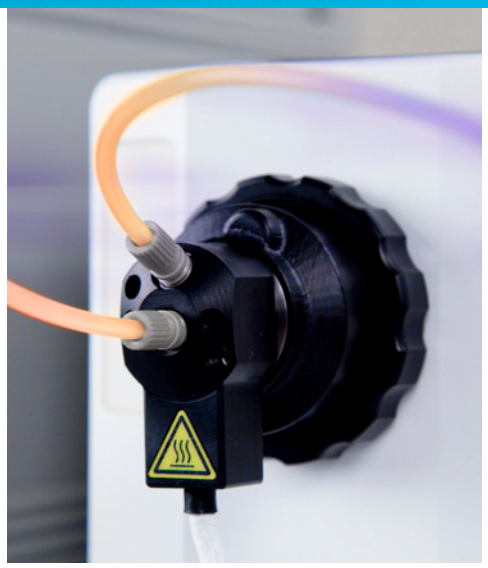
Enhanced Development and Control of Continuous Processes

Vapourtec R-Series™ and METTLER TOLEDO FlowIR™ Integration



Rapid Analysis and Optimization of Continuous Flow Reactions

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The development of flow chemistry and the resulting access to new process windows (temperature, pressure etc) has significantly expanded the range and scope of possible chemistries available to today's synthetic chemist. This is reflected in the dramatic increase in the variety and depth of published chemistry over the last few years. However, the development of suitable inline analytical techniques hasn't followed this trend. FlowIR™ offers a powerful non-destructive method to rapidly access reaction profiling and mechanistic data.

Reaction optimization often involves repetitive experiments to obtain the desired optimum conditions. The ability to carry out these individual reactions with automated synthesis platforms has freed the user from the time consuming task of repeating experiments. Flow chemistry is a synthetic development technique that lends itself to reaction optimization very well. With the application of software control, for example the Vapourtec Flow Commander™, a series of both continuous and discontinuous variables can be run in sequence and individually collected for analysis. However, when coupled with FlowIR™ offline analysis is not necessary and, as we hope to illustrate, rapid analysis of reaction optimization experiments can be obtained.

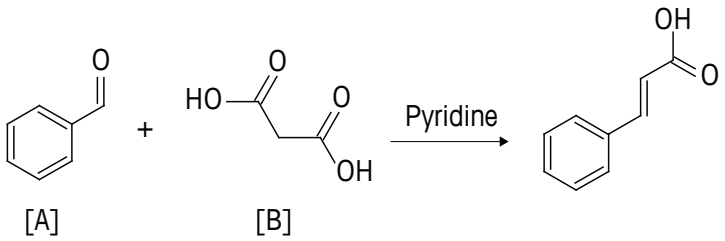
As a result of a collaboration between Vapourtec and METTLER TOLEDO, users of the Vapourtec R-Series™ and METTLER TOLEDO FlowIR™ now enjoy tighter integration. Reaction trend data from FlowIR™ can be logged and displayed in real time within the Vapourtec Flow Commander™ software, along with other reaction data, allowing users to visualize the progress of their chemistry in a single view. In addition the automated collection of reaction product peaks can also be triggered based on the values provided by FlowIR™, which translates to automated optimization.

This white paper highlights two examples of reaction optimization experiments using FlowIR™ as the key inline diagnostic tool. The chemistries were selected due to the fact that they are challenging to analyze using standard offline techniques. The examples illustrate FlowIR™ data collection and reaction monitoring for each example and highlight the data integration into the Vapourtec Flow Commander™ software.

METTLER TOLEDO

vapourtec

Doebner Modification of the Knoevenagel Condensation Reaction



This reaction is an ideal example to run under flow conditions. When carried out as a batch reaction it can involve a lengthy step wise addition of the malonic acid (B) to the benzaldehyde (A), depending on the reaction scale. This is followed by a gradual increase in the temperature to ~70°C where carbon dioxide is evolved resulting in a batch time between six and nine hours. The advantages flow chemistry offers here are the ease of scale-up and predictable and controllable gas evolution.

This reaction is especially suitable for optimization using FTIR spectroscopy because it is difficult to follow by standard laboratory LC methods. It involves a lengthy work up process to remove the pyridine from the reaction mixture. A series of two reaction optimization experiments were devised to show the effect of reaction temperature, residence time and stoichiometry on the product formation.

