In Situ Spectroscopy

Reaction Analysis and PAT Tools

From Research to Manufacturing

METTLER TOLEDO

Understanding Reaction Chemistry with ReactIR™ *In Situ* Analytical Tools

ReactIR is proven to have the inherent performance, *in situ* sampling versatility and intuitive, powerful reaction analysis software necessary to easily and rapidly provide comprehensive information and understanding about chemistry.

Over twenty years ago, METTLER TOLEDO developed an innovative technology, ReactIR, to enable chemists to thoroughly understand reaction chemistry. The fifth generation ReactIR™ has allowed chemists and engineers to design better, safer and more productive chemistry.

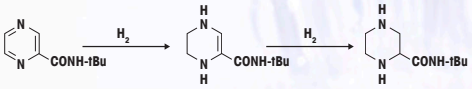
Facing the challenges associated with more complicated processes and under ever increasing schedule pressures, research and development chemists are turning to ReactIR and associated Process Analytical Technology (PAT) to generate critical process knowledge in less time.

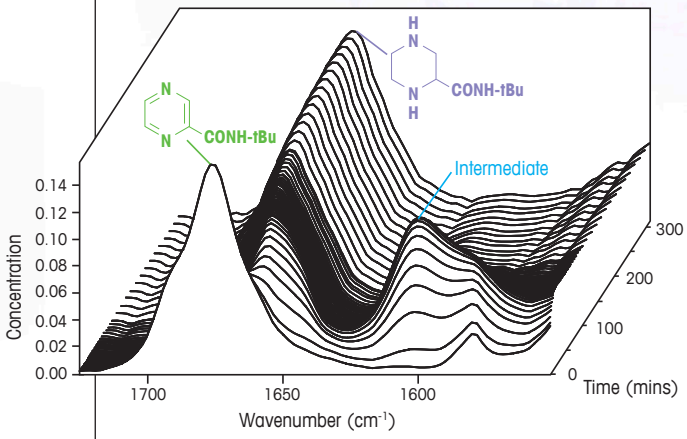
ReactIR, together with HPLC and NMR, is a primary tool for answering fundamental questions about how and why reactions and processes proceed and behave. ReactIR™ operates via the principle of Fourier Transform Infrared (FTIR) spectroscopy. However, chemists and engineers are interested in information, not just spectra. Therefore, ReactIR and iC IR™ reaction analysis software were designed as a powerful, comprehensive technology suite that utilizes FTIR spectroscopy data to allow the non expert to fully realize the power of the system and gain an improved understanding of their chemistry. This is in stark contrast to traditional FTIR spectrometers and operational software that are occasionally required to monitor chemistry.

Providing Answers for Chemical Reaction Analysis

- Unsurpassed spectroscopic performance for accurate and precise reaction species quantification
- Wide range of *in situ* sampling probes and flow cells interface with virtually all reaction vessels to eliminate errors associated with offline analysis
- Powerful software provides answers and eliminates difficulties associated with interpreting IR spectra
- Can monitor and analyze two completely separate reactions simultaneously

An Essential Tool for Understanding Chemistry





- **Tracks** concentration changes of all key reaction species
- **Identifies** reaction endpoint and key intermediate steps
- **Elucidates** reaction mechanism and kinetics
- **Relates** process variables to process performance
- **Minimizes** contact with potentially toxic reagents and/or solvents with *in situ* monitoring

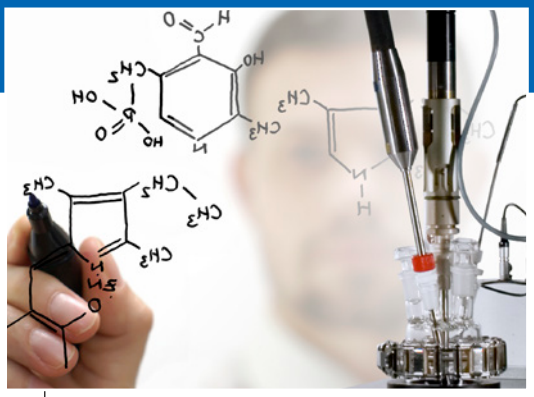
Improved Reaction Understanding
Faster Development and Improved Scale-up

