InsightMR

The Solution for online Process Monitoring

-NMR在线监控化学反应过程的解决方案

吕娟

Bruker Webinar, August 2016

Content

- Why reaction monitoring?

  为什么要进行反应监测？
- Reaction monitoring by NMR

  用NMR来进行反应监测
- InsightMR
  - Software part 软件功能介绍
  - Hardware part 硬件配置介绍
- Conclusions 总结

Lab

Why Reaction Monitoring

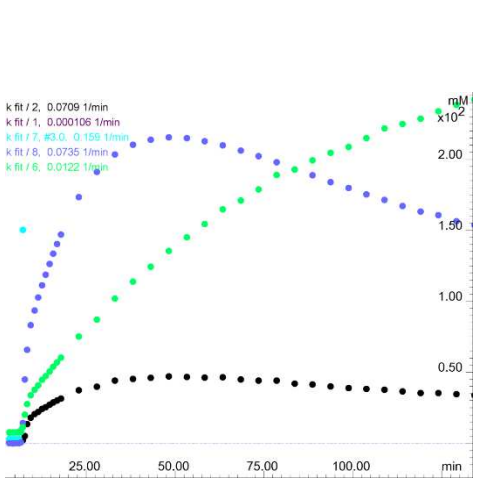
- Purpose:
  - Reaction completion determination 反应完成
  - In-situ yield determination 原位产率
  - **Reaction understanding**: mechanism 反应机制
  - Extracting kinetic parameters from the time course data: activation energy, rate constant
    提取动力学参数：活化能，速度常数（物化）
  - **Kinetic modelling** 动力学模拟
  - Process optimisation 工艺优化

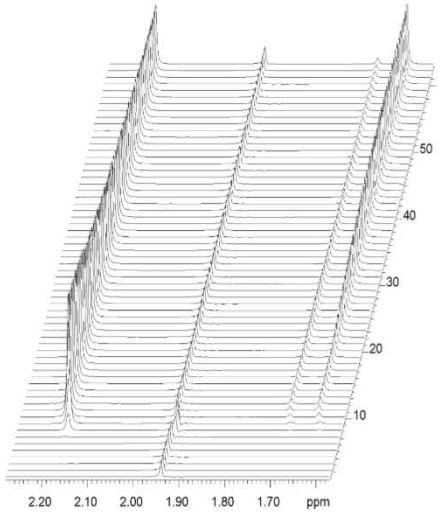
- Applications:
  - Chemistry (e.g. catalysis) 化学
  - Stability, degradation studies, crystallisation稳定性研究，降解研究，晶体化研究
  - Dissolution 分解
  - Bio transformations, fermentation生物转化，发酵
- Classic method – gained popularity recently. e.g. PAT –process control

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070305.pdf

Reaction Monitoring by NMR

Advantages





- Quantitative by default: no need to calculate response factors **定量**
- Information rich: possible to elucidate the structures of starting materials, products, and intermediates **定性**

Reaction Monitoring by NMR

Type of measurements

- **At-line** sampling then measuring in a tube (or transfer)
- **In-line**
  - monitoring reaction in an NMR tube

    problem: dead-time between mixing reagents(outside the tube)and acquisition. Not good for fast reactions

    not always real conditions(e.g. temperature)
  - reagents flow and mix just before entering the NMR probe or in the probe
- **On-line** reaction vessel next to the magnet. Sample flows out and then back

Special issue research article

MRC

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(wileyonlinelibrary.com) DOI 10.1002/mrc.4259

Reaction monitoring using online vs tube NMR spectroscopy: seriously different results

David A. Foley,[a]* Anna L. Dunn[a,b] and Mark T. Zell[a]

We report findings from the qualitative evaluation of nuclear magnetic resonance (NMR) reaction monitoring techniques of how each relates to the kinetic profile of a reaction process. The study highlights key reaction rate differences observed between the various NMR reaction monitoring methods investigated: online NMR, static NMR tubes, and periodic inversion of NMR tubes. The analysis of three reaction processes reveals that rates derived from NMR analysis are highly dependent on monitoring method. These findings indicate that users must be aware of the effect of their monitoring method upon the kinetic rate data derived from NMR analysis. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: NMR reaction monitoring; online NMR; reaction mechanism

