Enhanced Development and Control of Continuous Processes

A New Dimension for Flow Analysis

What's Happening in your Flow Chemistry?

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The desire to gain major improvements in product quality, yield, synthetic route, cycle time and safety in chemical processes have become key driving factors for chemists and engineers working in the chemical development and manufacturing environment in the pharmaceutical and fine chemical industries. In order to achieve these goals, scientists are actively seeking alternative chemical development methods such as modern continuous flow reactor technologies. These technologies provide the opportunity to address many of these issues as they allow for rapid testing, optimization, and scaling of chemical sequences, many of which are unsafe for batch operations.

One of the most convenient and nondestructive methods for real-time inline monitoring is mid-infrared (IR) spectroscopy. Not only does this technique allow the formation of products and reactive intermediates to be monitored in real time but immediate reaction feedback on the effect of changing a process parameter (flow rate, reaction temperature, stoichiometry etc.) is also possible, which results in an improved understanding and faster optimization of the flow process.

This White Paper will discuss how this approach has been successfully used to monitor product streams and dispersion effects in a continuous flow reactor, and then use that information to successfully perform a multi-step synthesis, where a third reagent stream is stoichiometrically controlled based on the output of the first part of the reaction.

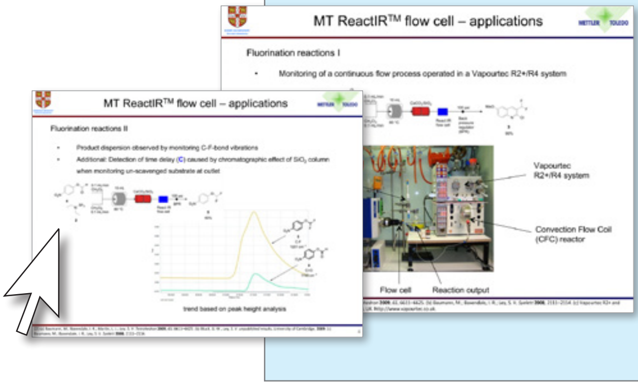
METTLER TOLEDO

Introduction

The fast optimization of a chemical reaction using a flow reactor is not necessarily a simple task. It is essentially a process of trial and error as conditions and flow rates are altered until a steady state is found, producing the desired product at the optimum yield. Use of traditional offline sampling technologies is a little bit like working 'blind'. A change is made, a sample collected, and an analysis performed. This all takes time and leads to delays in the optimization process as there is no way to decipher the impact a change will have on the system until after the analysis has been performed. A much more desirable solution would be to have an analytical instrument which provides instant feedback to any changes made in the system, making the optimization of the system both easier and significantly quicker. This approach would allow for the real time optimization and synchronized control of multi-step reactions.

Webinar Spotlight

The Application of the ReactIR™ Flow Cell to Continuous Processing Technology



MT ReactIR™ flow cell – applications

Fluorination reactions I

- Monitoring of a continuous flow process operated in a Vapourtec R2+/R4 system

MT ReactIR™ flow cell – applications

Fluorination reactions II

- Product dispersion observed by monitoring C-F-bond vibrations
- Additional: Detection of time delay (C) caused by chromatographic effect of SiO_2 column when monitoring un-scavenged substrate at outlet

trend based on peak height analysis

Professor Steven V. Ley, BP (1702) Professor of Chemistry, University of Cambridge, presents ReactIR™ DS Micro Flow Cell as a convenient inline analytical tool for continuous flow chemistry processing. Professor Ley demonstrates the technology in a wide range of applications including Curtius rearrangement using the Vapourtec R2+/R4, Butane-2,3-diacetal protection using the Uniqsis FlowSyn, Hydrogenation using the H-Cube Midi™ and Marshall reaction using Future Chemistry microfluidic devices.

To view this **FREE** online seminar series visit
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Monitoring Product Streams and their Dispersion

C.F. Carter, H. Lange, I.P. Baxendale, S.V. Ley, J. Goode, N. Gaunt, B. Wittkamp,
Org. Proc. Res. Dev., 2010, 14, 393-404.

Baumann, M.; Baxendale, I. R.; Martin, L. J.; Ley, S. V. Tetrahedron 2009, 65,
6611–6625.

