USING AN IR SPECTROMETER FROM METTLER TOLEDO FOR IN-LINE ANALYSIS OF CONTINUOUS FLOW EXPERIMENTS PERFORMED IN THALESNANO'S REACTOR SYSTEMS

INTRODUCTION

The evolution of chemical process design goes hand-in hand with the evolution of analytical instruments. By offering rapid parameter screening, optimization and scalability, continuous flow technologies brought with them a great leap forward in the life of chemists and chemical engineers working in the field of process design and synthesis. The implementation of real-time in-line component analysis is a crucial milestone that makes working with a continuous flow system more streamlined, broadening the horizons for all users.

Infrared (IR) Spectroscopy is one of the most versatile, non-destructive methods for real-time monitoring of chemical products and by-products. Limitations of traditional IR measurements such as the volatility of materials, possible toxicity, sample degradation and contamination can be minimized using in-line real-time analysis.

In this application note we feature the ReactIR™ 702L by Mettler Toledo coupled with ThalesNano's Phoenix Flow Reactor system to highlight key advantages and showcase a study for all chemists looking for a convenient platform for high-pressure, high-temperature continuous flow reactions with in-situ H_2 generation and in-line IR spectroscopic analysis.

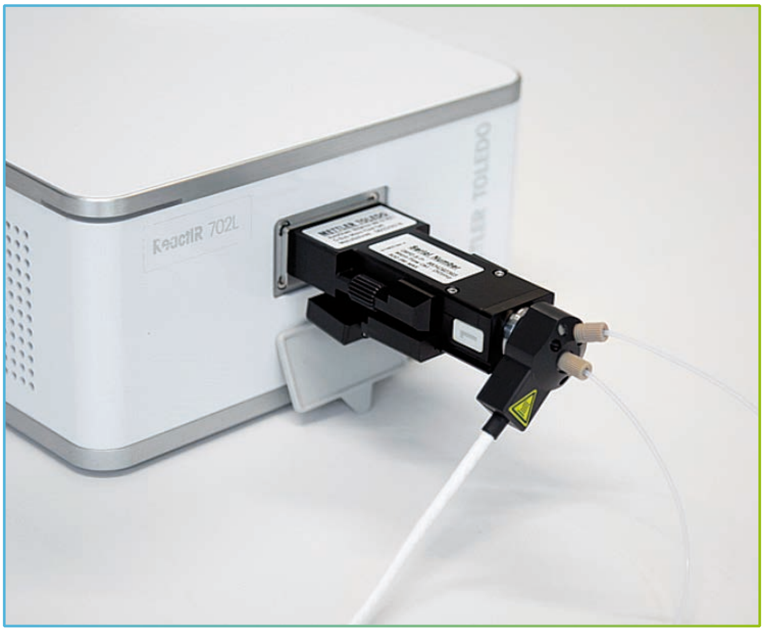
INSTRUMENTATION AND SAFETY CONSIDERATIONS

Capable of reaction temperatures up to 450 °C and pressures up to 200 bar, the Phoenix Flow Reactor allows users to carry out a wide range of homogeneous and heterogeneous catalytic reactions from the mg to the kg/ day scale based on the inserted catalyst column size. As with all ThalesNano instruments, safety is of utmost importance with configurable safety release valves and software features while using the system. Supplying H_2 gas for the reduction experiments, the H-Genie® utilizes patented technology to generate 99.99% purity H_2 gas via *in situ* water electrolysis. Designed with safety and ease of use in mind, this bench-top hydrogen generator provides accurate H_2 dosing up to 1000 NmL/min flow rate and 100 bar pressure while eliminating the risks associated with H_2 cylinders and other forms of hydrogen storage in laboratories. The ThalesNano Gas Module offers further possibilities for gas dosing in a Phoenix Flow Reactor system with a built-in MFC, allowing for the accurate dosing of 13 different gases, including CO_2 and gas mixtures, with flow rates up to 100 Nml/min and pressures up to 100 bar. The Gas Module Plus broadens the parameter scope with up to 1000 Nml/min gas dosing.