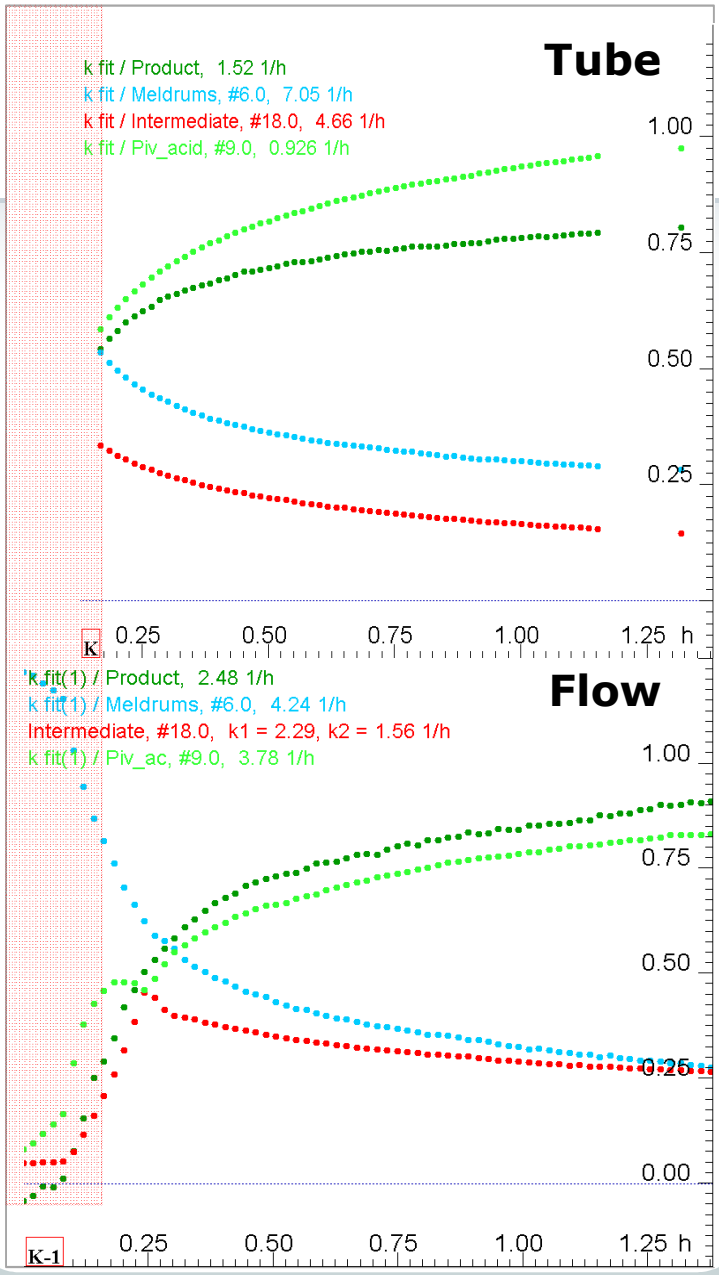
Introduction

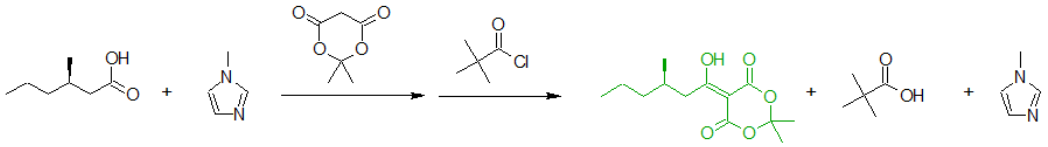
Nuclear magnetic resonance (NMR) is an extremely powerful tool for the analysis of reaction mixtures. Not only can NMR be used as a quantitative method of monitoring reaction processes, it also has the advantage of providing detailed structural information

vessel allows replication of reaction conditions while allowing for analysis in an essentially unperturbed state. There are examples of online NMR reaction monitoring being applied at both high and low fields.[6]

The third method, stopped-flow NMR (iii), is typically used for the detection of rapid kinetics (within 2.5–100 ms of reagents mixing), a