The Vapourtec R2+/R4 flow chemistry system in combination with solid-supported reagents and scavengers was used to perform fluorination reactions in a continuous mode. Using an inline analysis method, the effect of the solid supported reagents and scavengers on the product stream can be investigated (see Figure 1). The two fluorination reactions shown in Figures 2 and 3 were performed and the product stream analyzed using inline IR spectroscopy.

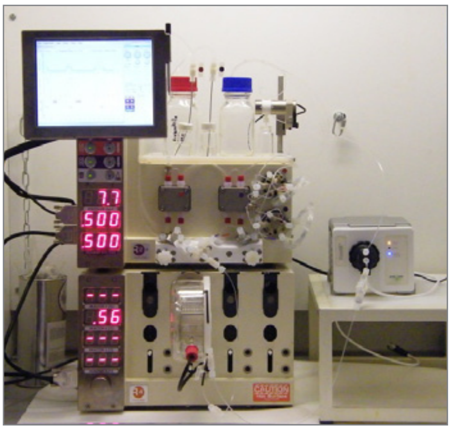

Figure 1. The Vapourtec R2+/R4 connected to METTLER TOLEDO FlowIR™

The intensity of IR energy absorbed at a particular wavelength is defined by Beer's law to be proportional to concentration. Therefore, it is possible, using an inline IR instrument, to track the relative concentration of individual components. This really becomes a useful measurement to make if it is possible to analyze data and report the result in real time, one of the main challenges of the optimization of these types of systems.

Figure 2 shows the relative concentration profiles of the reactants and products during the reaction. The graph clearly shows the formation of the product and confirms that the silica gel column is effective as a scavenger for the unreacted aldehyde (as none is detected with the reaction products). Interestingly, the expected time for the product to pass through the cell is 20min (A), which is calculated from the volume of material injected and the flow rate at which it is being pumped (4mL of material pumped at 0.2mL/min would take 20 minutes to pass through completely). Therefore, it would not be expected to detect any product after these 20 minutes. However, as a result of dispersion, diffusion, and chromatographic effects caused by the reaction setup, it can clearly be seen that it takes an additional 16 minutes (B) for all of the product to appear.