Challenges

- Fast development of the first batch of new compounds at scale
- Development of a viable synthetic route
- Screen critical parameters to resolve potential synthesis bottlenecks

- Reduce scale-up iterations
- Develop high quality process understanding
- Ensure transfer of safe and robust processes

Research and Early-Phase Development



Process Development

ReactIR™ Solutions

- Determine whether target compound has been synthesized and at what yield via *in situ* monitoring of all key reaction species
- Speed the development of a safe first production process of materials for early phase trials by quickly screening reaction conditions for safety and performance
- Develop enhanced process understanding by providing reaction mechanism and kinetics early in the development process

- Gain comprehensive process understanding by continuously monitoring the entire reaction leading to a more robust process with shorter development times
- Determine Critical Process Parameters (CPP) that ensure the process is within optimal design space
- Understand early indicators and fundamental causes of process variance and develop control strategies

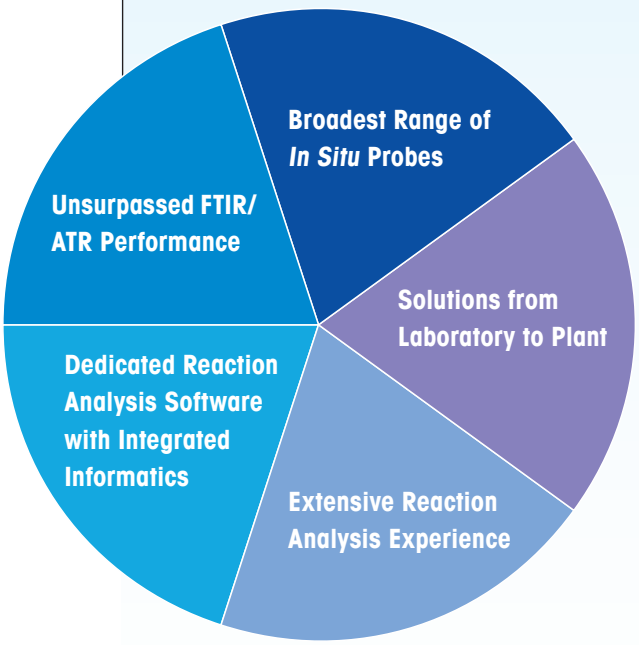
- Eliminate batch failure/costly rework
- Validation of process performance at scale
- Improve cycle time

Manufacturing

- Understand the fundamental causes of process upset and optimize parameters to minimize risk
- Through the use of METTLER TOLEDO PAT tools, ensure quality is designed into the process
- Obtain a more robust process that delivers product with the right target quality attributes

Over twenty years of solving customer process chemistry problems throughout industry and academia have resulted in ReactIR - a simple to use, robust reaction analysis solution that delivers critical information that is otherwise impossible to obtain.

ReactIR is the integration of these various sub-platforms into a versatile package that has been designed exclusively for reaction analysis.



www.mt.com/ReactIR

Learn more about the ReactIR™ integrated solution

Reaction Insight and Understanding

Study Real-World Chemistry
Under Actual Reaction Conditions

Traditional offline methods to analyze reaction chemistry, such as HPLC, NMR, GC, etc. share a common problem – when a sample is removed for analysis it may be altered or compromised resulting in significant analytical errors. ReactIR™ was developed for this very reason. It is ideal for studying chemistry as it actually exists in the reactor, eliminating time delays and errors resulting from "grab sampling" analysis.

Why *In Situ* FTIR Analysis over Offline Methods?

- A critical intermediate may be present that is lost in offline sampling
- Air, accidentally introduced when a sample was removed for analysis, can change the chemistry
- Reaction toxicity is significant enough to prohibit exposure
- The reaction is run under pressure and/or extreme temperatures - removing a sample may alter the chemistry, invalidating the analysis

ReactIR™ *In Situ* probes

- Temperatures from -120 °C to 400 °C
- Pressures from vacuum to 350 bar
- Superacids to highly basic chemistry
- Slurries and reactions with larger particles/bubbles present
- Highly oxidizing conditions
- Submillimolar concentration reagents
- Precise reaction temperature monitoring coupled with infrared monitoring
- Continuous flow chemical processes
- Integrated temperature sensor - reaction temperature trending with each spectrum