NMR

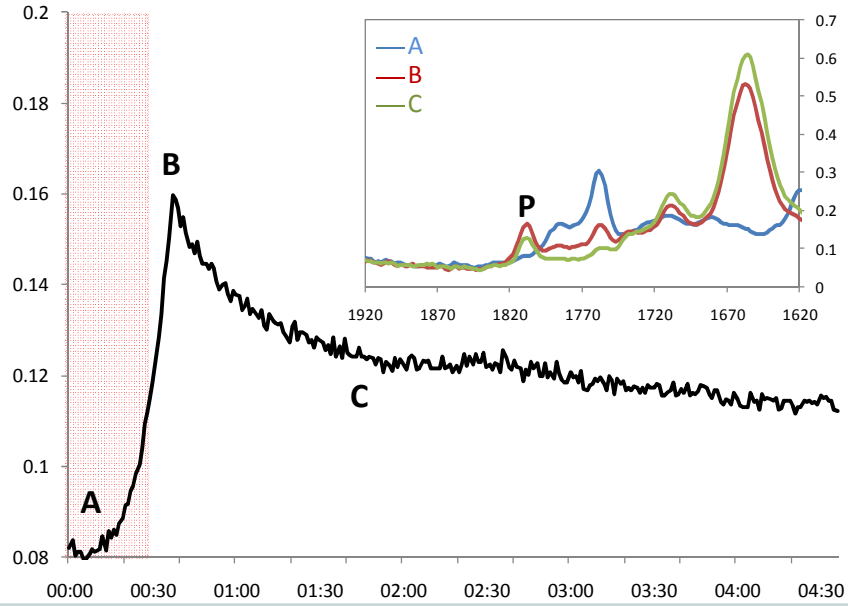




Flow *vs* Tube:

- ✓ Better captures the start of the reaction
- ✓ Mimics real reaction conditions: stirring, Te, P
- ✓ Enables the simultaneous acquisition IR, pH, MS

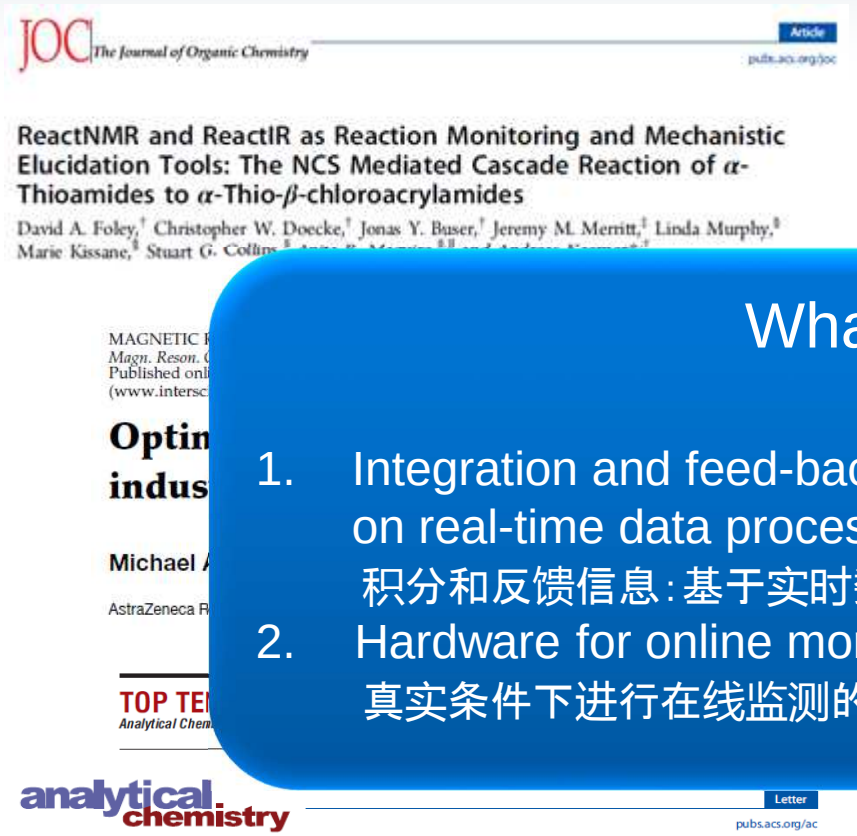
IR



Clegg, I. M., et.al.; *Anal. Methods*, **2012**, 4, 1498-1506 // Dunn A.L. et . al, MRC, DOI: 10.1002/mrc.4317

Reaction Monitoring by NMR

Unparalleled Information for Reaction Understanding



JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

ReactNMR and ReactIR as Reaction Monitoring and Mechanistic Elucidation Tools: The NCS Mediated Cascade Reaction of α-Thioamides to α-Thio-β-chloroacrylamides

David A. Foley,† Christopher W. Doecke,† Jonas Y. Buser,† Jeremy M. Merritt,‡ Linda Murphy,§ Marie Kissane,§ Stuart G. Collins,§