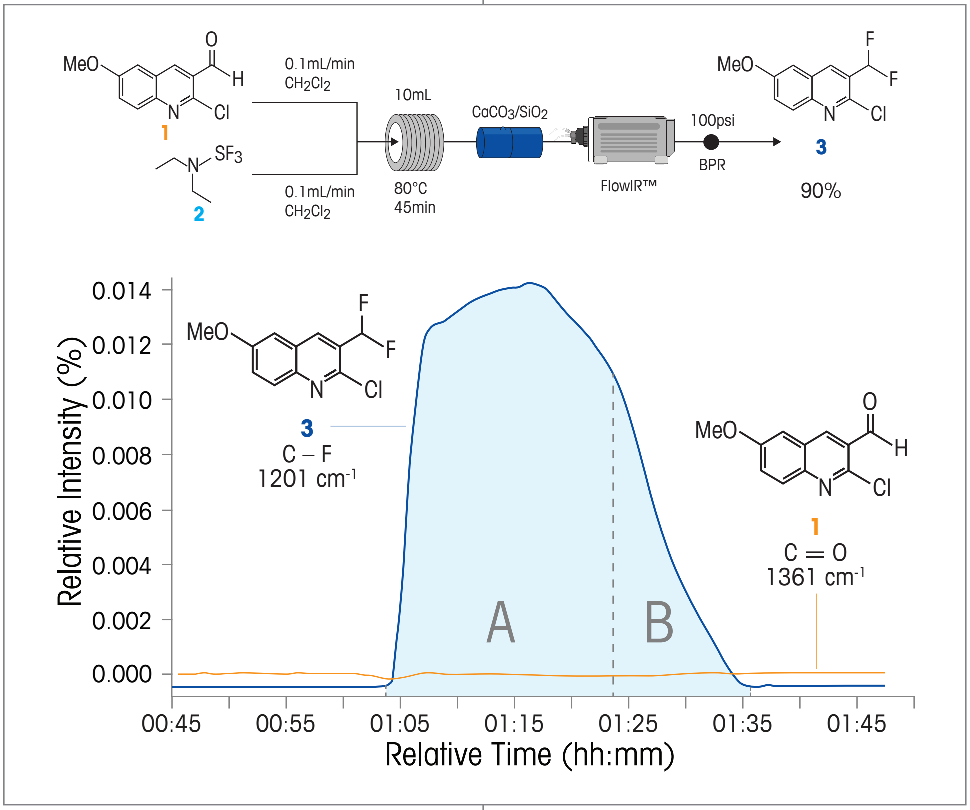

Figure 2. Reaction scheme for the fluorination of an aldehyde in flow using DAST along with FlowIR™ concentration profiles showing the formation of the product (blue) and the complete scavenging of the aldehyde (orange) by the silica gel column. The dispersion of the plug is also clearly observed.

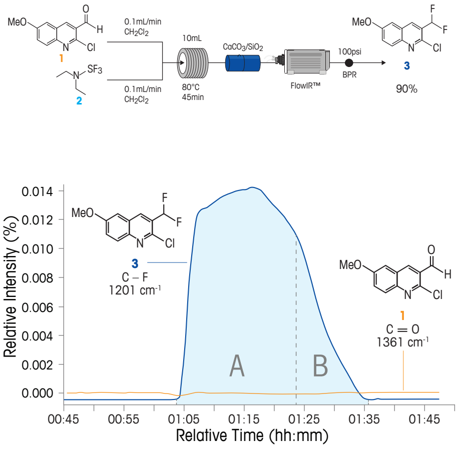

Figure 2.

In the reaction shown in Figure 3 the formation of the product can clearly be seen. In this case however it is observed that there is a time delay between the appearance of the product and the remaining unreacted ester (the ester in this case was not expected to be scavenged by the cleanup column). This time delay of five minutes represents the chromatographic effect of having the silica gel column inline.

This type of example demonstrates how an inline reaction monitoring strategy using inline IR spectroscopy can help scientists gain understanding of the formation of reaction products and the presence of unreacted materials in the product stream in real time. This information can clearly be used to determine the presence of starting materials in the product stream, when the product has formed, and could also be used to determine when steady state reaction conditions have been reached, so could be used as a real time trigger for fraction collection for example.

This technology also provides immediate understanding of the effectiveness of the scavenging column, as well as demonstrating the dispersion effect that inline columns have on the shape and length of the reaction plug which can be quite significant. Using this information it should be possible, for example, to extend the length of the silica gel column inline to achieve a separation of the product from the starting material by means of chromatography; i.e. performing flash column chromatography inline.