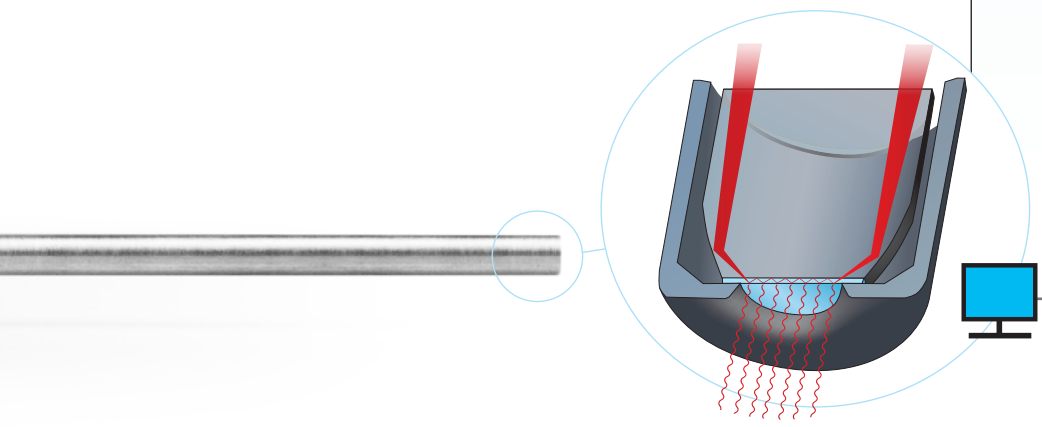
Tough Chemistry Challenges?

Just insert the probe and analyze – no matter what the chemistry!

- ✓ Highly Corrosive Chemistry
- ✓ High Temperatures and Pressure
- ✓ Slurries, Catalysts and Particles
- ✓ H_2O or any Organic Solvent-Based System
- ✓ Highly Acidic or Basic

Versatile ReactIR Probes make *In situ* FTIR Analysis Straightforward

In 1994, METTLER TOLEDO introduced the first FTIR *in situ* optical probe capable of handling a vast array of chemistries. Thousands of probes have been installed that have analyzed tens of thousands of chemistries. The patented DiComp™ probe uses a virtually indestructible diamond as the sensor and while over 80% of applications are successfully analyzed by the standard DiComp ™ probe, other probe variations have been developed to address specific requirements such as ultra high sensitivity analysis (ppm level) and homogeneous catalysis applications. Our many years of application experience has supported the development of a series of sampling technologies that allows the study of virtually any chemistry in the lab or the plant.



www.mt.com/ReactIR

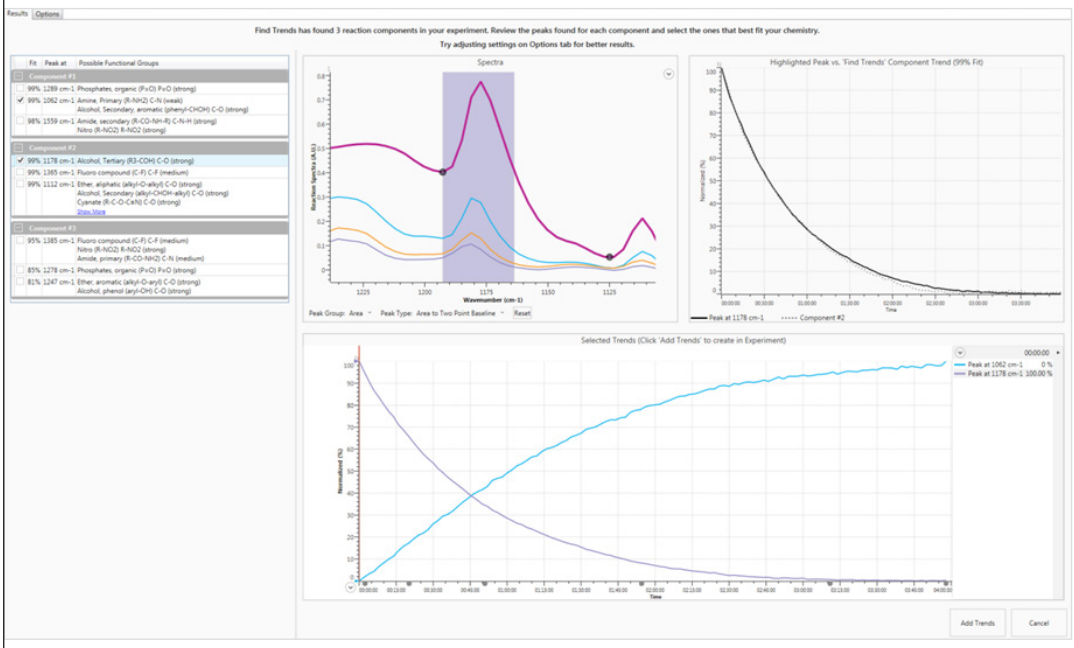
View the ReactIR™ Method of Measurement Video

