Enhancing Reaction Understanding with Online NMR Reaction Monitoring – Application to Chemical Route Development

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The quantitative nature of nuclear magnetic resonance (NMR) and the fact that it is structurally rich and non-intrusive makes the technique extremely powerful for the identification and characterisation of reaction intermediates, providing insights into the reaction mechanisms and kinetics of chemical reactions.

While many chemical transformations have been analysed in standard NMR tubes over the years, physical and chemical restrictions limit the types of reactions to which this form of NMR reaction monitoring is applicable. The lack of control over parameters such as mixing, temperature and pressure can have significant effects on the rate of a reaction. It has been demonstrated that the use of online reaction monitoring circumvents these limitations[1].

In this work, we demonstrate the complementarity of NMR and infrared (IR) spectroscopy and show the use of NMR to improve the understanding and robustness of the synthesis of an active pharmaceutical ingredient (API) precursor.
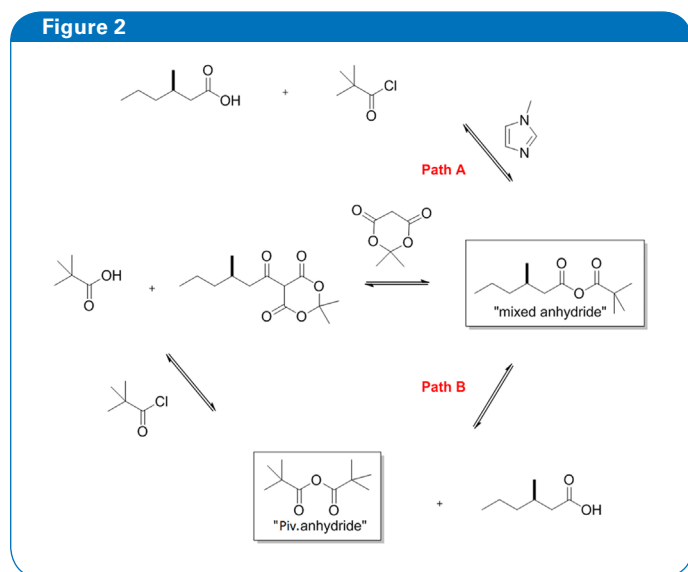
Results and Discussion

The reaction of 3-methylhexanoic acid (I) with Meldrum's acid (II) and pivaloyl chloride (III) to form the Meldrum's acid adduct (IV) is the first step of a telescoped reaction for the formation of an API[2]. The study of this first step by traditional process analytical technology techniques such as LC-UV or GC-MS was not feasible due to the reagents, intermediates and products lacking strong chromophores and readily decomposing with temperature.
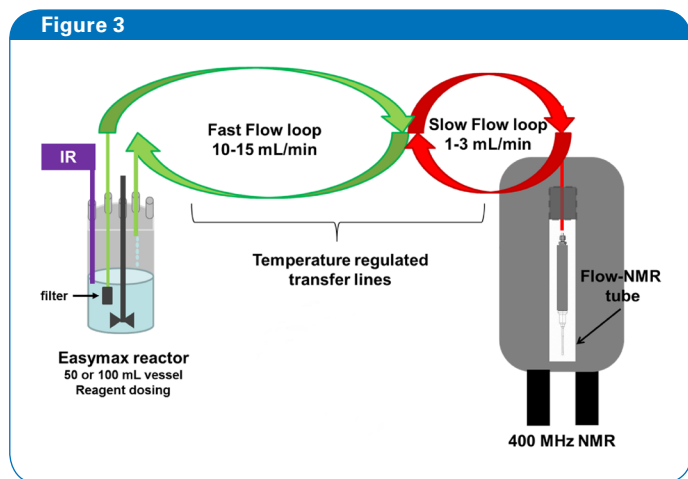
Figure 1
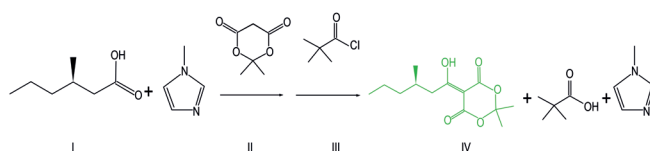
Consequently the course of the reaction was studied by 1D ^{1}H NMR spectroscopy to overcome these limitations. The ^{1}H NMR experiments revealed the presence of an unknown peak, which was in high abundance at the beginning of the reaction. An unknown peak, which first increases and then decreases during the course of the reaction, showing the typical behaviour of an intermediate, was also observed by FT-IR. However, the IR data were not sufficient to fully elucidate the structure of the intermediate, and consequently it could not be quantified. The use of 2D NMR combined with mass spectrometry revealed the unknown peak to be pivalic anhydride.