The in-line, real time conversion monitoring was carried out by the ReactIR™ 702L supplied by Mettler Toledo. The spectrometer was connected to the end of the reaction line, following the Pressure Module and Zaiput SEP10 phase separator. The ReactIR™ was setup with the 10 mL microflow cell containing a DiComp sensor. The ReactIR™ 702L's solid-state cooling technology allows a small footprint design and negates the need for liquid nitrogen.

These factors combined with the "always on" detector minimize setup time and offer great flexibility leading to optimized workflows and quicker results. The spectrometer can also be configured for batch sampling even in corrosive environments while covering a wide temperature and pressure range. ReactIR™ provides highly specific information on a multitude of crucial reaction parameters such as conversion, initiation and endpoint. The iC IR™ software experience is designed around user friendliness coupled with accurate data acquisition, visualization and processing.

Time resolved IR data can be interpreted through the trends created from 3D surfaces collected during the experiment. Continuous flow hydrogenation experiments are typically carried out at moderately high dilution; however the software's solvent subtraction feature provides a solution to the limitations of detection in many cases. The importance of detection limit concentration screening is also highlighted in the Ley group's work[1].



DISCUSSION AND RESULTS

Demonstration of the solvent subtraction feature in IC IR™

The IC IR™ software's solvent subtraction feature allows users to detect key signals of their reaction that are otherwise masked by the solvent. Measuring the clean solvent's spectrum prior to an experiment, followed by the measurement of the reaction mixture allows the software to provide the user with the solvent-subtracted data.

One example of this is presented on figure 1. The first 3D surface shows the time-resolved IR spectra of 0.05 M nitroindole reaction mixture in methanol. As one can see, this image is dominated by the solvent signal, hindering the analysis of the actual reaction mixture.

The second 3D surface shows the solvent subtracted surface of the same experiment, which revealed the weak signals of the dissolved materials, allowing for their analysis and quantification.

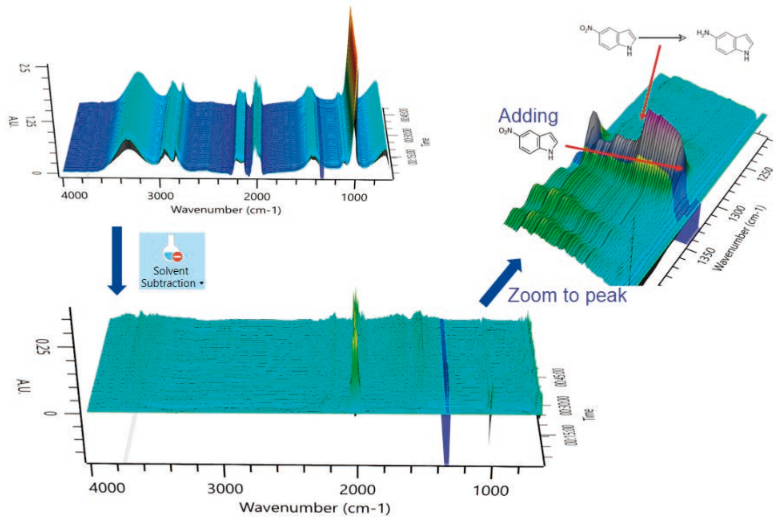


Figure 1: Spectra of 0.05 M Nitroindole solution in methanol before and after solvent subtraction

Following the continuous flow reduction of Nitroquinoline (1) for in situ parameter optimization

The continuous flow hydrogenation of a 0.05 M nitroquinoline solution was carried out using a 70 mm 10% Pd/C CatCart® as catalyst. The schematic representation of the reactor system, as well as the 3D surface measured by the ReactIR™ are depicted on figure 2. The diagram shows the most relevant (strongest) characteristic signals related to the starting material **1** (blue), the aminoquinoline intermediate **2** (red), and product **3** (green). The trends created from the surface plot show that before the introduction of H_2 in the system only the signal of the starting material **1** is present. Following this at 50 °C 10 bar pressure and 90 NmL/min H_2 flowrate, the intermediate (**2**) signal rises and the product **3** can be also seen. After setting up 150 °C, 40 bar and 90 NmL/min a significantly lower concentration of the intermediate **2** can be observed.

