Flow chemistry benefits from inline Raman

At Vapourtec we have seen the growing need for real time continuous reaction analysis and monitoring in flow chemistry. This was a key theme at the 8th Symposium on Continuous Flow Reactor Technology for Industrial Applications held in Delft in 2016, and many of our customers have asked what techniques are available to use with the Vapourtec flow reactor platform.

To respond to our customers and what they need, we have collaborated with different manufacturers of spectroscopic instruments to incorporate them into our flow path, and integrate their output with Flow Commander™ to enable continuous reaction monitoring in real time and crucially recorded with the same time base as the other experimental data. In 2011, we collaborated with Mettler-Toledo and integrated the FlowIR™ into Flow Commander™ and recently we collaborated with Bruker to do the same with the Alpha ATR-IR spectrometer. We have now also integrated Raman spectroscopy into Flow Commander™, providing a powerful and complementary spectroscopic tool for reaction monitoring and optimisation.

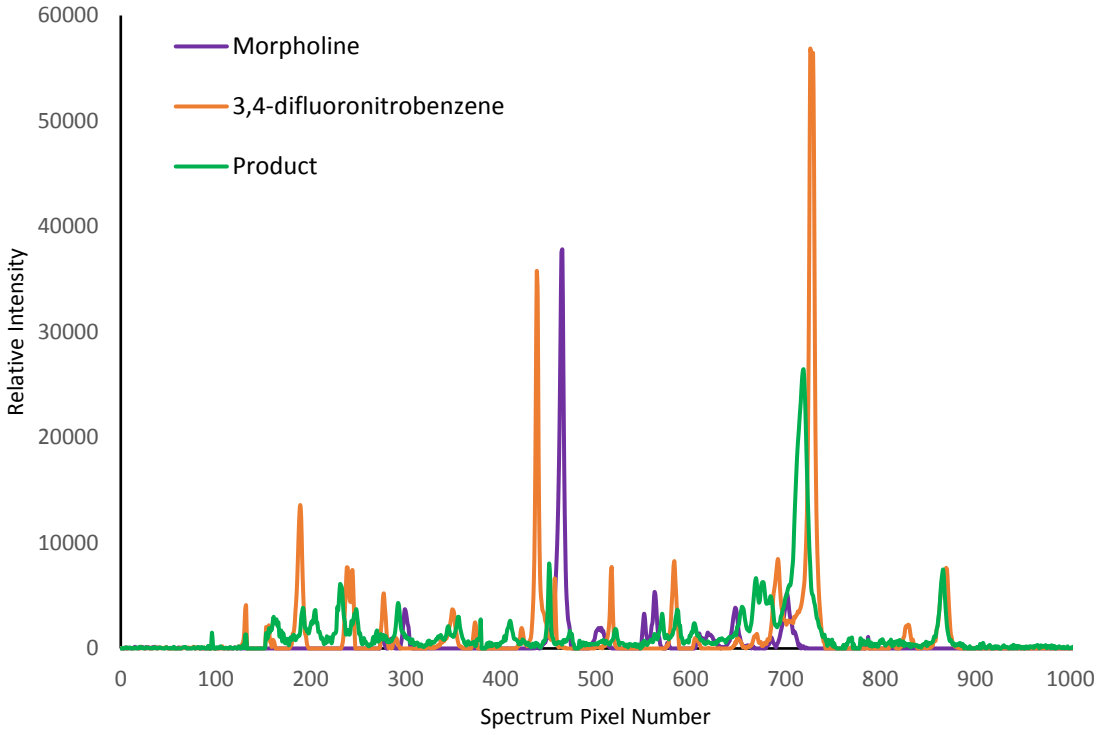

Figure 1: Overlay of 3 Raman spectra showing the unique fingerprint of each molecule. It is possible to identify unique peaks for each material, making it possible to track changes in concentration as the reaction progresses.

In recent years, Raman has become very affordable, and offers a number of advantages for real time monitoring in continuous flow: Raman is governed by different rules to IR and can often see materials

that are IR inactive. A Raman spectrum is a fingerprint unique to each molecule, see Figure 1, and it is often possible to identify isolated peaks that can be tracked during the course of a reaction; IR spectra can become highly complex to analyse if two materials contain the same functional groups, making it difficult to identify and track changes in the concentration of those materials.