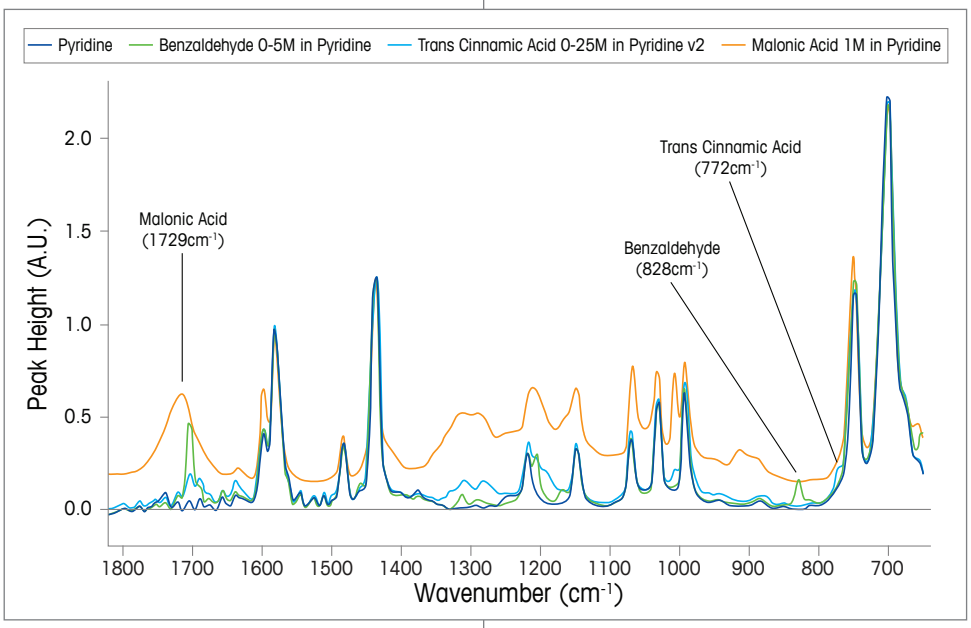


Figure 1. Reference spectra of the reaction components involved in the Doebner Modification of the Knoevenagel condensation reaction. The bands of interest for the three reaction components are indicated.

Reaction Setup

To optimize a chemical reaction an isolated infrared band needs to be identified for the desired product so it can be followed throughout the course of the reaction. Very often bands for the reagents can also be identified to assist in the understanding of the reaction. To achieve this, samples of the reagents and products (at the same concentration as required in the reaction) were injected into the sample head of FlowIR™ and their unique reference spectrum was collected. From this spectral library in the iC IR™ software, appropriate bands can be selected for each reaction component as shown in Figure 1.

The flow reactor was configured using a combination of the R2 pump module and R4 reactor module as shown in Figure 2. A 5mL PFA tubing reactor was installed and a 100psi back pressure regulator (BPR) fitted inline between the reactor outflow and the collection valve. The system was set in the pump configuration allowing the material to be introduced directly through the pumps. FlowIR™ was placed inline directly after the BPR and the output from this was connected to the collection valve. Reagent stock solutions A (1.0M benzaldehyde in pyridine) and B (1.0M malonic acid and piperidine (0.1eq) in pyridine) were prepared and a range of reaction conditions defined within the Flow Commander™ software. Residence times of 10 minutes were run at four temperatures (80°C, 100°C, 120°C and 150°C) followed by reactions of 20 minutes at 100°C and 120°C, before finally running a reaction of 30 minutes at 100°C as shown in Figure 3.

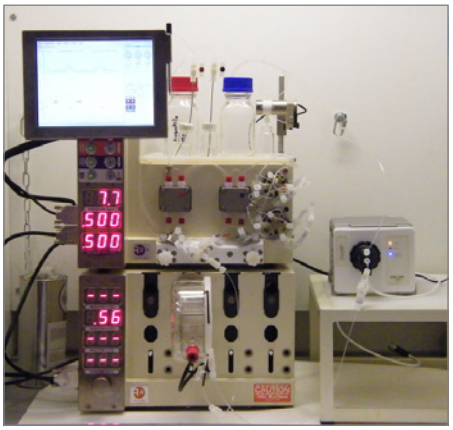


Figure 2. The reactor setup consisting of the Vapourtec R2 pump module and R4 reactor module along with METTLER TOLEDO FlowIR™

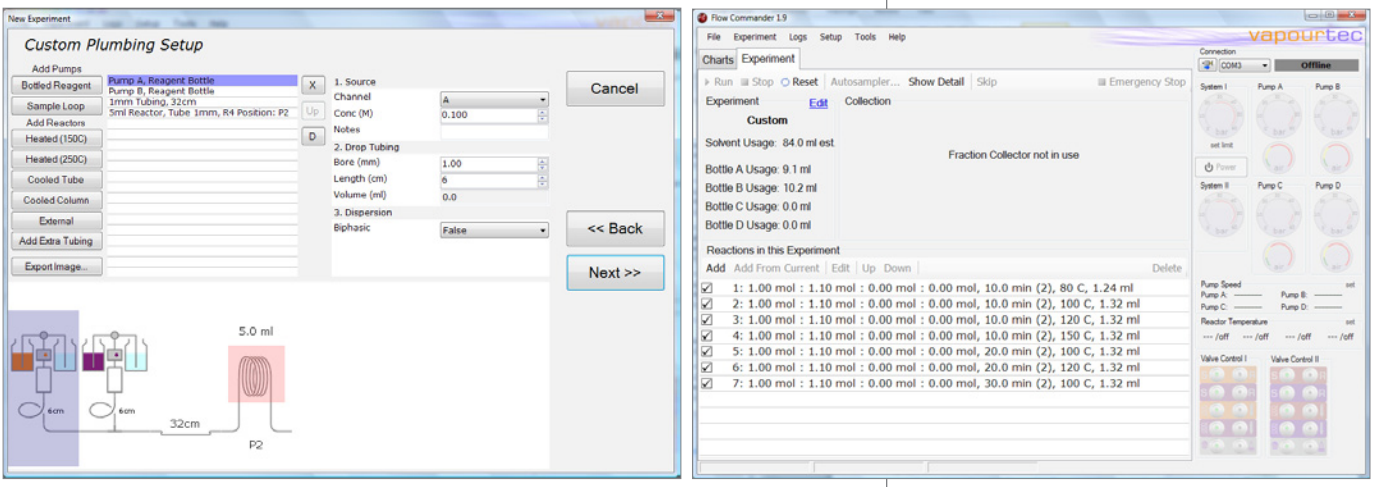


Figure 3. Screenshot of the Flow Commander™ software showing the reaction setup employed for the Doebner Modification of the Knoevenagel Condensation Reaction along with the automated setup of the reaction sequence

Results and Discussion

A FTIR spectrum of the output of the flow reactor was collected in real-time every 15 seconds using METTLER TOLEDO iC IR™ software. By selecting the peaks defined in Figure 1 and monitoring their peak height (which is proportional to their concentration) as a function of time, relative concentration trends for benzaldehyde, malonic acid and trans cinnamic acid for each reaction segment can be automatically displayed in real-time as shown in Figure 4. At the same time the measured trends are also automatically captured and displayed within Flow Commander™, as shown in Figure 5.