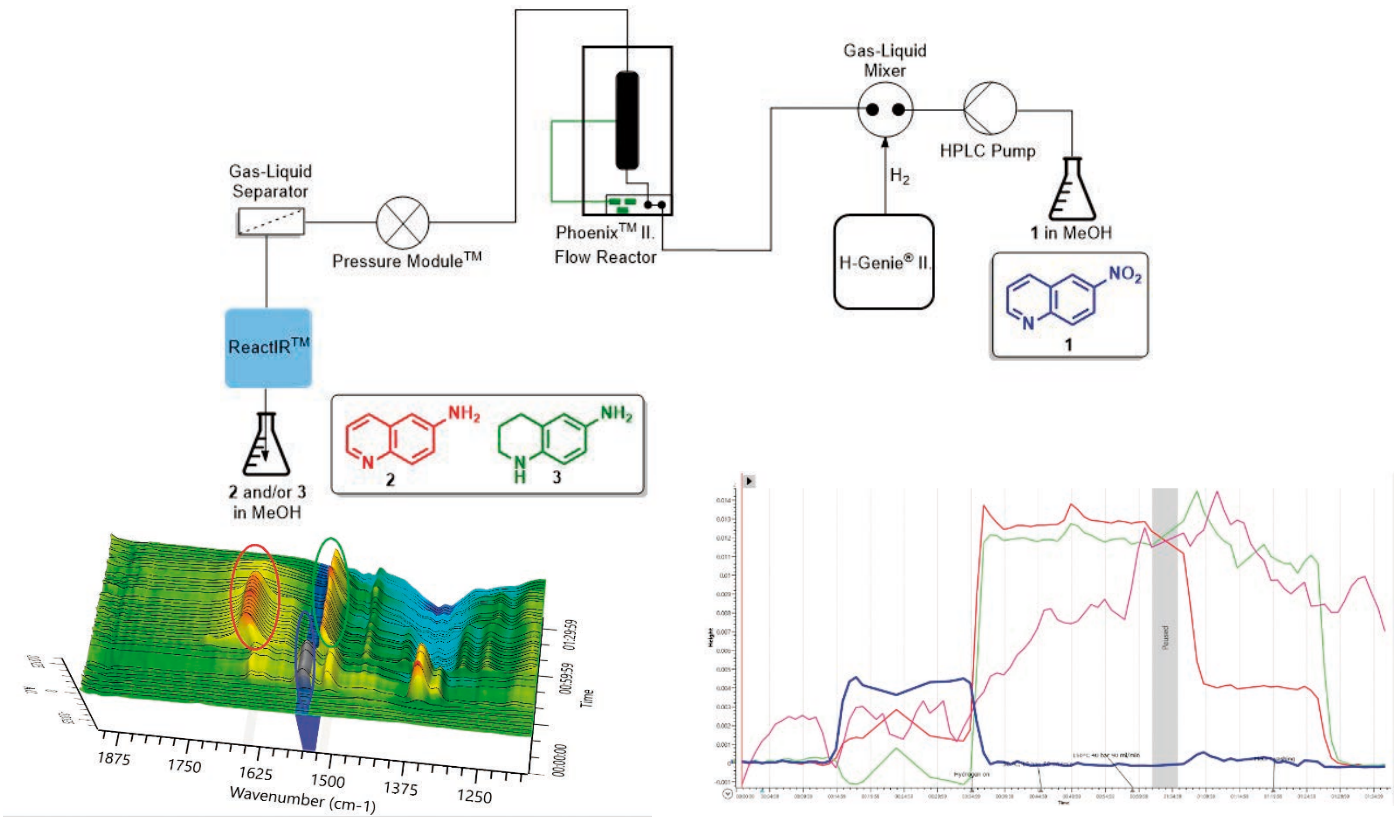
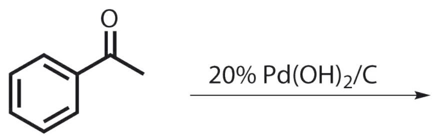


