

Reaction monitoring in small reactors and tight spaces

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A number of diverse analytical challenges face today's development chemist. For example, the emergence of combinatorial and high-throughput methods for rapid pharmaceutical and chemical development and the use of parallel arrays of small reactors for exploratory chemistry are becoming widespread. At the same time, entirely new approaches are being developed for synthetic chemistry. Supercritical carbon dioxide is emerging as a versatile and environmentally benign alternative to traditional solvents. This, too, presents challenges to development chemists and engineers who need real-time data on reactions inside compact, pressurized reactors. Compactly designed fiber-optic probes with full temperature and pressure capability offer a convenient way to open a mid-infrared spectroscopic "window" into reaction chemistry on a scale down to a few milliliters and under a wide range of reaction conditions.

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The ReactionView™ (Remspec Corp., Sturbridge, MA) (Figure 1) makes it possible to follow the progress of a chemical reaction in real time by following changes in the mid-IR spectrum. Since the fiber-optic cables are both rugged and flexible, and the probe head is slim (standard diameter of 6 mm), the device can be used with most standard laboratory glassware and with many commercial laboratory reactors and reactor arrays.

Ketene reaction

The formation of ketene intermediates is a crucial step in the synthesis of some important classes of compounds, including beta-lactones. The reaction is typically carried out at low temperature to facilitate accumulation of the highly reactive ketene species before addition of reagents for the next reaction step. Monitoring the formation of the ketene is a challenge; removal of analytical samples from the

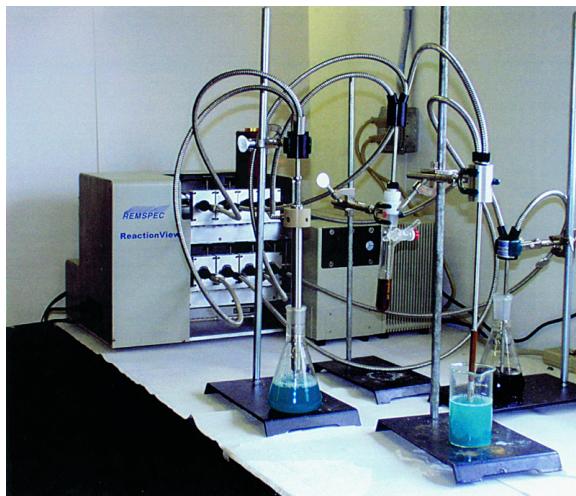
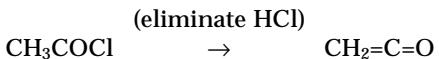


Figure 1 ReactionView-4 in use with standard laboratory glassware.

reactor invites degradation of the ketene before it is characterized, and can compromise the reaction conditions. A sensitive *in situ* method is needed, and fiber-optic FTIR spectroscopy lends itself well to this task.

Preparation of ketene from acetyl chloride is performed as follows:



This experiment was performed using a ReactionView system fitted with a low-temperature extension and liquid transmission head. The reaction was carried out at approx. -25 °C in a three-necked reaction tube equipped with a magnetic stir bar and purged with nitrogen. The probe was inserted through a standard thermometer fitting to fully immerse the head. After cooling the starting solution of Hunig's base (0.05 mmol) in methylene chloride (8.0 mL), data collection is begun (one spectrum every minute). Acetyl chloride was then added in increments of approx. 0.1 mL every 30 min.

Figure 2 shows selected spectra obtained just before, during, and after the addition of one incre-

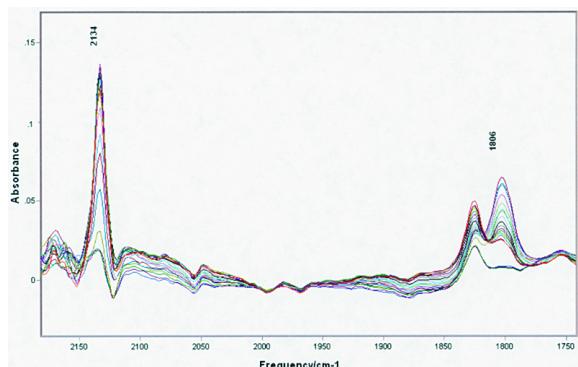


Figure 2 Selected mid-IR spectra of ketene reaction mixture over a period of 10 min.

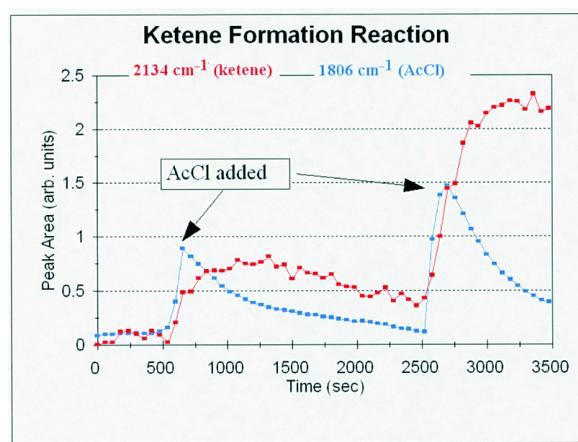


Figure 3 Spectral absorbance versus time for characteristic ketene and acetyl chloride peaks.

ment of the acetyl chloride. Two peaks were monitored: the ketene C=C=O stretch at 2134 cm^{-1} and the acetyl chloride C=O stretch at 1806 cm^{-1} . The heavy red trace represents the final spectrum in the group; clearly, the ketene peak is growing as the acetyl chloride peak diminishes.