The reaction profiles shown in Figure 4 provide a simple visual record of the effect of the reaction temperature and residence time which can be quickly and easily interpreted. For the initial reaction conditions of 10 minutes and 80°C it is evident that the product trend (shown in light blue) shows that under these conditions essentially no reaction took place.

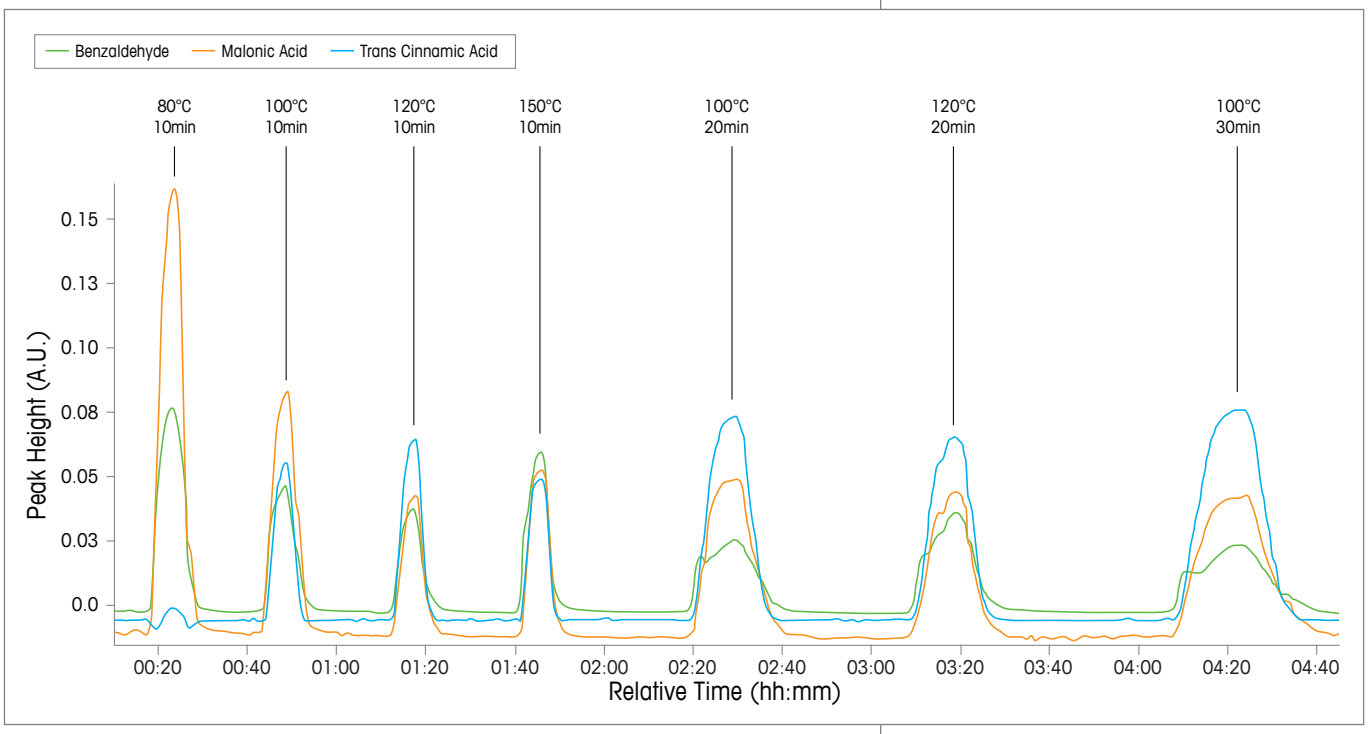


Figure 4. Peak height analysis of the three bands specified in Figure 1 showing how their relative concentrations change with reaction temperature and residence time. The reaction stoichiometry was fixed at 1:1.1 (Benzaldehyde: Malonic acid).

However, keeping the residence time fixed and increasing the reaction temperature increases the product formation as expected, although a decrease was observed above 120°C. Increasing the residence time to 20 minutes at 100°C, again improved the conversion.

One advantage of displaying the IR trends within the Flow Commander™ software, as shown in Figure 5, is that the calculated dispersion model can be compared against the actual dispersion profile from the data captured by FlowIR™. In this case an excellent correlation is found, but if multistep reactions are performed or scavenging columns employed this may no longer be true. In these cases FlowIR™ profiles can be used to automatically trigger the optimum fraction collection for HPLC analysis via the Vapourtec Flow Commander™ software.

FlowIR™ trend data is calculated using a simple peak height analysis and provides a relative concentration trend, since the intensity of IR radiation absorbed by a particular wavelength is proportional to concentration (as defined by Beer's law). To convert this into a quantitative analysis, a model needs to be developed using samples of known concentrations. Therefore five solutions were prepared within the concentration range of the experiments (0.1-0.5M) and directly injected into FlowIR™ using a syringe adaptor to collect their spectrum.

