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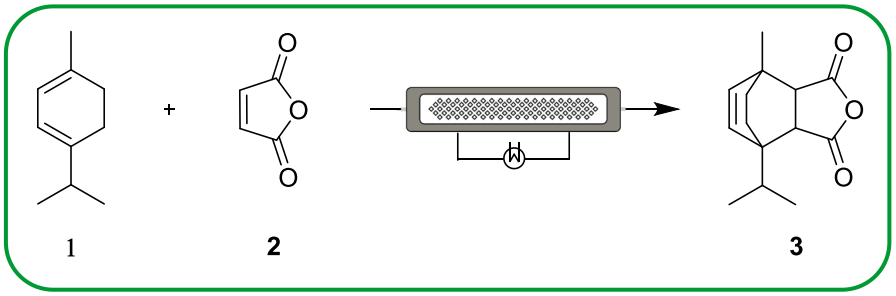
Application Note 3

The use of the HANU reactor in combination with non-invasive inline Raman spectroscopy as tool for a real-time kinetic study of a Diels-Alder reaction

Data courtesy of AJINOMOTO BIO•PHARMA SERVICES, *authored by dr. ir. Nicola Piens and dr. ir. Iris Wauters*

1. ABSTRACT



Scheme 1. Diels-Alder reaction between α-terpinene and maleic anhydride

The Diels-Alder reaction between α-terpinene and maleic anhydride was performed in the HANU™ reactor in order to determine the reaction kinetics through the process window via Raman spectroscopy.

2. BACKGROUND

The HANU™ reactor is equipped with a transparent window covering the entire process channel in order to allow irradiation of the reaction mixture and drive photochemical reactions. As an extra benefit, this window can also be used in non-photochemical applications as inspection window to detect events such as color change, precipitation, *etc.*. In addition, through-window non-invasive process analytical techniques (PAT) can be applied to monitor concentration changes of reaction components at every stage in the process channel.

As forecasted in 2003 by Fletcher *et al.* (*Electrophoresis*, **2003**, 24, 3239-3245), Raman spectroscopy has become a reliable chemical imaging tool in microreactor channels. In particular inline Raman measurements through a fused quartz screen in the reactor channel have been described as a fast and efficient non-invasive method to acquire kinetic data in microreactors (Röder, *Org. Process Res. Dev.*, **2015**, 19, 1286-1292), especially due to the possibility to perform real time monitoring at different locations throughout the channel.

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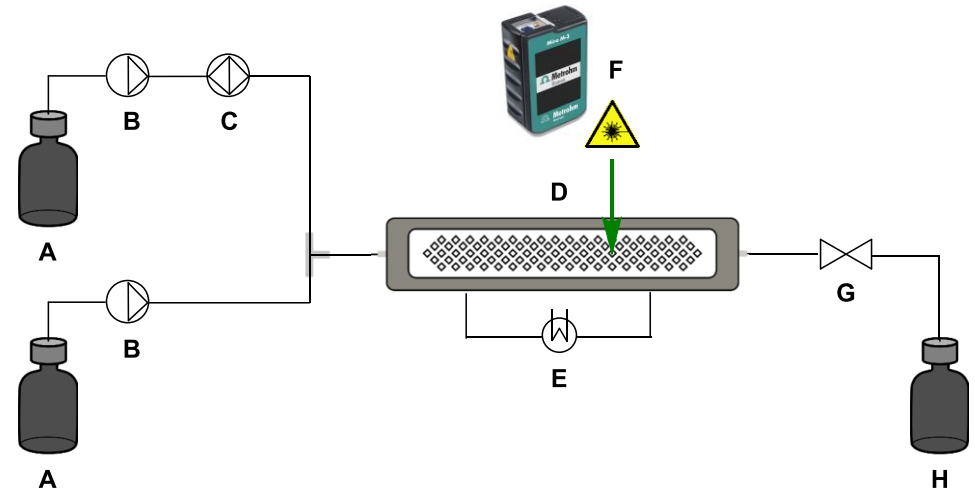
3. EXPERIMENT

3.1 Setup

The setup with the HANU™ reactor is depicted in Scheme 2. The HANU™ reactor assembly (Model: HANU HX 15-316L-CUB) consists of a baseplate that includes cubic static mixing elements with an integrated heat-exchanger to thermostat, a total reactor volume of 15 mL, and is made of stainless steel 316L. The HANU™ reactor was placed in a dedicated PTFE housing to minimize heat loss, and was connected to a Huber circulator. A handheld Metrohm instant Raman analyzer (MIRA M-3 Advanced Package) was used with an XLWD attachment lens (focal length of 18 mm) to measure through the quartz reactor window at different distinct locations along the process channel (Figure 1A).



A. Recipients with starting material
B. Metering pumps
C. Pulsator
D. HANU™ reactor
E. Circulation thermostat
F. Handheld Metrohm instant Raman analyzer
G. Dome-loaded BPR (set to 5 bar)
H. Recipient with crude product

Scheme 2. Setup of the experiment

3.2 Procedure

A first recipient was filled with 250 mL 3.0 M solution of maleic anhydride in THF, a second recipient was filled with 250 mL α-terpinene. The dome-loaded BPR was pressurized to 5 barg. The two flows, respectively pumped equimolar at 0.97 and 0.53 mL/min to obtain a residence time of 10 minutes, were mixed via a T-piece prior to entering the HANU™ reactor. The pulsation frequency was 3 Hz and pulsation amplitude of 0.06 mL (2.1 mm center-to-peak amplitude in the process channel). The reaction was performed at 80 °C. After 30 minutes (3x residence time), Raman spectrums were recorded with the handheld spectrometer through the quartz reactor window at distinct locations along the process channel and a sample of the crude was collected.

