

Raman-based endpoint detection of a heterogeneous etherification reaction

Introduction

This application note describes in-line Raman spectroscopy at the pilot scale to detect the endpoint of a heterogeneous etherification reaction.¹ Fast, real-time Raman measurements enabled automated closed-loop feed-forward/feedback control and remote process monitoring by process chemists 200 miles away.

Process chemistry & control strategy

Synthesis of a type II diabetes treatment known as “Compound X” involved the etherification of phenol **2** with chloropyrazine **3** to produce ether **1** (Figure 1).

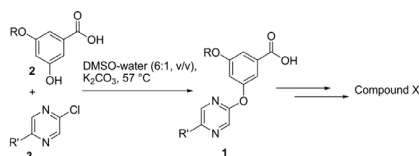


Figure 1: The etherification reaction was a critical step in the synthesis of Compound X. The heterogeneous reaction was measured in real-time by *in situ* Raman spectroscopy. Raman spectra were used to provide a reaction endpoint measurement. Reprinted with permission from Ref. 1. © 2014 American Chemical Society.

There were financial and scientific reasons to pursue in-line endpoint detection. Because the etherification was a heterogeneous reaction, off-line sampling may not be representative of the reaction mixture. In-line detection of excess chloropyrazine **3** prevented it from being present downstream where it can cause crystallization of an undesirable final product polymorph.

Ultraviolet-visible spectroscopy (UV/Vis) and Raman spectroscopy were initially selected as in-line measurements. Initial tests showed that either UV/Vis or Raman could be used

to qualitatively follow the reaction. Raman spectroscopy was chosen to develop a calibration model because of its much greater chemical specificity.

Raman in a pilot plant environment

The etherification reaction is described by Hart et al.¹ Raman spectra were obtained using a Raman analyzer fitted with a Raman probe head with a short focus immersion optic.

The analyzer and fiber optic probe had demonstrated compatibility with process chemistry and integration with process control software. A PLS2 calibration model was developed in the laboratory (250 mL reaction volume) by correlating Raman data to HPLC measurements. The model was transferred to the pilot plant (1500 L reaction volume) and used to predict the reaction endpoint.

The process monitoring system used in the pilot scale portion of this study is shown in Figure 2. The Raman instrument and its computer hardware were located in a laboratory and connected to the reaction vessel in the process environment via a patch panel.

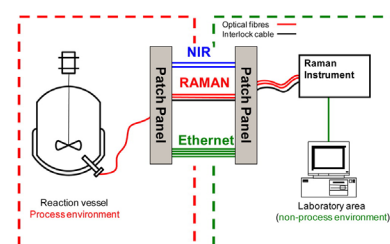


Figure 2: The process monitoring system used by Hart et al. in Ref. 1 in the paper by Hart et al. A patch panel provides instrumental access to the process environment from the laboratory area. Reprinted with permission from Ref. 1. © 2014 American Chemical Society.

① All Raman analyzers and probes referenced in this application note are Endress+Hauser products powered by Kaiser Raman technology.

Benefits at a glance

- Accurate detection of reaction endpoint maximizes process efficiency and eliminates unwanted reactants downstream
- Raman spectroscopy provides in-line measurement of heterogeneous reaction for real-time endpoint monitoring
- Successful model transfer was demonstrated by moving a calibration model created on a laboratory scale reactor (250 mL) to a larger pilot-plant scale reaction vessel (1500 L)

Logistical considerations of operating Raman in the pilot plant included a risk assessment on potential ignition sources. The laser is a potential ignition source, and safety requirements limit the laser intensity to 35 mW at the probe head. With this low laser intensity, a longer integration time (3 minutes) was needed. Collecting spectra in 3 minutes was found to be suitable for reaction measurement and control.

Results

The endpoint of the reaction was referenced to the %w/w of ether 1. The theoretical limit was calculated to be 14.7 %w/w assuming complete conversion of the reactants, and the endpoint was considered achieved at >99% of this value.

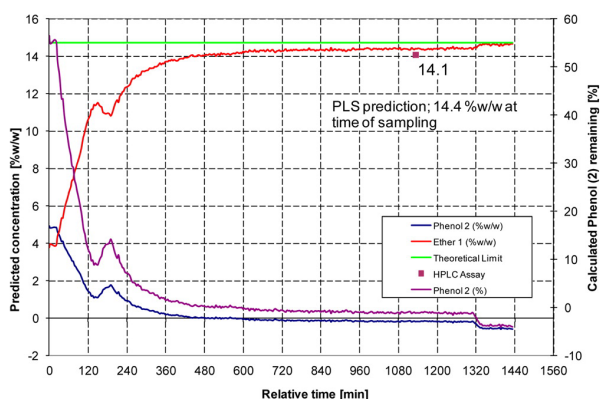


Figure 3: Predicted reaction profile as determined by Raman spectroscopy, compared to an offline HPLC assay. The disturbance at ~180 minutes is due to a line wash after the gradual addition of the reagents. Reprinted with permission from Ref. 1. © 2014 American Chemical Society.

The PLS2 multivariate calibration model was then used to predict the concentration of ether 1 in the reaction mixture in real-time. The results from one of the reaction runs are shown in Figure 3. The reagent addition phase occurs in the first 180 minutes, followed by a line wash (visible in the plot as a small disturbance due to dilution). An off-line HPLC sample was taken at a predetermined time point at ~1100 minutes. Raman predictions (14.4 %w/w) were similar to HPLC (14.1 %w/w), as validated by a comparison of the uncertainty of the HPLC data and the prediction uncertainty of the model. The Raman process analyzer was capable of detecting the endpoint several hours sooner than the manual off-line measurement method by HPLC.

On the basis of results from the 1st pilot plant batch, it was determined that in-line Raman spectroscopy with the PLS2 model could be used as the sole process control technique for this reaction. Cost and plant efficiency savings from detecting the early endpoint were realized with a very quick return-on-investment.

Conclusion

In situ quantitative Raman spectroscopy significantly improved the process efficiency for this heterogeneous etherification reaction by detecting the endpoint much more accurately than traditional off-line analysis. Adding this critical feedback loop allowed for remote management of this chemical process.

References

1. R.J. Hart, N.I. Pedge, A.R. Steven, K. Sutcliffe. "In situ Monitoring of a Heterogeneous Etherification Reaction Using Quantitative Raman Spectroscopy". *Org. Process Res. Dev.* **2015**, 19(1): 196–202. 10.1021/op500027w.