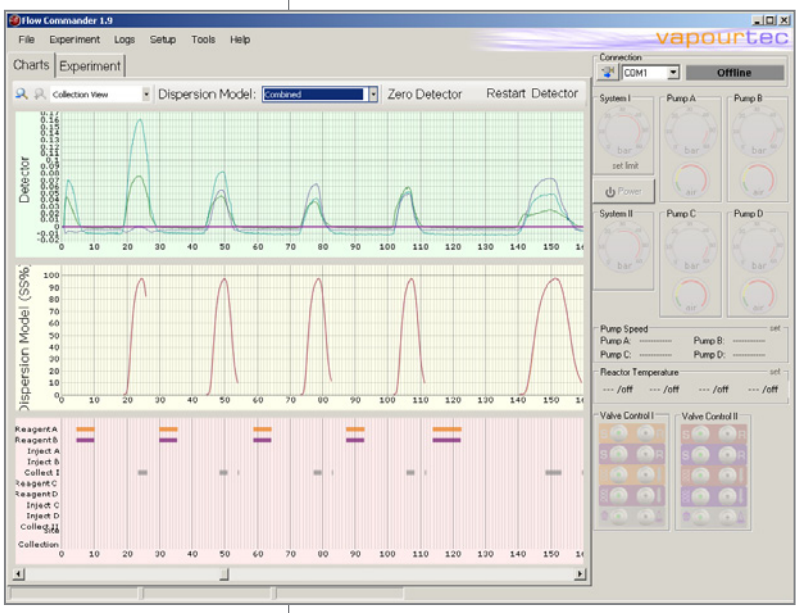


Figure 5. Vapourtec Flow Commander™ software showing the integrated FlowIR™ trend data along with the calculated dispersion profiles

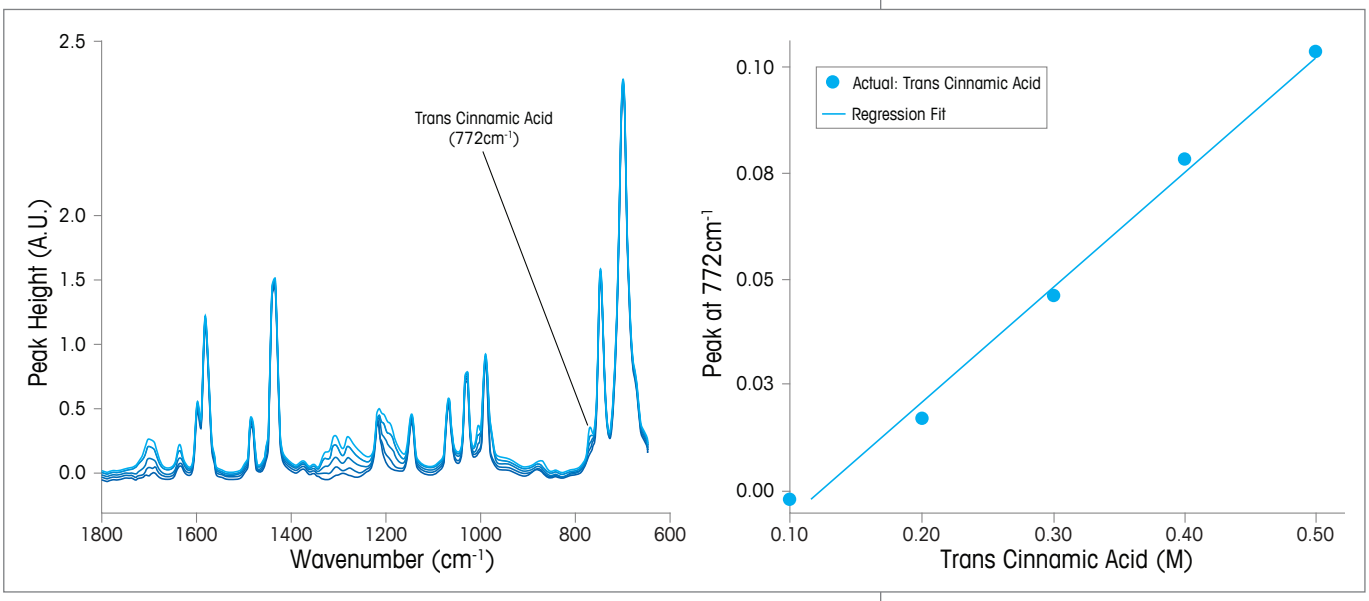


Figure 6. A simple trans cinnamic acid concentration calibration curve calculated by measuring the peak height of trans cinnamic acid at 772cm^{-1} with two baseline points (781 and 765cm^{-1}) in five calibration samples (0.1-0.5M)

A simple univariate calibration model was developed using iC Quant™ software, which showed an excellent correlation between the known trans cinnamic acid concentration and the peak height of the trans cinnamic acid band at 772cm^{-1}, as shown in Figure 6. The model was then used to predict the trans cinnamic acid concentration of each of the segments, as shown in Figure 7.

From this initial two parameter reaction optimization experiment, a basic set of conditions were determined from which to carry out a further study looking at a third reaction parameter. The next experiment looked at the effect of changing the stoichiometry of the reactants. The same system set up and reagent solutions were used, but in this case a residence time of 20 minutes and a reaction temperature of 100°C were used with four variations in stoichiometry. The final segment in this experiment was run at steady state. Figure 8 shows the relative concentration trends measured with the changes in stoichiometry. It is evident that the conversion to the trans cinnamic acid product was only improved by approximately 4% on going from 1 to 1.2 equivalents of Malonic acid. Additionally, increasing the number of equivalents further did not improve the conversion and in all cases actually caused a decrease. The exact cause of the decrease is unclear since no evidence of a by-product or impurities were detected using FlowIR™. The ability to measure multiple components in the reaction mixture can be very useful. The increasing concentration of the Malonic acid can very clearly be seen, and therefore provides a simple confirmation that the desired flow rate change has in fact taken place.

