppm, respectively. The ^{1}H signal was acquired in the presence of carbon decoupling sequence to suppress the ^{13}C satellites from the organic solvent.

Results

To effectively measure a reaction carried out in a protonated solvent, the performance of the solvent suppression method is crucial. This performance relies on the high homogeneity of the magnet, resulting in very narrow line widths. With the WET solvent suppression scheme, the solvent peaks of the protonated solvent, methanol, in this case, were well-separated from the starting material and product signals. This separation is essential to prevent the signal overlap that would occur without suppression. A good example is the signal of the CH_2 protons of the product, adjacent to the hydroxy group (highlighted in olive green in Scheme 2 and Fig. 1). Without effective solvent suppression, this signal would overlap with the methanol peak.

Scheme 2: Deuteration of the double bond of Cinnamyl alcohol.

To facilitate the interpretation of the spectra, we assigned colors to both the signals and the corresponding protons in the structure. The green-marked protons of the double bond in the starting material exhibit a multiplet around 6.5 ppm. This signal disappears upon successful deuteration, giving rise to two new signals at 1.7 ppm and 2.6 ppm, which are marked in purple and turquoise. The signal of the blue CH_2 in the starting material -direct neighbors of the hydroxy group- appears as a doublet at 4.1 ppm. This signal shifts to 3.5 ppm upon conversion of the starting material into the product, where it is marked in dark green. It maintains its doublet nature since there is no new proton neighbor after deuteration—only the same proton as before and a new deuterium. For comparison, Fig. 1 also shows the spectrum of the hydrogenated product, where a triplet is observed for the dark green marked signal also at 3.5 ppm. Here the group gets another proton as a direct neighbor and caused of this it results in a triplet. The signal of the CH marked in turquoise at 2.6 ppm appears as a doublet for the deuterated product instead of the doublet of doublets observed after the hydration. The differences between the product after hydration of the cinnamyl alcohol and after deuteration of the cinnamyl alcohol are presented in Fig. 1.
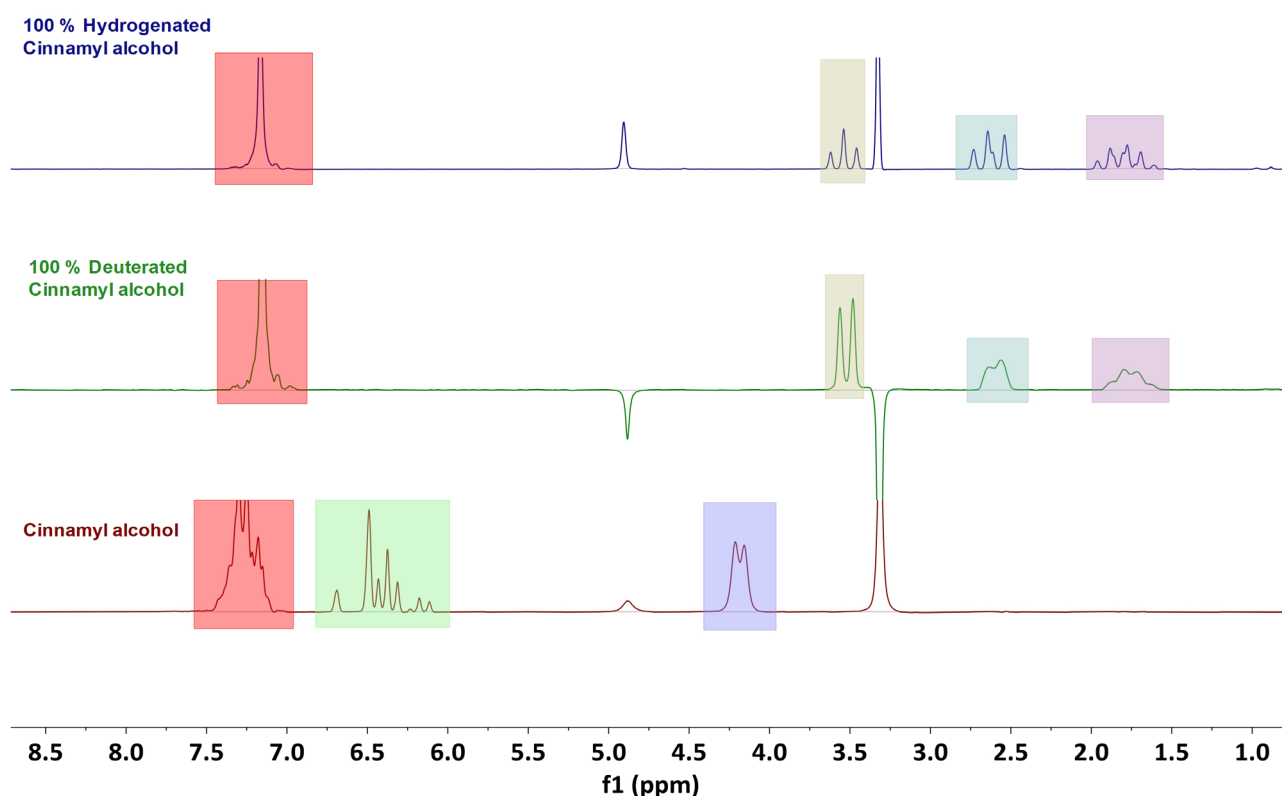
Figure 1: Spectra of the starting material (bottom) deuterated cinnamyl alcohol (center) and hydrogenated cinnamyl alcohol (top).
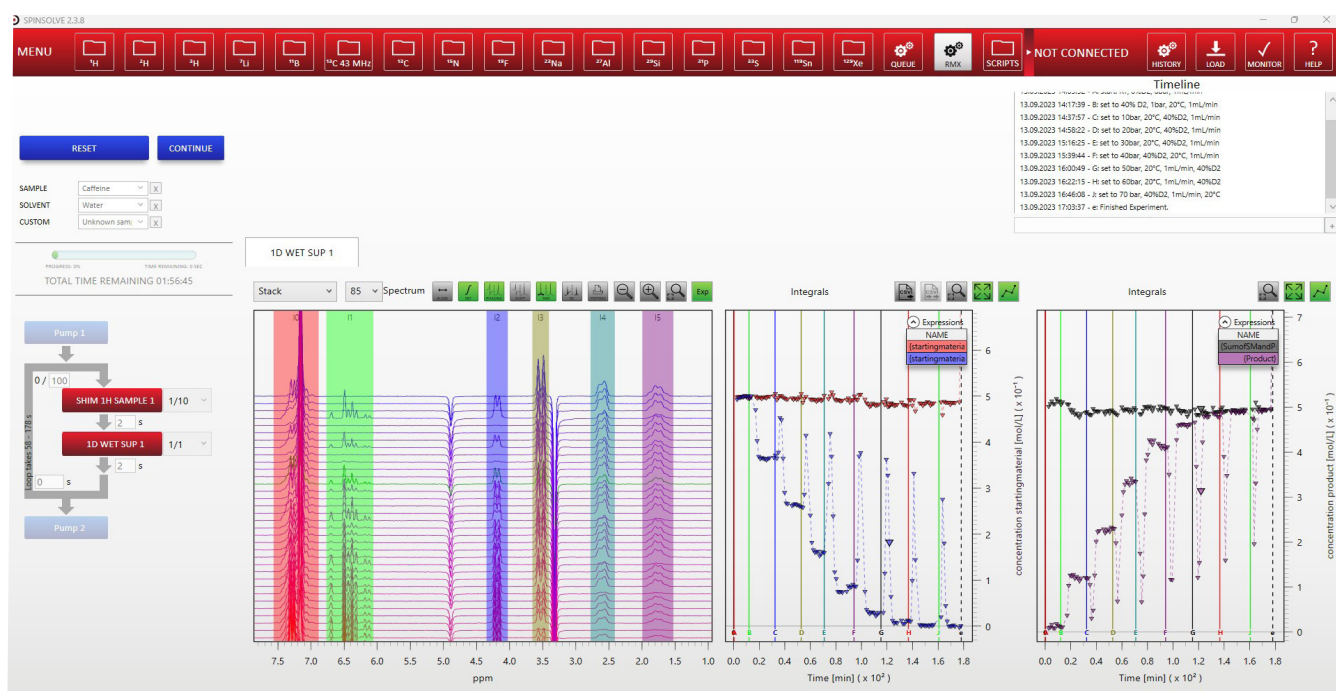
Figure 2: Snapshot out of the RMX Software module monitoring the deuteration of Cinnamyl alcohol.