Figure 2: Schematic representation of the system, 3D surface spectra and conversion trends

Utilizing in-line IR measurements during CatCart® quality control

Catalyst cartridge quality control experiments were carried out using the ReacIR™ to verify catalyst activity in real time. A 0.05 M solution of acetophenone (**4**) in MeOH was reduced using a 20% $Pd(OH)_2$/C CatCart® at a given set of experimental parameters traditionally used for our CatCart® QC tests. As depicted on Figure 3, the carbonyl signal in the starting solution disappeared completely once the H_2 reached the CatCart®, revealing 100% conversion, justifying the sufficient activity of the tested CatCart® batch. At approximately 1000 cm^{-1} the signals of product **5** appear, however, since the product is an alcohol, hence its signals coincide with the solvent methanol signals. Even though solvent subtraction allows the user to visualize the appearance of the new product, fitting a trendline to this signal is not recommended for quantification. However, utilizing the in-line IR measurements in this way still provided our CatCart® manufacturing department with useful and quick insight to catalyst performance compared to traditional analytic methods.



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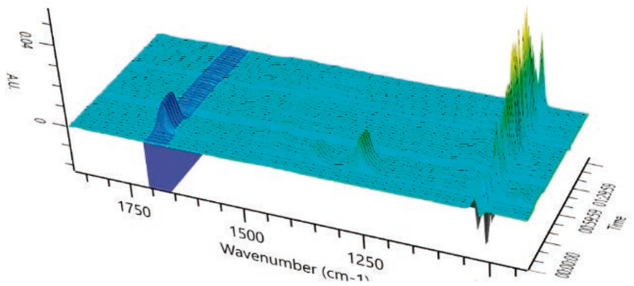

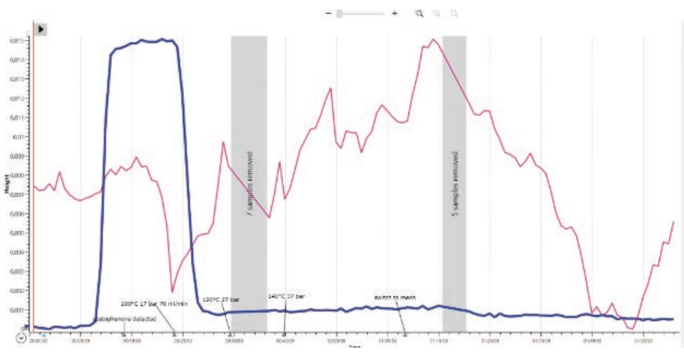

Figure 3: Monitoring the hydrogenation of acetophenone (**4**) for CatCart® QC

SUMMARY AND CONCLUSIONS

The inclusion of real time in-line reaction monitoring is a great advancement towards an already stable and established continuous flow synthetic platform. Mettler Toledo's ReactIR™ 702L and its software, iC IR™ is a highly capable and versatile option for those who would like to take their ThalesNano platforms one step further. The experiments highlighted in this application note are great examples of the many uses of an in-line IR spectrometer for research, production and quality control in flow chemistry.

REFERENCES

[1] Catherine F. Carter, Heiko Lange, Steven V. Ley, Ian R. Baxendale, Brian Wittkamp, Jon G. Goode, and Nigel L. Gaunt: ReactIR Flow Cell: A New Analytical Tool for Continuous Flow Chemical Processing, *Organic Process Research & Development* **2010** 14 (2), 393-404.

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