The presence of the pivalic anhydride intermediate as well as the fact that the reaction was not dose-controlled lead to the conclusion that there must be a second mechanistic pathway, path B, as shown in Figure 2.


Figure 3

Laboratory set up illustrating how the reaction mixture is pumped from the vessel, though temperature regulated transfer lines, to the flow tube[4,5] placed in the coil area of the NMR probe.

Figure 2

Proposed reaction mechanism, showing the mixed anhydride intermediate in pathway A and the pivalic anhydride, explained by mechanistic pathway B.

An analogous reaction with commercially available 3-methylpentanoic acid, in place of 3-methylhexanoic acid, was monitored by online NMR reaction monitoring[3], by placing a reaction vessel next to the NMR spectrometer and flowing the reaction mixture through the magnet as illustrated in Figure 3.

The comparison of inline, online NMR and FT-IR monitoring data (Figures 4 and 5) illustrates the complementarity of these methods. FT-IR measurements were performed *in-situ*, giving high resolution data from the beginning of the reaction. However FT-IR data is not quantitative and insufficient to elucidate the full structure of the main reaction intermediate. Inline (standard tube) NMR gives quantitative data, but lacks information regarding reaction initiation. Online (flow) NMR data was acquired much closer to reaction initiation, and allows the presence of early forming intermediates to be observed, first increasing and then decreasing in parallel with the behavior observed by FT-IR.

Experimental

The reaction was carried out in acetonitrile at 25°C in an EasyMax reaction vessel (Mettler-Toledo). Online reaction monitoring was performed using Bruker InsightMR flow tube[5]. The temperature of the transfer lines were regulated using a Julabo FP-50-HE heating circulator with Syltherm XLT temperature regulation fluid. The flow rate through the system was 3 mL/min regulated by a dual piston pump (Lab Alliance Prep 100, Scientific Systems, Inc. State College, PA, USA), and spectra were acquired on the flowing solution on a Bruker 400 MHz AVANCE III equipped with a BBFO probe or a Bruker 600 MHz AVANCE III NMR spectrometer with a TXO probe. ^{1}H NMR spectra were acquired with four scans, 30° pulse angle and 10 s relaxation delay. Data was analysed using Dynamics Center 2.2.4.

Figure 4
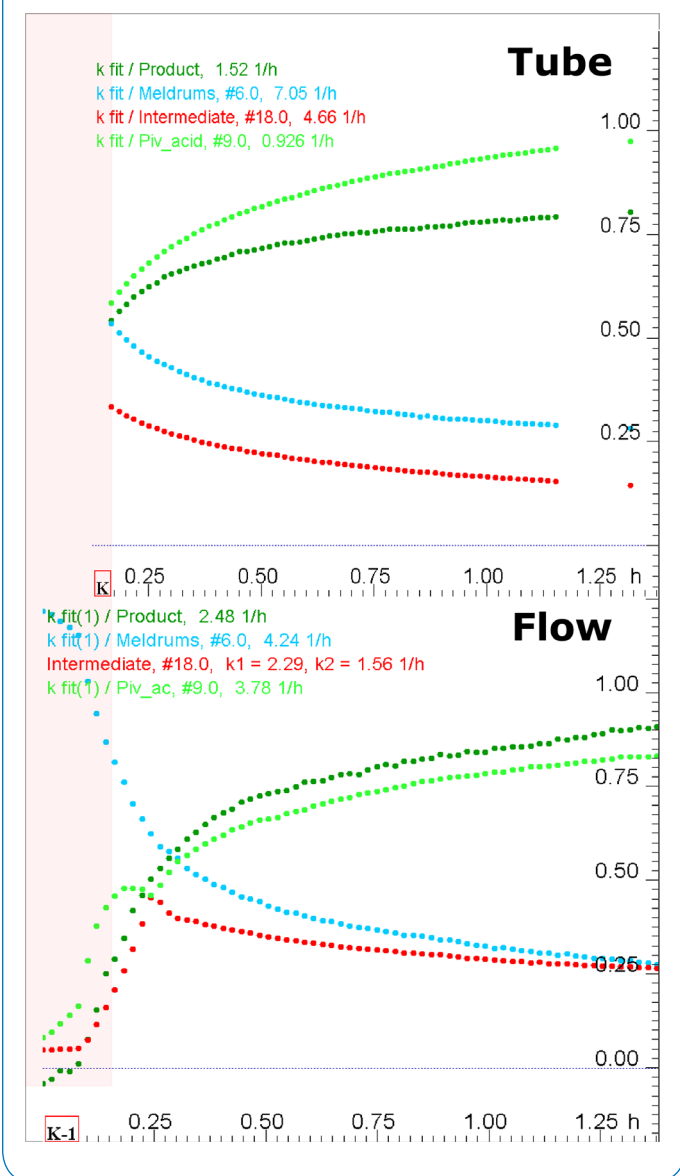
Kinetics profiles (equivalents vs time) obtained from inline (standard NMR tube, top) and online (flow, bottom) NMR measurements.