Intuitive, Intelligent iC IR Software
Transforms Data into Information

iC IR™ software was designed to take infrared data and convert it into useful and meaningful information about chemical reactions, in real time. The result of an extensive research project on how scientists analyze reactions, iC IR allows chemists and engineers to quickly gain an understanding of their chemistry.

ReactIR collects data in the mid infrared spectral region, which provides characteristic fingerprint region bands that are associated with fundamental vibrations in the molecules of interest. iC IR takes this spectral data and converts it to reaction information that is then used for understanding the reaction chemistry. All key reaction species are tracked as a function of concentration and time, while the reaction takes place.

Feature Focus: One Click™ Reaction Profiling



Looking for the correct functional bands to profile in a reaction can often take a few hours for a complex reaction. The Find Trends function takes over 20 years of expert knowledge and profiles a reaction with a single click. Find Trends simultaneously generates orthogonal models of the reaction to provide the user with the best confidence of how to follow the reaction. The higher the correlation between the models, the higher the result confidence.

Software Spotlight: A Faster Way to Optimize Chemistry

iC Kinetics™ software helps chemists and engineers quickly optimize chemical reactions by automatically developing a kinetic model that describes the influence of various experimental parameters on the rate of a chemical reaction. The kinetic model can be used to simulate the effect of concentration and temperature on the performance of the reaction.

This information is generated in fewer experiments than a traditional approach, leading to a faster method to understand and optimize chemical reactions.

iC Kinetics:

- Optimize reactions faster
- Study process robustness
- Understand catalyst performance
- Analyze reaction driving forces