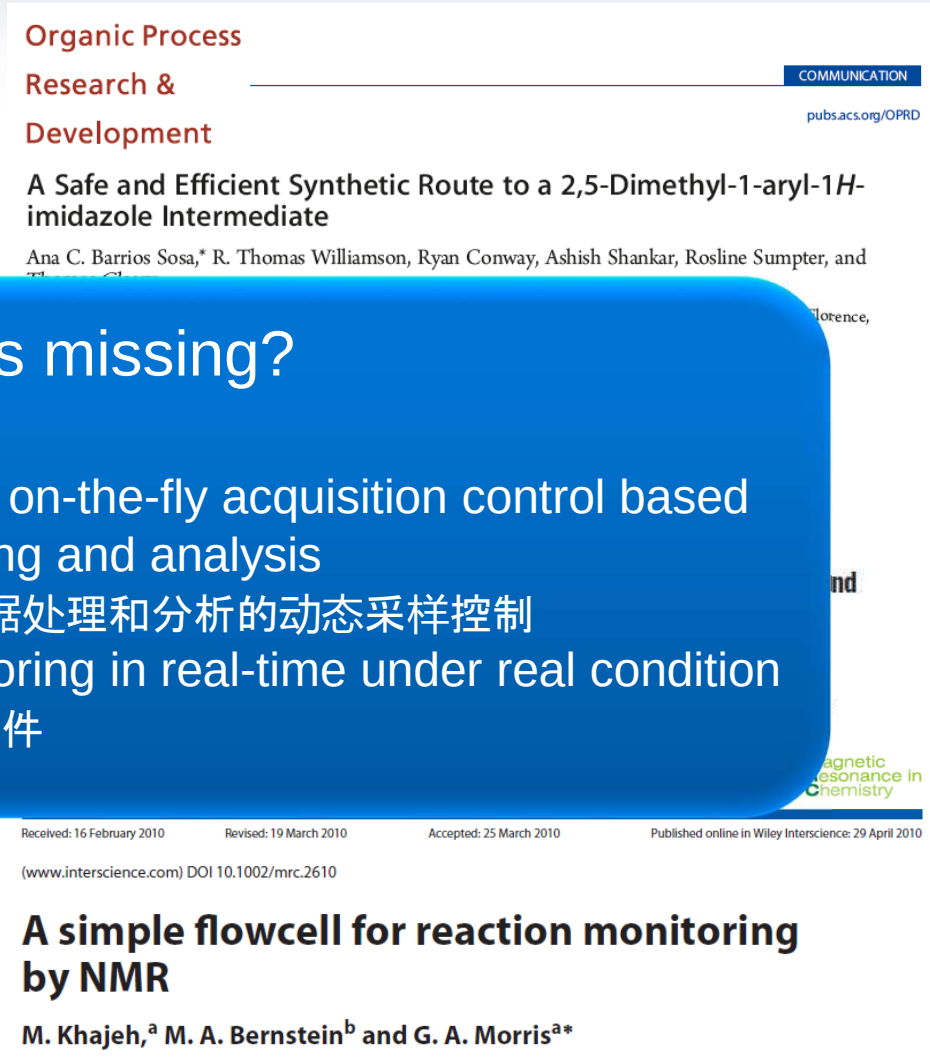
analytical chemistry

Letter

pubs.acs.org/ac

Online NMR and HPLC as a Reaction Monitoring Platform for Pharmaceutical Process Development

David A. Foley,* Jian Wang, Brent Maranzano, Mark T. Zell, Brian L. Marquez, Yanqiao Xiang, and George L. Reid



Organic Process Research & Development

COMMUNICATION

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A Safe and Efficient Synthetic Route to a 2,5-Dimethyl-1-aryl-1*H*-imidazole Intermediate

Ana C. Barrios Sosa,* R. Thomas Williamson, Ryan Conway, Ashish Shankar, Rosline Sumpter, and

Received: 16 February 2010 Revised: 19 March 2010 Accepted: 25 March 2010 Published online in Wiley Interscience: 29 April 2010

(www.interscience.com) DOI 10.1002/mrc.2610

A simple flowcell for reaction monitoring by NMR

M. Khajeh,[a] M. A. Bernstein[b] and G. A. Morris[a]*

What's missing?

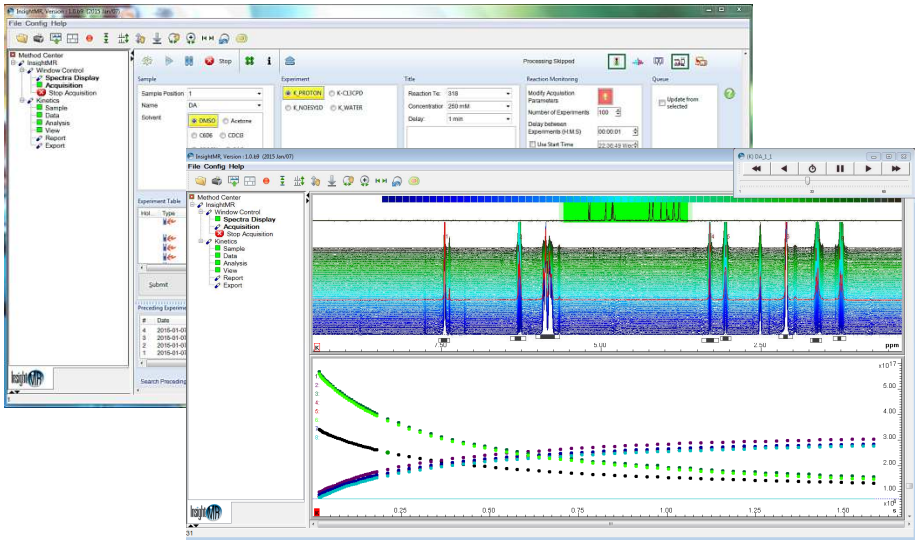
1. Integration and feed-back: on-the-fly acquisition control based on real-time data processing and analysis
   积分和反馈信息:基于实时数据处理和分析的动态采样控制
2. Hardware for online monitoring in real-time under real condition
   真实条件下进行在线监测的硬件