Conclusions

Online reaction monitoring by NMR enables a chemist to i) obtain kinetic information of chemical processes much closer to reaction initiation, ii) simultaneously monitor the reaction by NMR and other techniques such as MS, IR, UV and pH, iii) gather quantitative information in real-time under laboratory conditions of stirring, temperature and pressure. Studies in static NMR tubes provide good mechanistic and structural information particularly for labile or reactive intermediates. However, caution should be applied when relying on kinetic data acquired from systems lacking adequate mixing[1].

NMR reaction monitoring complements IR spectroscopy in the laboratory, enhancing process understanding and supporting *in-situ* IR process monitoring in pilot and manufacturing plants.

Figure 5
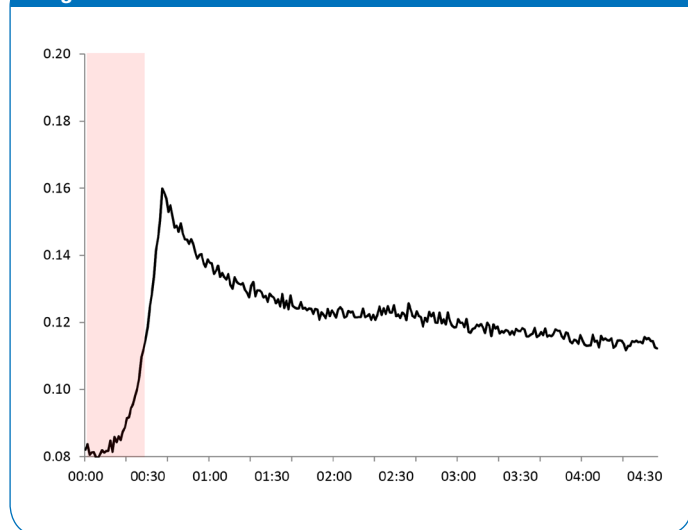
Mid-IR kinetic profile [absorbance at 1810 wn vs time (h)] for the pivalic anhydride intermediate.

References

[1]   Foley D. A., Dunn A. L., Zell M. T., *Magn. Reson. Chem.*, 2015, DOI: 10.1002/mrc4259

[2]   Clegg, I. M., Gordon C. M., Smith D. S., Alzaga R., Codina A.; *Anal. Methods*, 2012, 4, 1498-1506

[3]   Dunn A. L., Codina A., Foley D. A., Marquez B. L., Zell M. T., *Magn. Reson. Chem.*, 2015, DOI: 10.1002/mrc.4317

[4]   Foley D. A., Bez, E., Codina A., Colson K. L., Fey M., Krull R, Piroli D., Zell, M. T., Marquez, B. L., *Anal. Chem.*, 2014, 86, 12008

[5]   www.bruker.com/insightMR, accessed 07 Nov 15

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