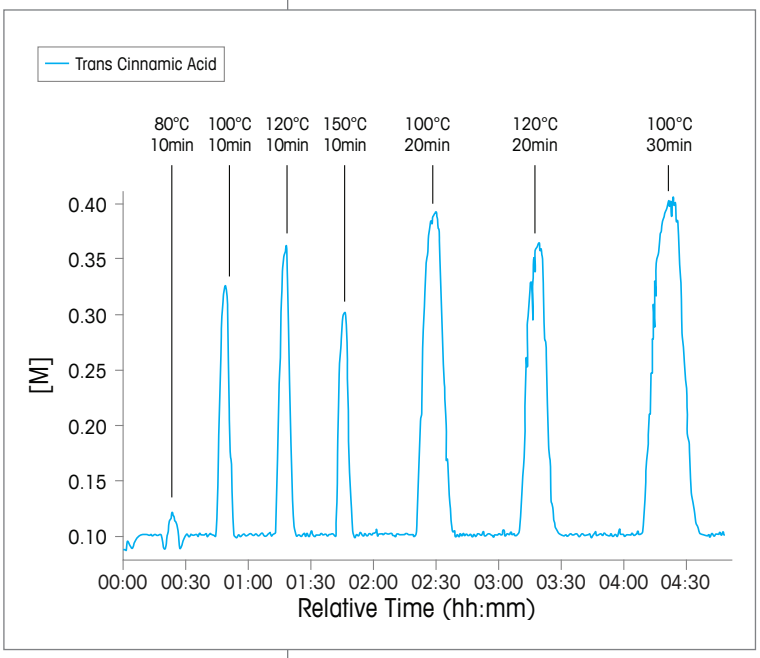


Figure 7. Predicted trans cinnamic acid concentration of each of the seven segments

It is well known that optimum reaction conditions only occur when at a steady state in continuous flow systems, and this experiment shows an IR profile which illustrates this clearly. We can see from the benzaldehyde trend that in the non-steady state regions at the beginning and end of the segment the concentration is much higher than in the steady state region. This is due to the dispersion of the plug and the resulting dilution of the regents at the beginning and end of the segment. The rate of reaction is consequently slower with these lower concentrations, which leads to the observed trends. This effect will become more pronounced the greater the dispersion, and although in itself this is not a problem, it does mean that for short plugs and long residence times it is necessary to be very specific regarding where fraction collection occurs for offline analysis.

It should be noted that although this reaction evolved carbon dioxide gas, which was clearly seen leaving the reactor and entering FlowIR™ (see Figure 9), the system handled the gas liquid interface very well and delivered continuous useable data. This is due to the fact that the ATR sensor is only sensitive to the liquid phase and only measures a 1-2 micron layer on the ATR sensor.

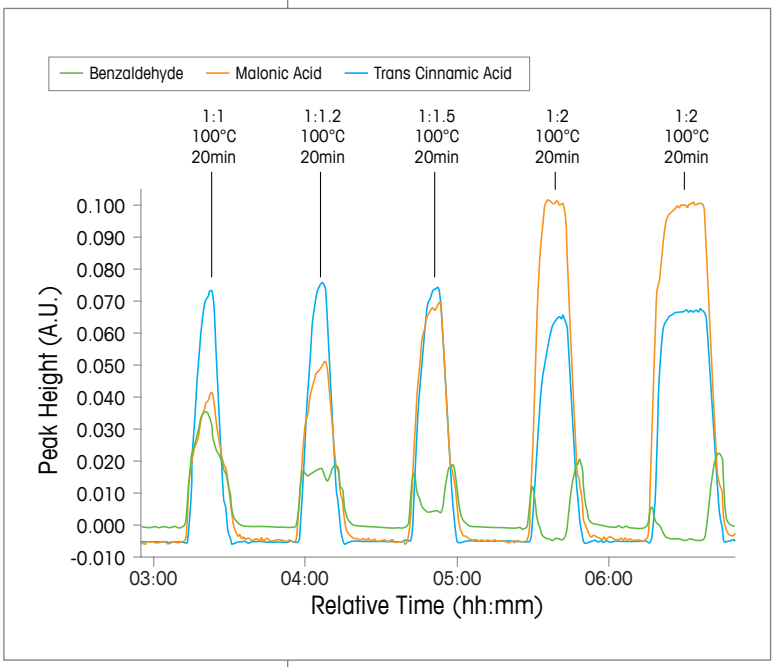


Figure 8. Peak height analysis of the three bands specified in Figure 1 showing how their individual concentrations change with reaction stoichometry (keeping the reaction temperature and residence time fixed at 100°C and 20 minutes)

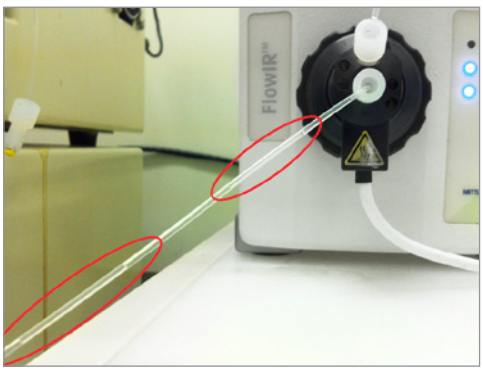


Figure 9. Carbon dioxide bubbles (marked) seen entering FlowIR™. No effect on the detected signal was observed under these challenging conditions.