Reaction Monitoring

InsightMR

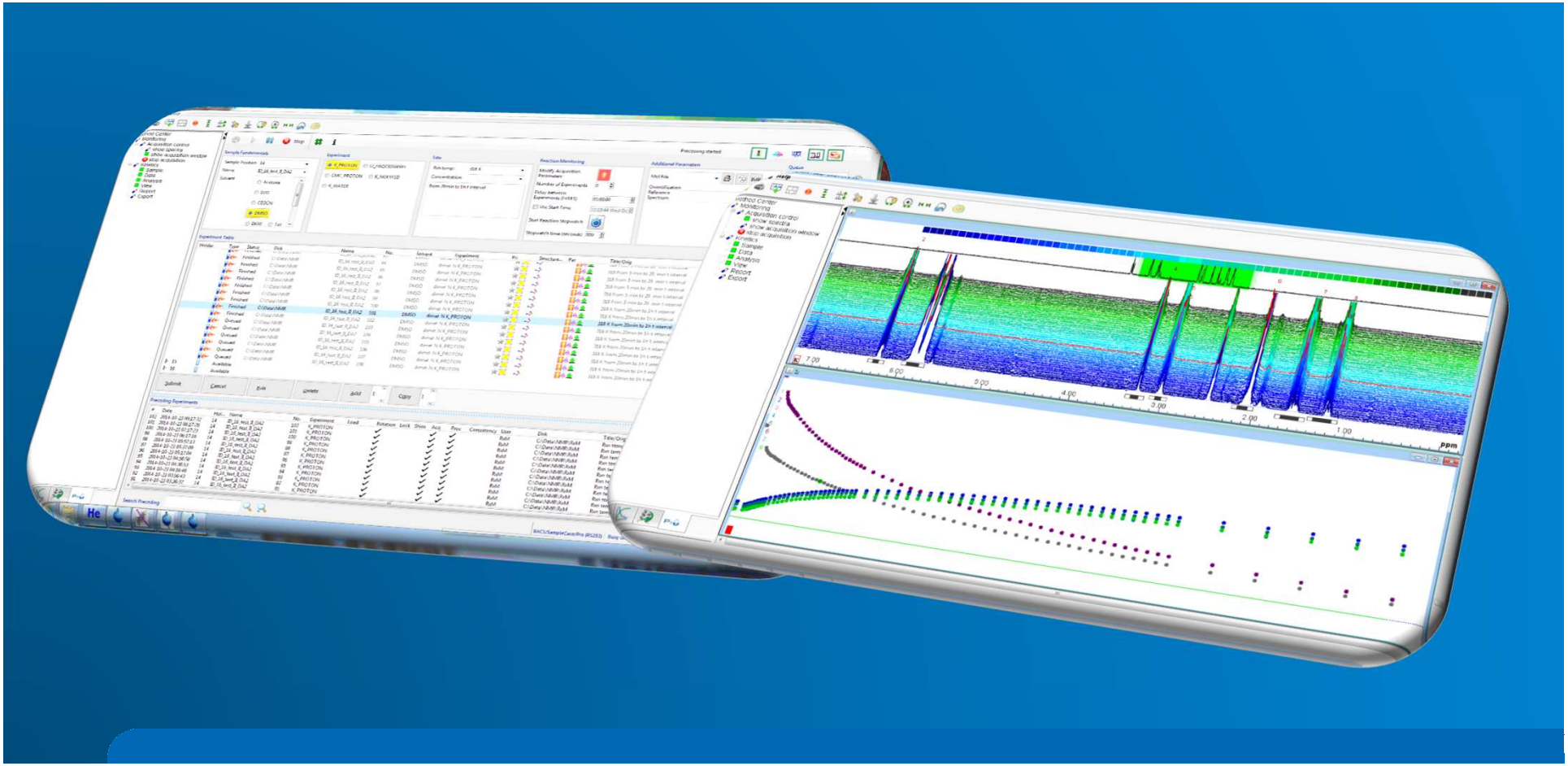
The Solution for Process Monitoring

*InsightMR flow tube**



InsightMR software:
TopSpin+IconNMR+Dynamic center
(TS 3.5 Windows)