Figure 2 displays a screenshot from our Spinsolve software following the full reaction experiment. On the left side, you can observe the loop defined to monitor the reaction in a continuous loop. A WET SUP experiment is conducted after every loop, and a "Shim on Sample" is performed every ten experiments to keep optimum shimming conditions for the best solvent suppression quality. The spectra collected during the reaction are shown in stack mode in the center, where the integration regions can also be identified. The plots on the right side (shown in more detail in Fig. 3) depict the concentrations of the starting material and the product calculated from the values of the integral regions. The blue curve in Fig. 3a corresponds to the concentration of the starting material obtained from the integral of the signal of the protons marked in blue and green in Scheme 2. The red curve reports the integral of the region at 7.25 ppm, which contains all the aromatic protons from both the starting material and the product. The integral of this region is expected to remain constant throughout the entire conversion, as the decrease in the concentration of the starting material leads to an increase in the concentration of the product (no intermediates are observed). Figure 3b shows the concentration of the product calculated using the integrals of the purple, turquoise, and dark green regions. All three belong to the product and can be averaged for better accuracy. The black curve in Fig 3b is the sum of the starting material and product, the blue and green signals each correspond to two protons of the starting material, and the dark green, purple and turquoise marked signals, represent the four protons of the product. In summary, they should reflect the mass balance of the reaction and are proof that no byproduct is formed during the deuteration of the double bond.