www.mt.com/iCKinetics

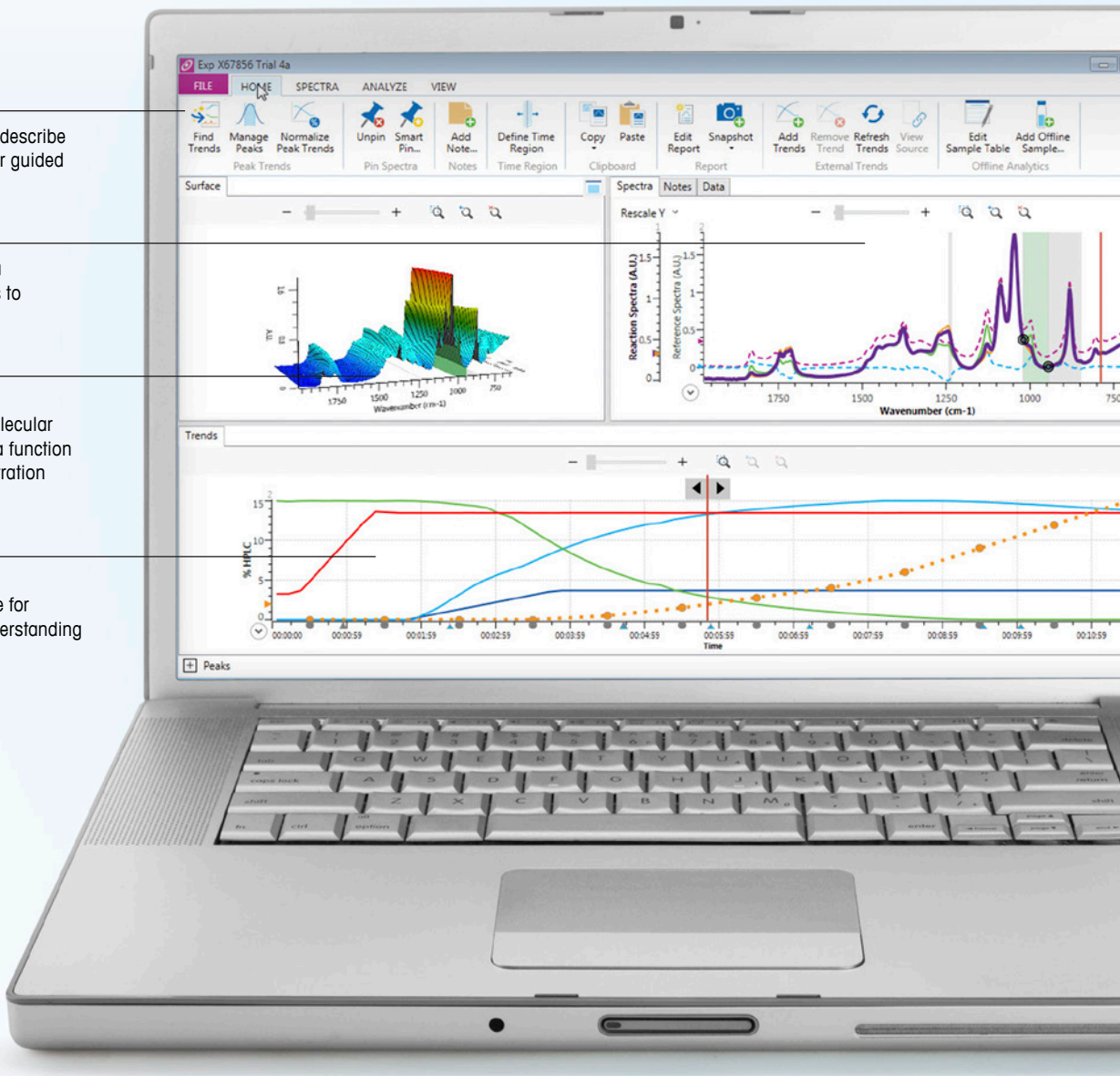
Learn more about Powerful Data Interpretation

Ribbon-based controls describe the optimal workflow for guided reaction analysis

Compare single spectra of reaction components to reference spectra

Visualize entire reaction process in 3D for a "molecular video" of chemistry as a function of time, relative concentration and functional group

Compare trends of key components in real time for immediate reaction understanding



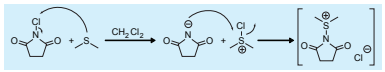
Proven Results for Virtually Every Class of Chemistry

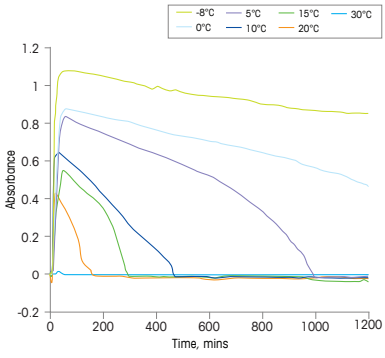
After thousands of reactions and hundreds of reaction classes successfully monitored by ReactIR, METTLER TOLEDO has developed *in situ* FTIR as a seminal methodology alongside NMR and HPLC for understanding and scaling-up complex chemistry.

METTLER TOLEDO is the world leader in *in situ* spectroscopy technology and provides scientists with tools to continuously monitor a chemical reaction for a deeper understanding of reaction kinetics, mechanisms and pathways.

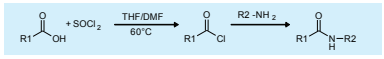
Two decades of working with chemists and engineers to understand and improve chemistry has developed into a product suite that can tackle a wide range of chemistries under many different reaction conditions.