One Step Synthesis of Substituted Indazoles

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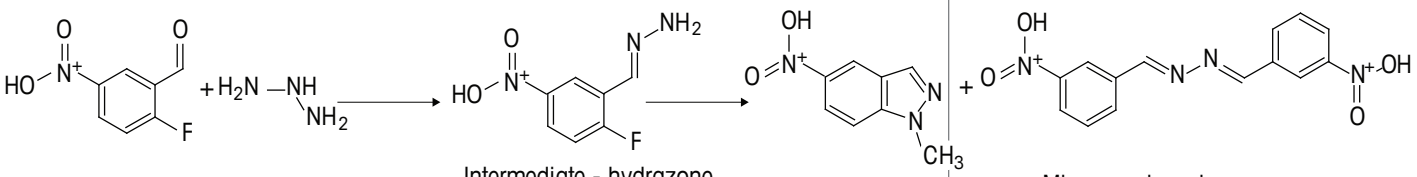


This reaction, published by Wheeler et al, shows the formation of substituted indazoles from benzaldehydes and should illustrate the potential power of both systems. The use of hydrazines under forcing conditions are well known and together with the long (3-36hr) batch reaction times this reaction is well suited to flow chemistry. This reaction also forms a number of intermediates under mild conditions that can be followed by their unique IR profiles as a means to optimize this type of reaction. The authors explored the variation of solvents on the reaction profile and found DMA to be the best solvent in this case. It was also found that reducing the residence time below 15 minutes at 150°C had little effect. Therefore taking the lead from the published results we set out to duplicate the reaction optimization to show we could follow the reaction and it's intermediate with FlowIR™.

Reaction Setup

An IR library of the reagents and the desired product was prepared and appropriate IR bands were selected for each component. The flow reactor was configured as in the previous example, except for a high temperature 10mL stainless steel tubing reactor that was installed with a 250psi back pressure regulator (BPR). The system was set in the pump configuration, allowing the material to be introduced directly through the pumps. Reagent stock solutions of 0.25M 2-Fluoro-5-nitrobenzaldehyde in DMA and 0.25M methylhydrazine and DIPEA (1.05eq) in DMA were prepared and a range of conditions defined within the Flow Commander™ software. Residence times of 15 minutes were run at four temperatures (25°C, 50°C, 100°C and 150°C) with stoichiometry of 1:1 and then these were repeated at 100°C and 150°C with a stoichiometry of 1:1.2.

Results and Discussion

An IR spectrum of the output of the flow reactor was measured every 30 seconds and the resulting relative concentration trends for the indazole, azine and the intermediate for each reaction segment were displayed in real time, simultaneously within iC IR™ software as shown in Figure 10, and within Flow Commander™ software, as shown earlier. The first reaction profile measured with a 15 minute residence time and a reaction temperature of 25°C demonstrated that although the intermediate is formed there is very little conversion to the indazole product. In fact no evidence of residual benzaldehyde could be found within the IR spectrum suggesting that its conversion to the intermediate is quite fast, even at this low reaction temperature. Increasing the reaction temperature to 50°C, 100°C and 150°C increased the conversion of the intermediate into the desired indazole product. It is interesting that the relative concentration of the unwanted azide product stays fairly constant and as might be expected is dependent on the concentration of the indazole. Increasing the hydrazine excess from 1 to 1.2 equivalents increases the formation of the indazole by approximately 4% (based on the qualitative trend intensities).

To show this data in a format that may be more familiar, the relative concentrations of the three reaction components have been plotted as a function of temperature, keeping the stoichiometry and the residence time fixed at 1:1 and 15 minutes respectively, as shown in Figure 11. It is evident from the data shown in Figure 10 and the plot shown in Figure 11 that the effect of increasing the reaction temperature above 150°C should also be investigated as the optimum reaction conditions may well require a temperature above 150°C.