The stability of the black curve demonstrates the quantitative analytical capability of NMR spectroscopy throughout the entire reaction time. The vertical lines in different colors indicate the times when changes in the reaction conditions were implemented in the flow reactor. These lines are automatically generated every time a note is included in the timeline (top right window in Fig. 2). The jumps in concentration occur immediately after modifying the settings of the reactor (positive on the left graph and negative on the right graph) are observed because the H-Cube® Pro temporarily stops the hydrogen/deuterium flow until the new conditions (temperature or pressure) are reached in the reactor. After reaching the new steady state the reactor automatically resumes the hydrogen/deuterium flow.

The stability observed for the concentration values reported by the Spinsolve once the steady-states are reached speaks for the robustness of the H-Cube® Pro and the accuracy of the Spinsolve to quantify the concentrations of both starting material and product. The fast response of the reactor and the precision in the determination of the conversion facilitates the optimization of the reaction conditions in flow.
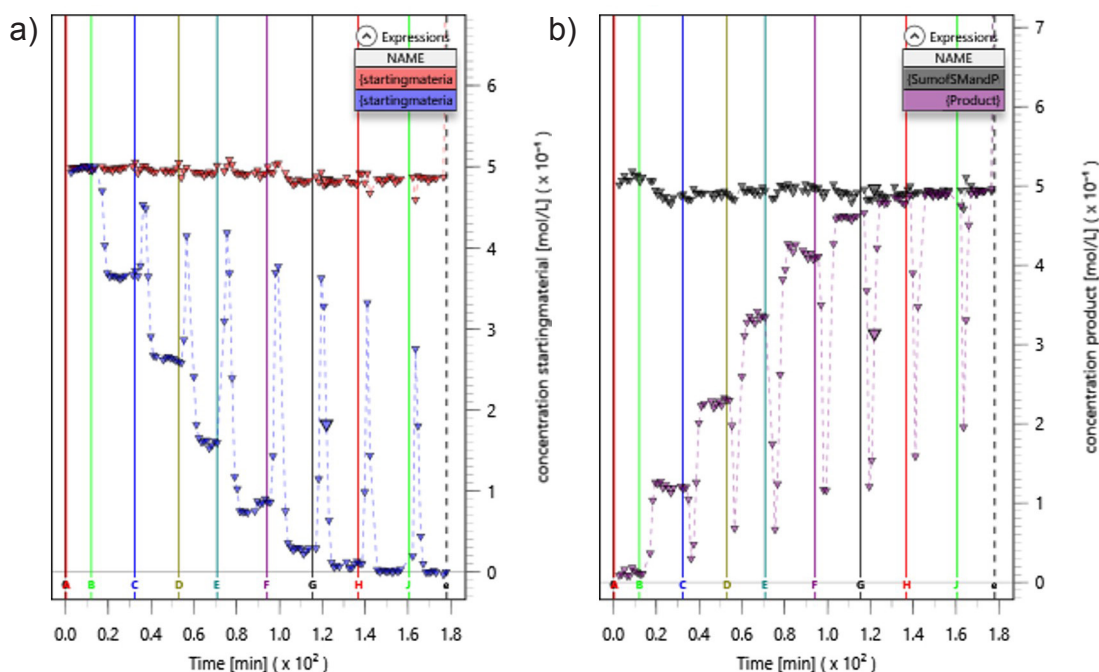
Figure 3: Concentrations of the starting material (a) and product (b) as they are delivered by the Spinsolve RMX software module. The red curve in (a) corresponds to the concentration obtained from the aromatic signals, which can be understood as a mass balance during the reaction. The black curve in (b) is the addition of the starting material and the prouct signals.

Conclusions

This blog post highlights the application of an H-Cube® Pro flow reactor for deuteration reactions, as opposed to hydrogenation, achieved by a simple substitution of water with heavy water in the reservoir at the rear of the H-Cube® Pro instrument. The reaction progression can be accurately monitored using a Spinsolve 80 MHz benchtop NMR, employing the WET solvent suppression experiment, and measuring the ^{1}H nucleus. The post also demonstrates the remarkable stability of both the NMR spectrometer and the reactor, which consistently reveal a steady state for the concentrations of starting material for each reaction condition set in the reactor. The very high homogeneity of the ULTRA magnet used in the Spinsolve makes it possible to achieve highly efficient solvent suppression, which facilitates the integration of the different signals required to monitor the reactions in protonated solvents.