InsightMR Software



InsightMR software part

Key features

- A single interface for automated acquisition control, interactive processing and analysis, resulting in real-time kinetic profiles

  自动采样控制、交互式处理和分析的单一界面，可完成实时动力学轮廓

- Acquisition and real-time analysis of a series of 1D NMR spectra, using different nuclei and interleaved experiments

  支持对一系列采用不同核和隔行扫描的1D NMR谱图进行采样和实时分析

- On-the-fly acquisition parameters adjustment based on real-time kinetic data

  基于实时数据处理和动力学轮廓计算，进行即时采样参数调整

- Simultaneous monitoring of multiple reactions at the same time using parallel acquisition and analysis capabilities

  运用平行采样和分析的功能在同一时间对多个采样进行同步监控

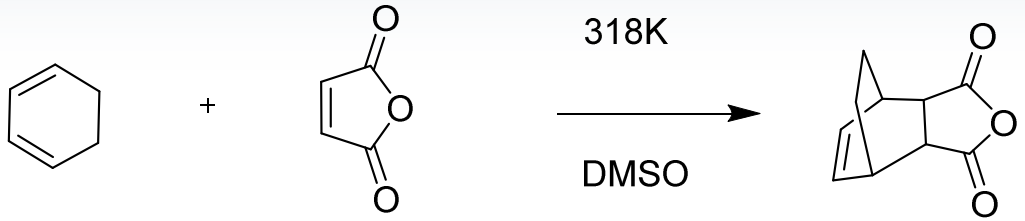
- Default kinetics parameters provided for both deuterated and non-deuterated solvents

  提供默认的动力学参数设置，能够容易地设置实验来观测氘代溶剂或非氘代溶剂中的反应过程

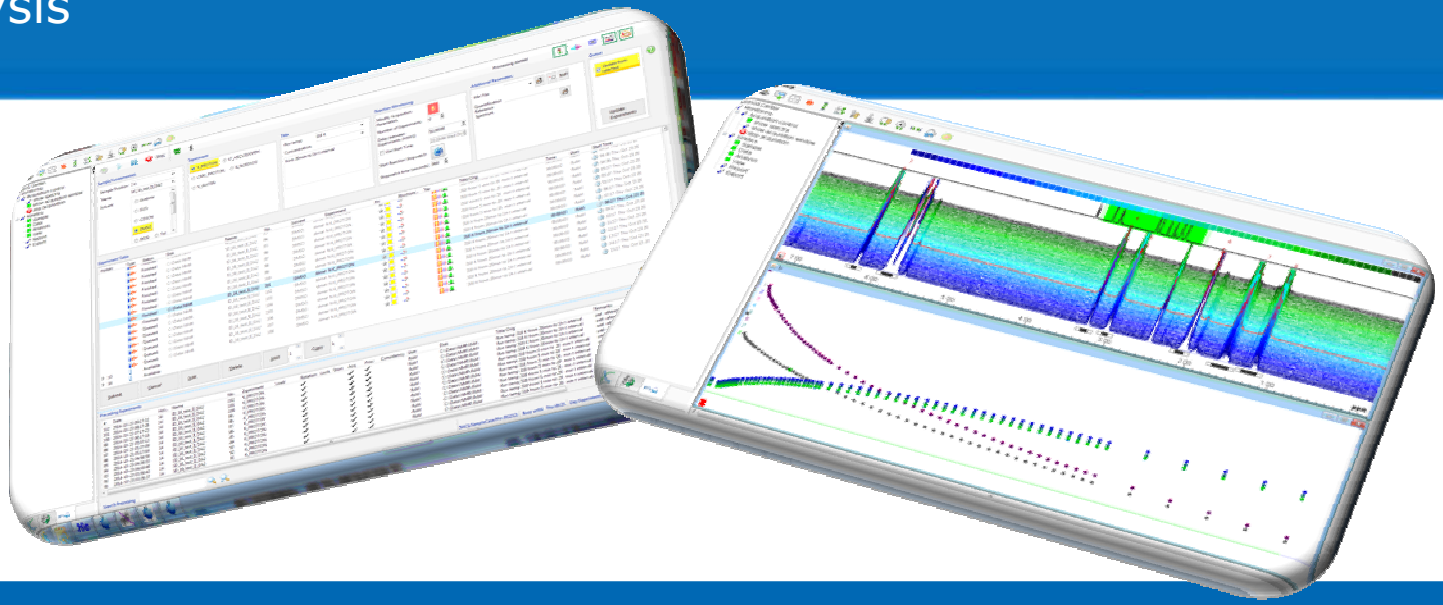
InsightMR software part

- A single platform for acquisition control, interactive processing and data analysis