Figure 3 is a plot of the peak areas for the ketene and acetyl chloride peaks versus time for the first hour of the reaction. The graph clearly shows that the acetyl chloride peak increases sharply as the reagent is added, then diminishes as it is consumed. The peak at 2134 cm^{-1} due to the product ketene develops after the addition of the acetyl chloride, lagging by a time of no more than 1 min. After formation, the ketene slowly disappears; this may be due to the presence of moisture traces or to improper temperature control.

Methanolysis of acetyl chloride

Another useful basic reaction is exemplified by the acid-catalyzed reaction of methanol with acetyl

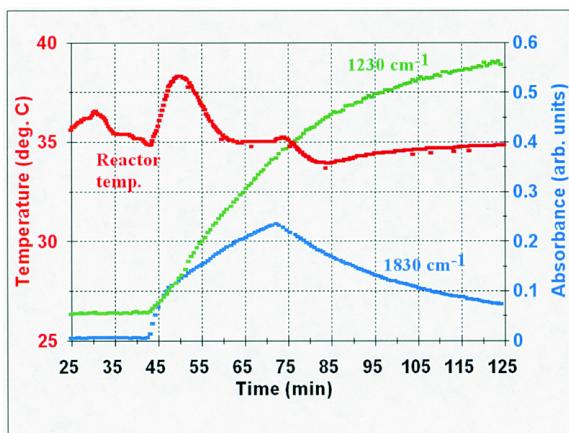


Figure 4 Characteristic mid-IR peaks of acetic anhydride (1830 cm^{-1}), methyl acetate (1230 cm^{-1}), and reactor temperature versus time during a methanolysis reaction.

chloride to form methyl acetate. Since the probe is very slim, it can be fitted easily into commercial reactors, and on this occasion a FlexyLab™ reactor (Sys-tag AG, Ruschlikon, Switzerland) was used for simultaneous tracking of the thermal behavior of the reaction and the spectroscopy. A high-temperature probe with a zinc sulfide attenuated total reflectance (ATR) crystal was inserted through a port originally designed for a particle sizing accessory.

This experiment was run isothermally at $35\text{ }^{\circ}\text{C}$, and the FlexyLab capabilities were used to control and track the temperature. After filling the reactor with methanol and a drop of concentrated sulfuric acid, and stabilizing the temperature, the addition of acetic anhydride was begun at an average rate of 1.7 g (0.03 mol) per minute. The methanolysis reaction is exothermic. The FlexyLab controller was programmed to maintain a steady $35\text{ }^{\circ}\text{C}$, but a minor temperature excursion took place as the anhydride was added. The graph in *Figure 4* shows the reactor temperature versus time, as well as characteristic peaks from both the anhydride and the methyl acetate product.

Supercritical carbon dioxide

The use of supercritical carbon dioxide as a reaction solvent has been a major research topic for several years, and the technology is fast approaching the point of widespread commercialization.¹ The ReactionView probe is well adapted to fit into laboratory-scale continuous flow reactors, for instance, and some interesting results have been obtained from hydrogenation reactions and hydroformylation reactions² carried out under supercritical or near-supercritical conditions in carbon dioxide.

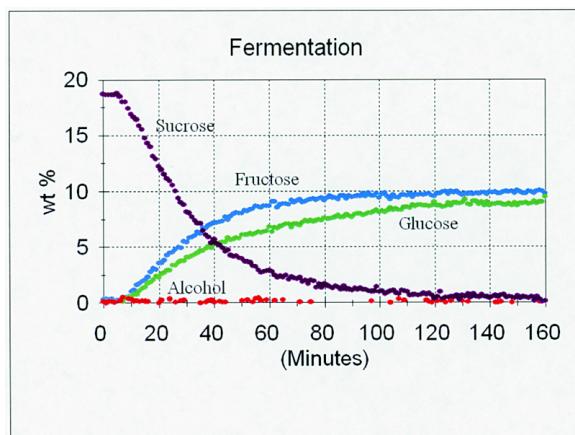


Figure 5 Sugar and alcohol concentrations versus time during a fermentation reaction, as determined by chemometric analysis of real-time, mid-IR data.

Fermentation reactions

Fermenters represent a further type of reactor in which direct reaction monitoring is a challenge. The need to analyze soluble species in the presence of optically opaque material such as yeasts rules out the use of transmission techniques, and off-line methods make real-time monitoring impossible. In situ ATR methods using a ReactionView are ideally suited to this type of analysis. The power of this approach can be demonstrated by monitoring a simple sucrose fermentation with *Saccharomyces cerevisiae* (baker's yeast). Since the mid-IR spectra of sucrose and the fermentation products (glucose, fructose, and ultimate ethanol) fall in the same small spectral area, chemometric methods are needed to identify and follow the development.

However, once a robust calibration has been developed, it is easily automated. Also, **Remspec** fiber-optic probes have the advantage that calibrations can be transferred between probes. *Figure 5* shows the results of mid-IR monitoring of such a reaction during the first 2.5 hr (for more details, see Ref. 1).

Conclusion

By opening up a "spectroscopic eye" into chemical reactions, real-time FTIR monitoring makes parallel process development and rapid process characterization much easier. When the spectroscopic capability is combined with automated reactor control and other techniques such as calorimetry, the technique becomes an extremely powerful tool for understanding and optimizing chemical reactions and for streamlining the entire process development pathway.

References

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2. Haji S, Erkey C. Investigation of rhodium catalyzed hydroformylation of ethylene in supercritical carbon dioxide by in situ FTIR spectroscopy. *Tetrahedron* 2002; 58(2):3929-41.

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