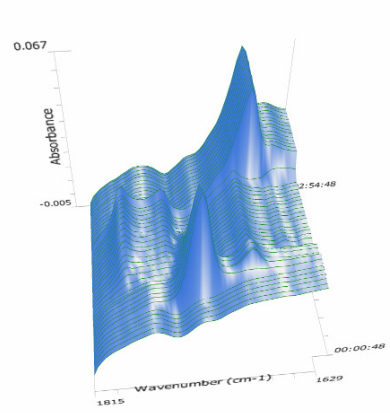
Easily Analyze Chemistry - Even Under Challenging Conditions



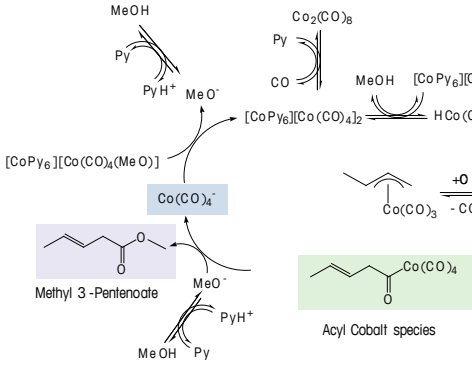


Highly Acidic or Basic

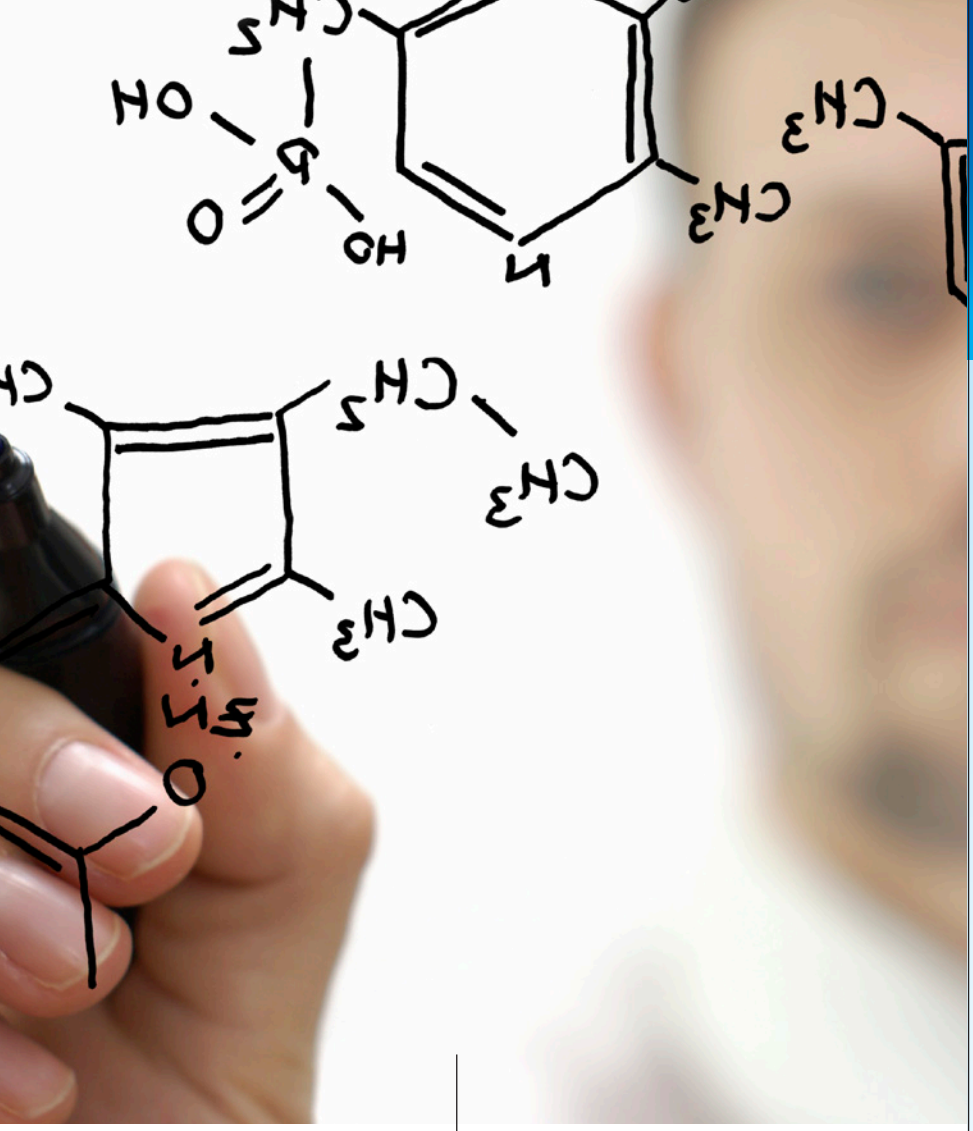




Highly Oxidizing and Corrosive



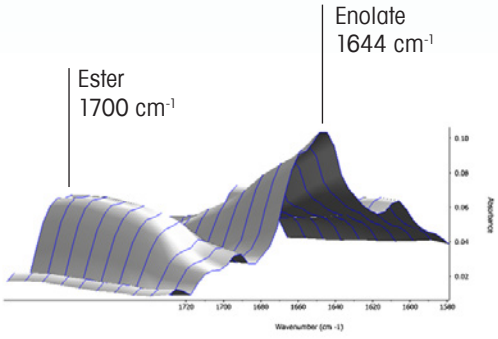
Temperature and Pressure Extremes



Application Spotlight

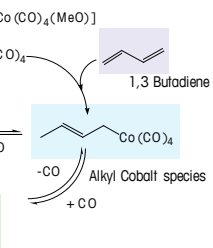
Demanding Sensitivity for Low Concentration Chemistry

Enolates and related carbanions generated using the hindered non-nucleophilic base lithium diisopropylamide (LDA) have attained a prominence in organic chemistry enjoyed by few reagents. Due to the important role of enolates in organic chemistry, their instability under ambient conditions and relative low concentration reactions (millimolar), an *in situ* method capable of trending concentrations and reaction progress in real time is valuable. In fact, several advantages of *in situ* spectroscopy compared to *ex situ* techniques can be demonstrated with the following example: the LDA-mediated enolization of an ester (tert-butyl proprionate). By using an *in situ* SiComp™ (silicon ATR) extended pathlength probe, conversion of this ester to the enolate can easily be monitored, especially given the millimolar concentration level and the very low reaction temperature (-78°C).



ReactIR has enabled scientists to develop a better understanding of their chemistry for a wide range of applications including:

- Organic synthesis
- Organometallic chemistry
- Continuous flow chemistry
- Catalysis
- Biocatalysis
- High pressure chemistry
- Low temperature chemistry
- Green chemistry
- Polymer synthesis
- Kinetics
- Highly reactive chemistry
- Slurries, catalysts and particles



We ran out of space, but not applications!
Visit **www.mt.com/ReactIR** for more information

A Product Family Providing Solutions
For Product and Process Development