A Quick Demonstration
Simple Diels Alder



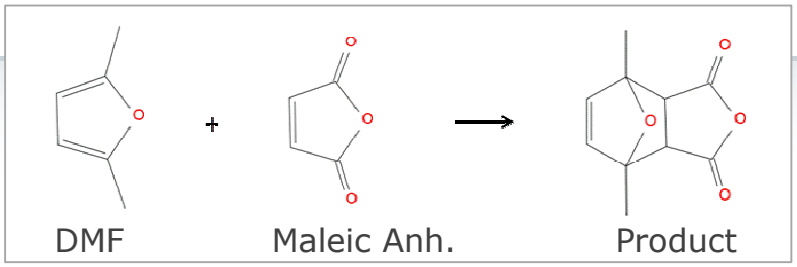
Key Message: Fully integrated acquisition, data processing and analysis



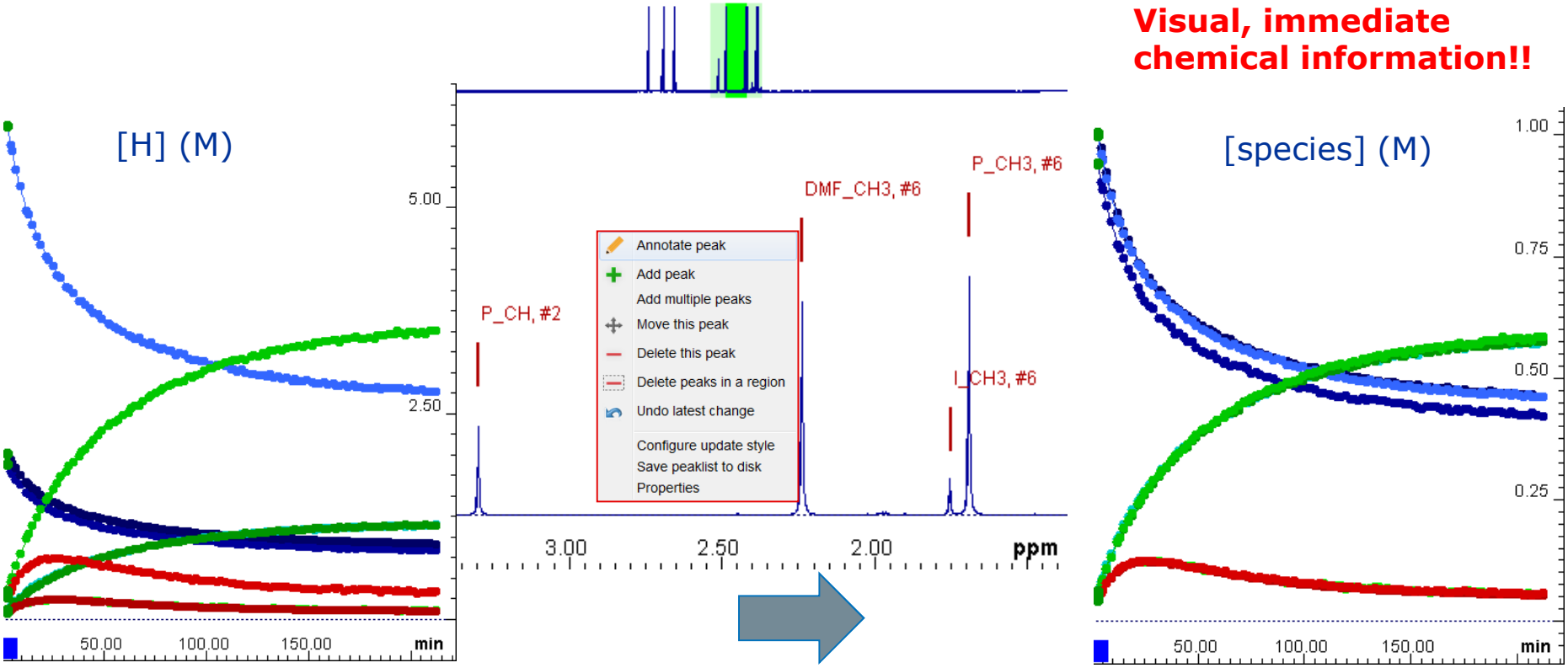