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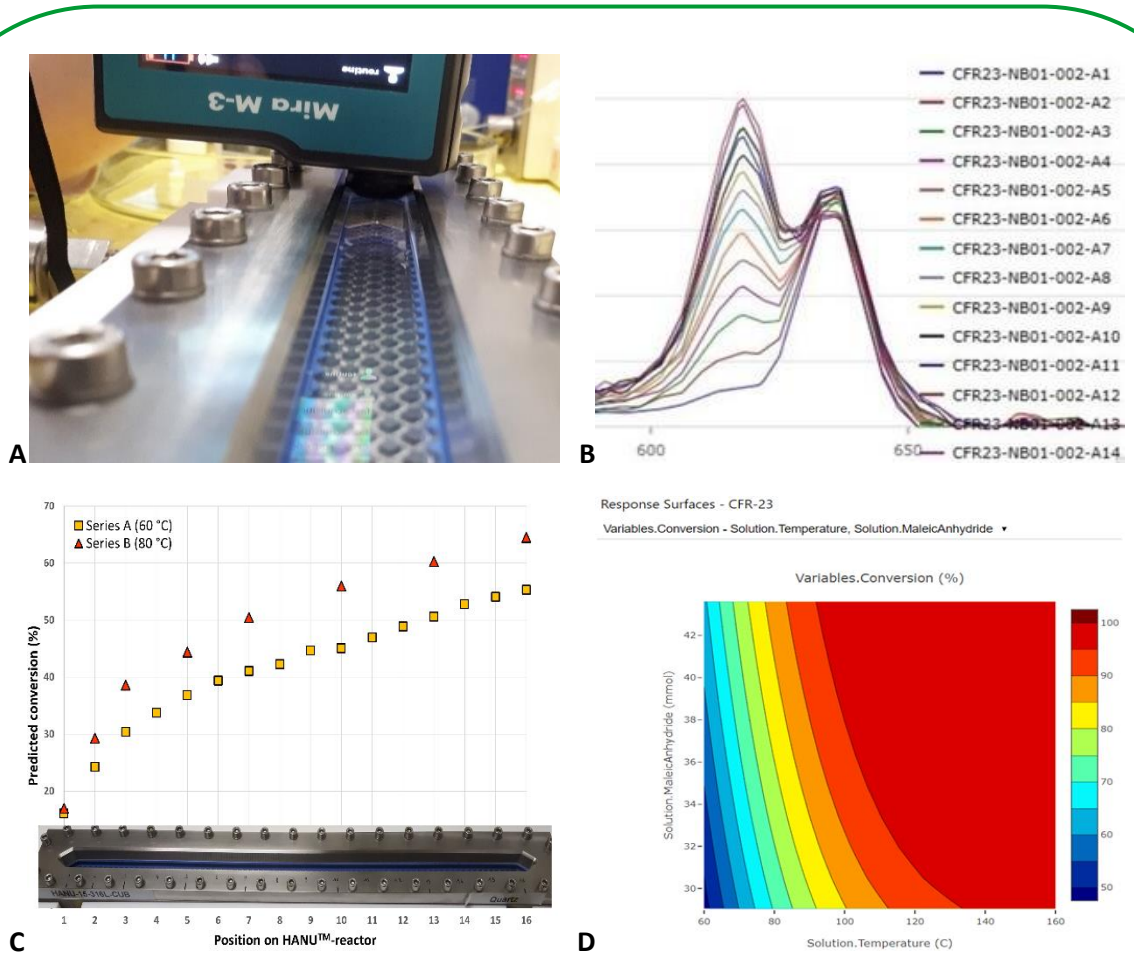
3.3 Results

^{1}H NMR analysis of the crude showed that 65% conversion of α-terpinene had taken place, which showed a good resemblance with a 66% conversion obtained when a 15 mL (1 mm ID) coiled stainless steel tubing was used (at same temperature and residence time) instead of the HANU™ reactor. Subsequently, this procedure was repeated at varying temperatures (18 – 60 °C) and residence times (2 – 4 – 8 – 16 minutes). Based on the Raman spectra and ^{1}H NMR conversions a multivariate model was constructed using Unscrambler software (Camo Analytics). This model was then used to calculate the conversion from the Raman spectra measured at different locations throughout the HANU™ reactor (Figure 1B) and create the kinetic profile of the investigated Diels-Alder reaction (Figure 1C). Finally, DynoChem modeling software (Scale-up Systems) was deployed to fit the kinetic parameters (k and E_a) and easily make *e.g.* contour plots (Figure 1D) for flow process development purposes.



A. MIRA (Metrohm Instant Raman Analyzer) M-3 handheld spectrometer positioned on the HANU™-reactor
B. Increasing characteristic Raman signal of the Diels-Alder adduct in the process channel
C. Predicted reagent conversions on their respective positions in the process channel
D. Contour plot of the reaction in scope created via DynoChem modeling software (Scale-up Systems)

Figure 1. Kinetic elucidation of the Diels-Alder reaction between α-terpinene and maleic anhydride

4. CONCLUSION

In summary, through-window handheld Raman analyses at different locations throughout the HANU™ reactor allows the fast determination of the full kinetic profile of a Diels-Alder reaction at different temperatures, showcasing the potential of the HANU™ reactor to retrieve valuable kinetic information in a real-time and non-invasive manner for accelerated flow process development.

For more detailed information about this application note or the HANU™ reactor in general, please contact Creaflow at info@creaflow.be.