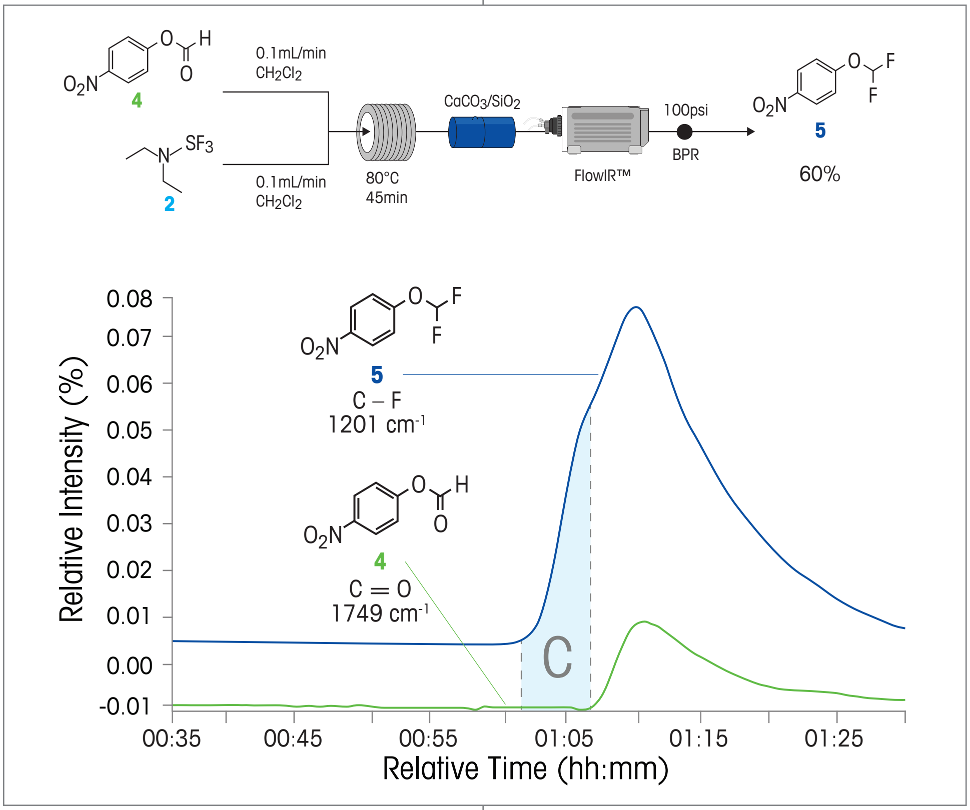

Figure 3. Reaction scheme for the fluorination of an ester using DAST along with FlowIR™ concentration profiles showing the formation of the product (blue) and the time delay between the appearance of the product and the remaining unreacted ester. This delay represents the chromatographic effect of having the silica gel column inline.

Multistep Synthesis – Controlled Addition of a 3rd Stream

H. Lange, C. F. Carter, M. D. Hopkin, A. Burke, J. G. Goode, I. R. Baxendale and S. V. Ley, Chemical Science 2011, 765-769.

Zizheng Qian, Ian R. Baxendale, and Steven V. Ley Chem. Eur. J. 2010, 16, 12342 – 12348.

The unavoidable dispersion of a reaction "plug", combined with the difficulty of making a controlled addition of exact stoichiometries of reagents to a product stream, presents significant issues when performing multi-step sequences in flow. Poor control is wasteful on small scale and requires additional purification. A more elegant solution to this "3rd-stream problem" would be to control the flow rate of the third pump in real-time by using the measured concentration of the initial product. This can be achieved by tracking a product-specific band measured *in situ* by FlowIR™ (Figure 4).

This approach was demonstrated using two simple reagent streams (4-chlorobenzophenone (1) and 3-methyl-4-nitroanisole (2)). The peak height detected for the initial product plug of compound (1) (Figure 4a) was automatically converted in real time to a flow rate for a third pump, which dispensed a solution of compound (2). A second measurement point positioned inline at the outlet of the mixing chip, was used to measure the concentration profiles of both reagents using bands specific to each one (Figure 5).

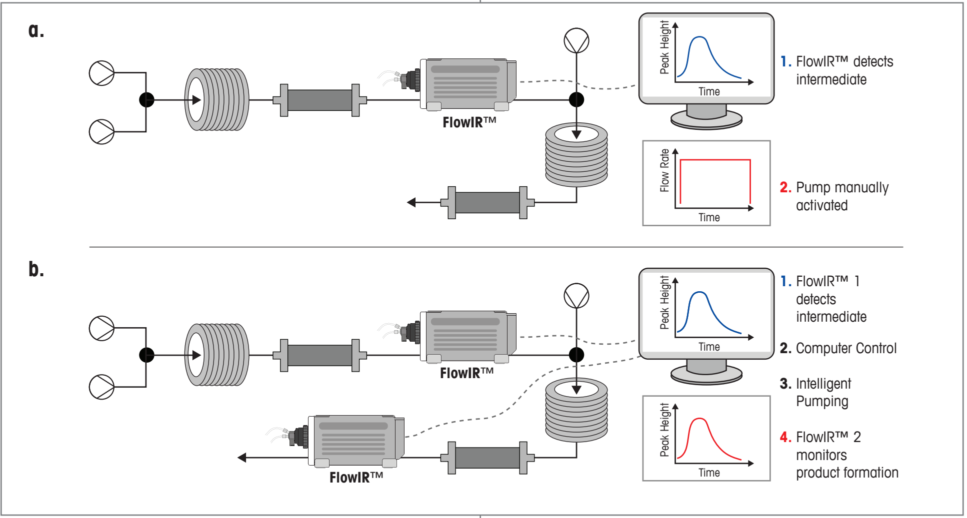

Figure 4. (a) Current situation - use the IR to generate a dispersion curve of the intermediate and manually switch the pump on (b) Alternative solution - use real-time concentration of a product specific band from FlowIR™ and convert it into a flow rate that allows the third stream to be dispensed proportional to the concentration of the intermediate via LabVIEW.