There are other advantages to Raman: water absorbs IR very strongly, and often dominates spectra of samples that are not dry. However, water scatters light very weakly and so does not dominate Raman - spectra are not degraded by a wet sample, and indeed it is possible to obtain spectra from aqueous solutions using Raman; Glass and quartz are also typically transparent to Raman, allowing flow cells to be constructed easily and without the need to use complex materials; The Raman probe is connected to the light source using optic fibre, which means that only the probe needs to be in place in the flow system, the spectrometer can be situated elsewhere.

We have used Raman, in tandem with IR and alone, to monitor a number of reactions and have found that the molecular fingerprinting has proved invaluable in identifying features of the spectrum that can be used to track changes in the reaction in real time, see figure 2. Using Raman in this way enables rapid reaction optimisation, the operator simply watches the reaction monitoring and tunes the conditions until starting materials are consumed.

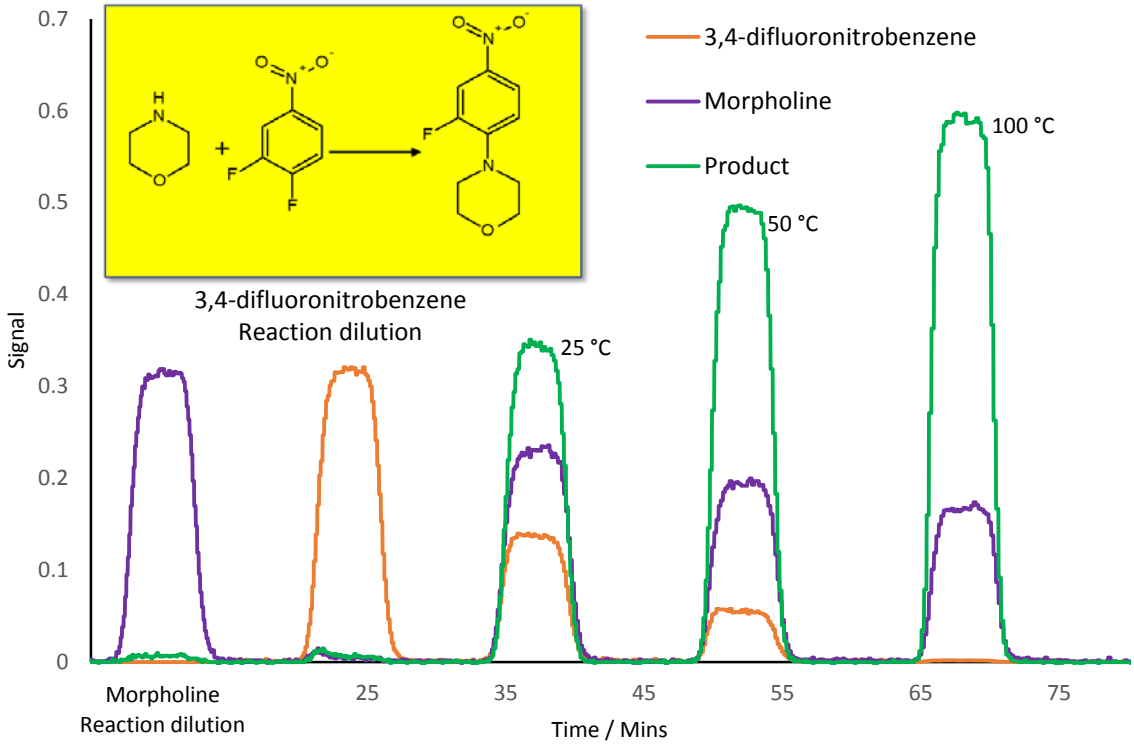

Figure 2: Tracking of unique peaks from the spectrum shown in Figure 1. It is easy to follow the consumption of the reagents (morpholine is in excess) and to see the increase in product formation as a function of temperature through the course of the reaction.