ReactIR is used in the lab for organic synthesis, process development and as a Process Analytical Technology (PAT) tool to enable scientists to gain a deeper insight into their chemistry. It is one of the most valuable tools for measuring and understanding reaction progression, initiation, conversion, intermediates and endpoint. ReactIR determines if the desired reaction occurred and provides associated endpoint determination without offline analysis.

ReactIR 45m

ReactIR 15

Whether you're an expert or a first time user, there is a ReactIR uniquely suited to you and your application. ReactIR 15 is the ideal tool for synthetic organic chemistry development and ReactIR 45m is uniquely designed for the demanding requirements of kinetics and quantitative analyses.

MultiplexIR™
Double the productivity of your ReactIR 45m with multiplexed fiber probes and an automated lab reactor system, EasyMax™

FiberConduit™
Easy to position and reproducible for fast setup and accurate results

DS Micro Flow Cell
Inline continuous chemistry monitoring. Monitor single or multiple streams with one system.

Mirrored Conduit
Ideal for complete measurement window and ultra high pressure or temperature applications

Intrument Performance Assurance (IPA) Module
High quality data assurance – NIST polystyrene calibration and validation of wavenumber axis

Application Spotlight

Faster Structural Information in Real Time

Continuous flow chemistry is essential for improving product quality and yield, as well as increased personal safety. Combining the highly molecular specific nature of FTIR to continuous flow chemistry enables researchers, scientists and engineers to quickly and easily develop continuous flow processes for their products that would otherwise be developed via a traditional batch process. ReactIR™ with the DS Micro Flow Cell is a seamless, *in situ* measurement and monitoring solution for continuous flow chemistry processing. DS Micro Flow Cell provides real time chemistry knowledge for virtually any class of compound with the minimum amount of time and material.