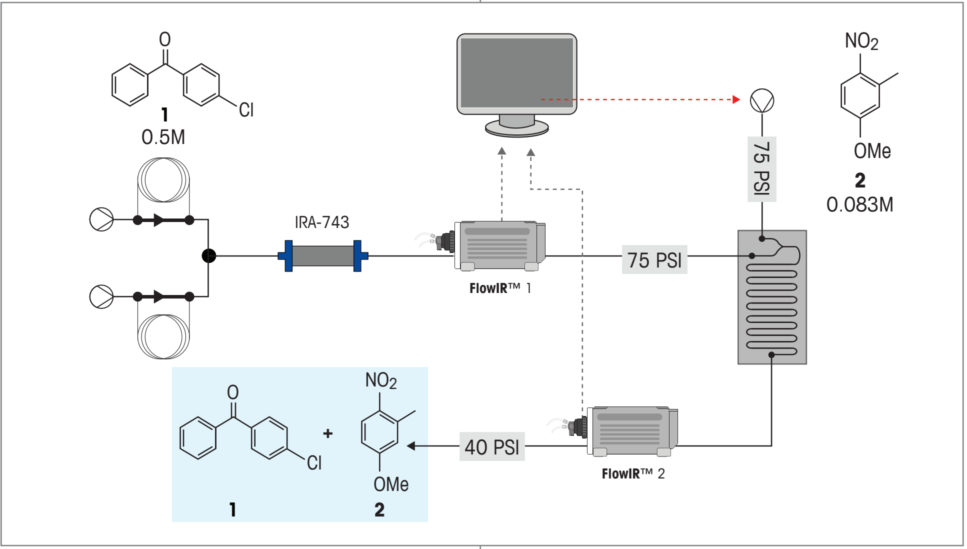

Figure 5. The experimental setup to prove that the dispersion curve of the 1st reagent could be mapped by the IR and used to accurately dispense a 2nd reagent proportional to the concentration of the 1st reagent.

Conclusion

The desire to gain major improvements in product quality, yield, synthetic route, cycle time coupled with the incredible drive for increased personal productivity within the pharmaceutical and fine chemical industries has led to the development of a number of novel methodologies that enable the development and use of chemical reactions that were previously unusable, thereby expanding the available classes of chemistry and employment techniques to the chemists. One of these methodologies is the real time monitoring and control of continuous flow chemistry.

As demonstrated in the previous examples, it is now possible not only to use continuous flow chemistry as a 'chemistry enabler' and a productivity driver, but also to speed up the development time of that process by using real time inline analytical tools such as FlowIR™.

The examples cited here show that this type of technology can be used to accurately determine dispersion effects, leading to the ability to accurately apply a third stream via a feedback controlled flow that exactly matches the required amount of reagent to the output of the first flow reactor. This leads to improved product yield and reduced purification steps. In addition, this technology can be used to:

- Gain faster structural information in real time
- Immediately determine when steady-state conditions are reached
- Immediately detect reaction start/end point
- Detect transient intermediates
- Gain critial information without the need to sample

Enabling Technology: FlowIR™

METTLER TOLEDO FlowIR™ is a compact Fourier Transform Infrared (FTIR) spectrometer which has been designed specifically for *in situ*, real-time monitoring of a continuous flow stream. The sensor consists of an integrated nine bounce attenuated total reflectance (ATR) crystal (Diamond or Silicon) that provides access to the full infrared spectral region. A removable head allows for easy cleaning and with a 10µl or 50µl internal volume it can be used with both micro and mesoscale flow technologies. The heads can be heated up to 120°C and cooled to -40°C and are rated to 50bar. OmniFit connections (1/4-28-UNF) enable FlowIR™ to be easily connected to any flow system. The compact nature of FlowIR™ means that it can be connected inline at any point of the flow reaction setup, depending on the issue that needs to be addressed (monitoring product formation, monitoring intermediates, etc.).

FlowIR™

Our People

METTLER TOLEDO has a global network of Technology and Application Consultants with extensive research and industry experience supporting organic chemistry, chemical development and scale-up.

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Website

We are online at the METTLER TOLEDO website (www.mt.com/autochem), where you can find additional detailed information on our products and applications – including an extensive list of upcoming and on-demand webinars.

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