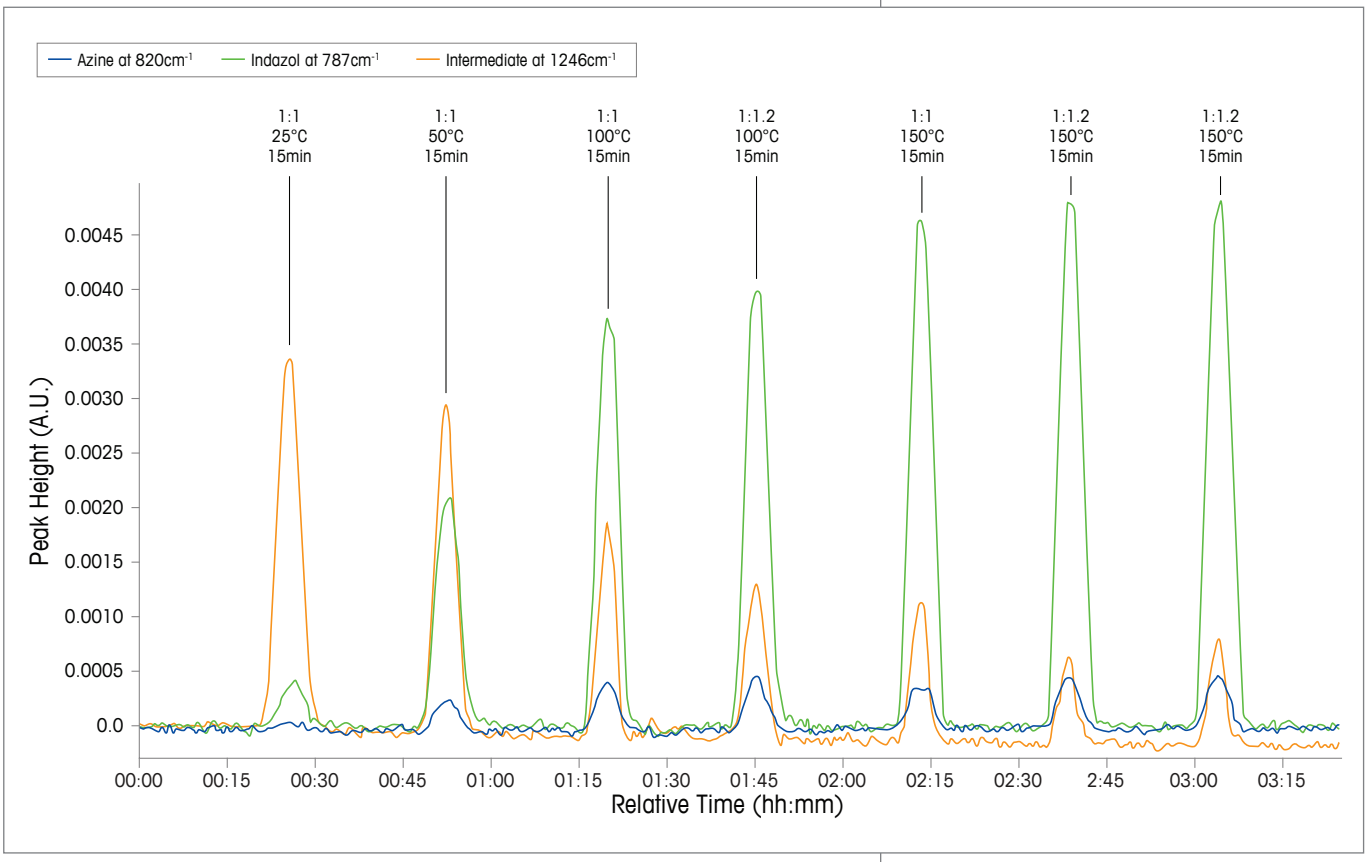


Figure 10. Peak height analysis of the reaction components of interest showing how their relative concentrations change with reaction temperature and stoichiometry

Based on the results of the first experiment, where the optimum conditions appeared to be a reaction temperature of 150°C with a stoichiometric ratio of 1:1.2 and a residence time of 15 minutes, it was decided in the next series of optimization experiments to investigate the effect of changing the residence time and increasing the reaction temperature to 200°C. The solutions and reactor setup remained unchanged.

Figure 12 shows the relative concentration trends measured after changing both the residence time and reaction temperature. Decreasing the residence time to five minutes had an adverse effect on the relative concentration of the desired indazole even when the reaction temperature was increased to 200°C. Increasing the residence time to 30 minutes at a reaction temperature of 150°C did not improve the conversion to the indazole. If anything, azine formation increased. Finally increasing the reaction temperature to 200°C with a residence time of 15 minutes did improve the relative concentration of the indazole by approximately 6%.

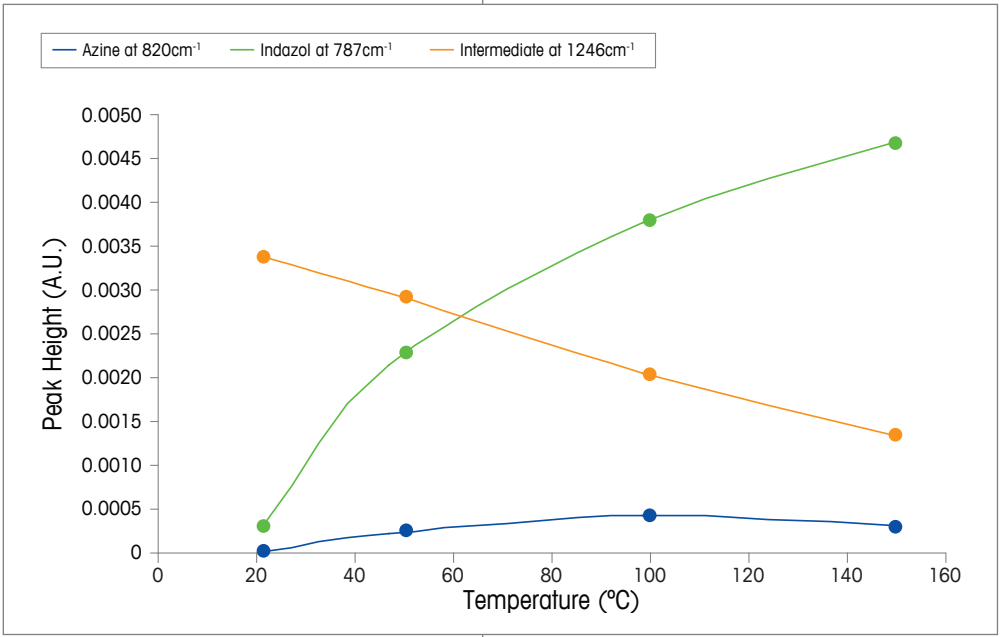


Figure 11. Plot of the relative concentrations of the three reaction components as a function of temperature, keeping the stoichiometry and the residence time fixed at 1:1 and 15 minutes, respectively