- Steady-state determination
- Reaction mechanism/pathway
- Immediate reaction start point
- Detection of transient intermediates
- Eliminates sampling
- Universal (fits with any flow system)
- Monitor up to two flow systems simultaneously

Solutions from the Lab to the Plant
Scale up, Pilot Plant, and Manufacturing

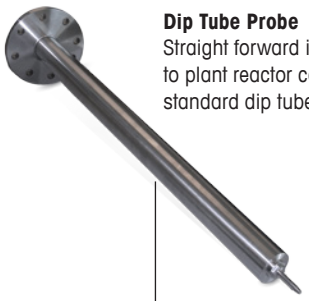
ReactIR is used for scale-up studies, campaigns and production monitoring. It provides non-destructive, rapid, quantitative chemical analysis of key reaction components in the reactor. ReactIR for production supports the design of safe and robust processes that build quality into the commercial process. This allows process consistency, batch repeatability and eliminates failure at the manufacturing scale.

For pilot plant, campaigns and process monitoring applications that require operation in a classified environment. ReactIR™ for production applications provides real-time information and critial process parameters.

ReactIR 45P

Application Spotlight

Flow Cell
Fast or slow loop integration for in-process industrial monitoring

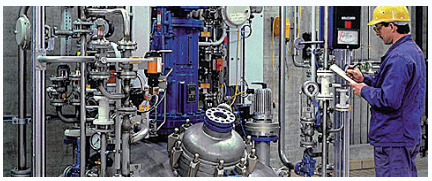


Dip Tube Probe
Straight forward interface to plant reactor cover via standard dip tube

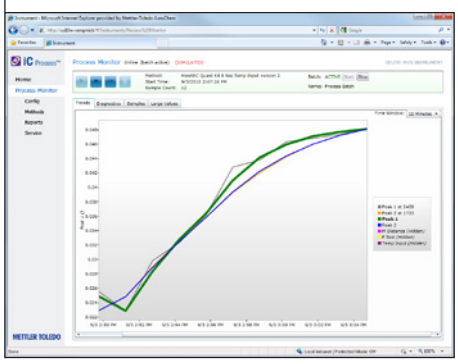
Hydrogenations
Understand reaction kinetics and selectivity to develop a safe, efficient and scalable manufacturing process for the hydrogenation of pyrazine caboxamide to form piperazine carboxamide. ReactIR™ allowed the identification of the intermediate species and its reactivity enabling the development of a safe, efficient manufacturing process.

Green Process Design
Understanding the mechanisms of chemical reactions to develop green, competitive technologies. ReactIR™ provides information of detectable species in solution under reaction conditions in real time and can be used for kinetic and thermodynamic studies.

Intrument Performance Assurance (IPA) Module
High quality data assurance – NIST polystyrene calibration and validation of wavenumber axis



Chemical Development
Develop robust processes suitable for the manufacturing environment. ReactIR™ is proven to be a very useful technique in scale-up support, mechanism elucidation, and identification of short-lived intermediates.

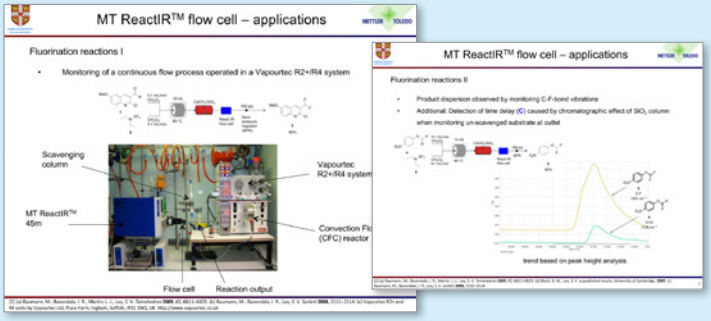


Software Spotlight: Linking Laboratory to Production
Specifically designed for the production environment, iC Process™ enables the transfer of Critical Control Parameters (CCP) determined in the laboratory

Learn More with our
Technical Webinar Program

Our live and on-demand webinars (online seminars) provide application and industry information relevant to you. These interactive presentations, provided by industry experts and our own applications team, give you an opportunity to learn more about your specific area of interest.

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



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™
- Marshall reaction using Future Chemistry microfluidic devices

Additional topics include reaction kinetic analysis, recent advances in organic chemistry, organic synthesis and reaction analysis, process development and scale-up, process monitoring and much more!

▸ **www.mt.com/ac-webinars**

www.mt.com/ReactIR

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