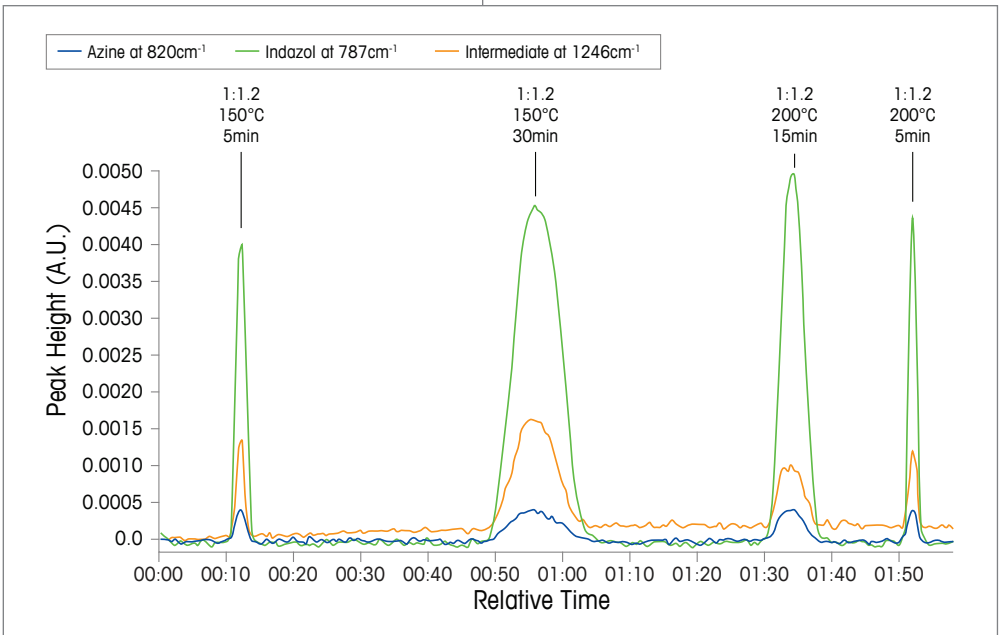


Figure 12. Peak height analysis of the reaction components of interest showing how their relative concentrations change with residence time and reaction temperature

Conclusion

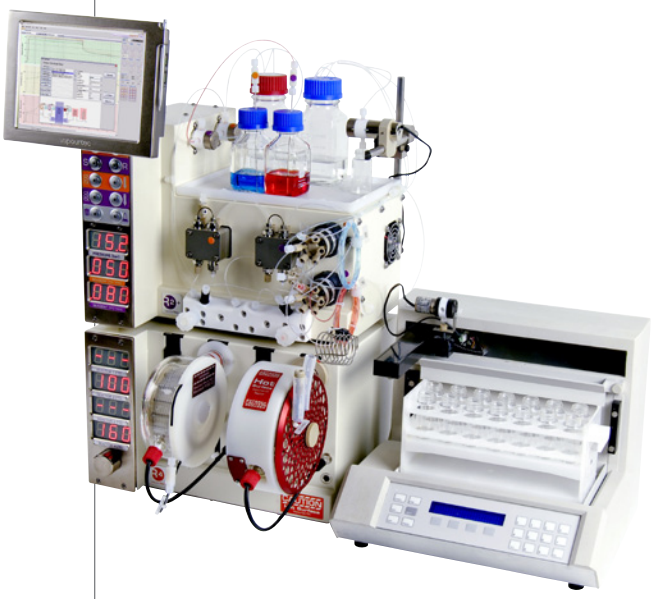
This work shows that the integration of FlowIR™ with the Vapourtec system can lead to significant time savings when performing optimization studies as the ability to automate the process and analyze the data *in situ* allows the user to perform other experimental work. The two examples discussed here not only show the value of FlowIR™ as an inline analytical tool when standard offline analysis methods are challenging, but also provides a very visual and immediate indication as to whether the optimization is going in the right direction without having to wait for offline results.

As flow chemistry matures and multi-step sequences and downstream processing become more common, the ability to analyze and control chemistry *in situ* will become ever more important. The ability to collect the correct fraction for impurity analysis, for example, will still be very important and can be facilitated by FlowIR™ *in situ* analysis technology. Doing this without some sort of *in situ* analysis tool will be extremely difficult.

Enabling Technologies: Vapourtec R-Series™ and METTLER TOLEDO FlowIR™

The Vapourtec R-Series™ integrated flow system is modular in design and supports a range of different reactor types enabling almost any flow chemistry conditions the chemist may require. The ability to connect both an autosampler and fraction collector expands the range of available applications making it very efficient at reaction optimization and array synthesis. Flow Commander™ control software provides complete automation of the Vapourtec R-Series™ platform and associated external equipment. By automating all the mundane set up and calculation steps, Flow Commander™ allows for more structured and reproducible experiments. Its key features include modeling of axial dispersion through the entire reactor network, the ability to log and store data for producing charts and reports, interface to detection, auto samplers and fraction collection systems, and run routine tasks and extended optimization experiments unattended.

FlowIR™ is an *in situ* FTIR system designed for continuous flow chemistry, and enables a chemist to see the chemical composition of the output of the continuous flow system in real time, thereby providing structural information across a wide range of functional groups/chemistry. The small footprint (equivalent to a Knauer micro HPLC pump) allows the unit to be positioned virtually anywhere, making it flexible, and minimizing its impact on the limited space available. The interchangeable FlowIR™ sensors (diamond and silicon) allow the user to quickly and easily swap sensor types to meet a broad range of application needs. With a sampling head volume of 50µl or 10µl it is compatible with both micro and meso flow systems. No liquid nitrogen for detector cooling and no instrument purge requirement make this system simple to use for synthetic chemists, while maintaining the high level performance expected by traditional ReactIR™ technology. The intuitive iC IR™ software makes setting up and analyzing experiments quick and simple.



Vapourtec R-Series™

FlowIR™

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