Functionality Overview

Answers to Chemical Questions

Concentration Profiles

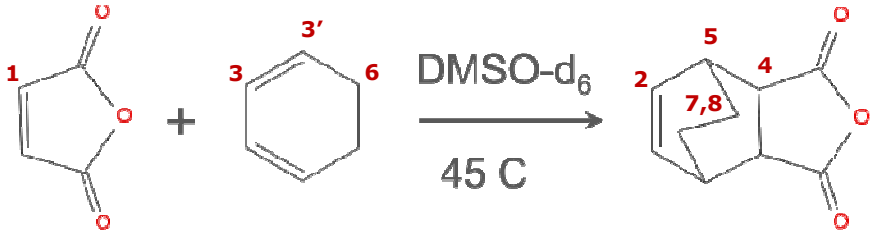


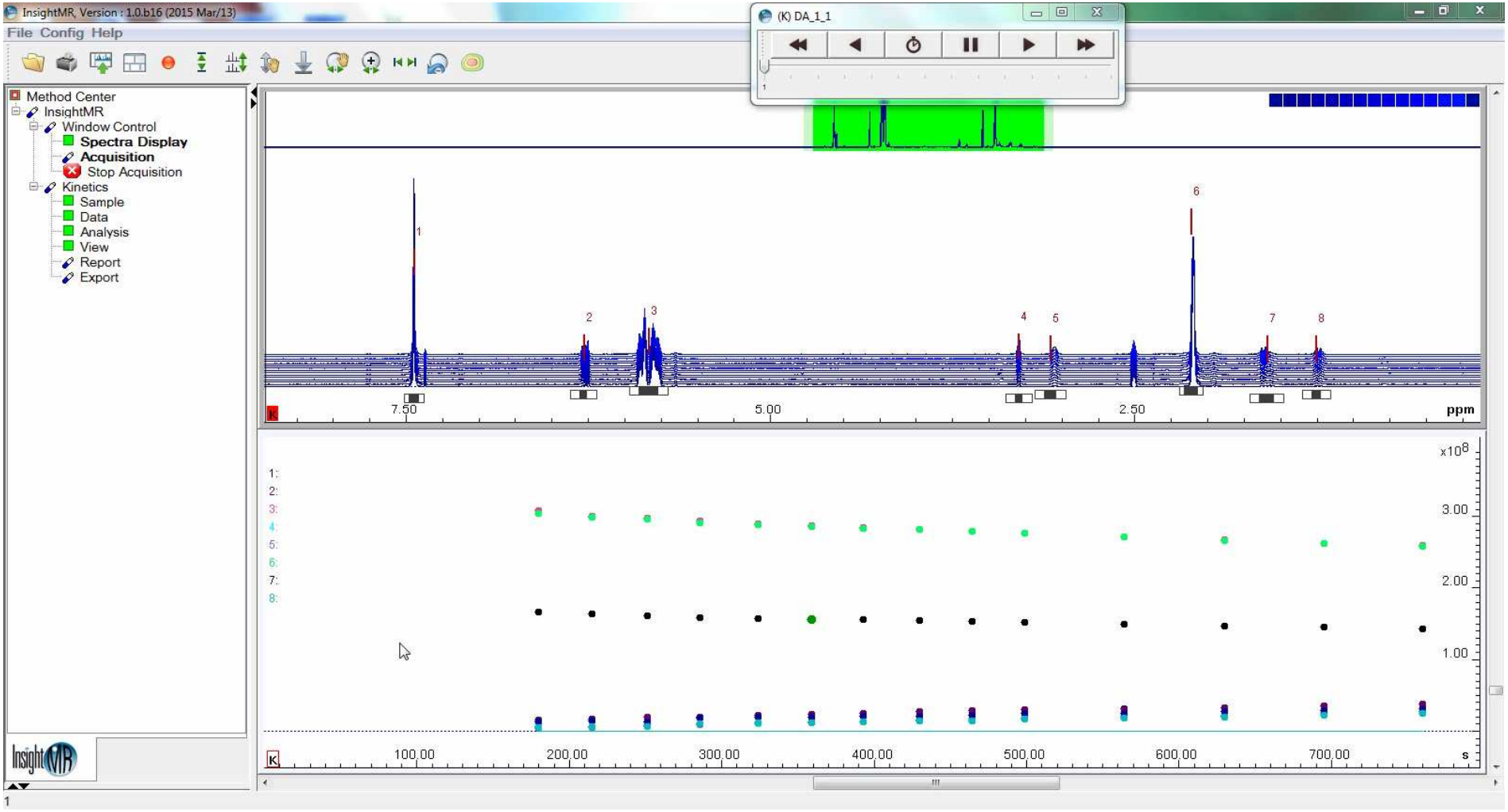
Visual, immediate chemical information!!



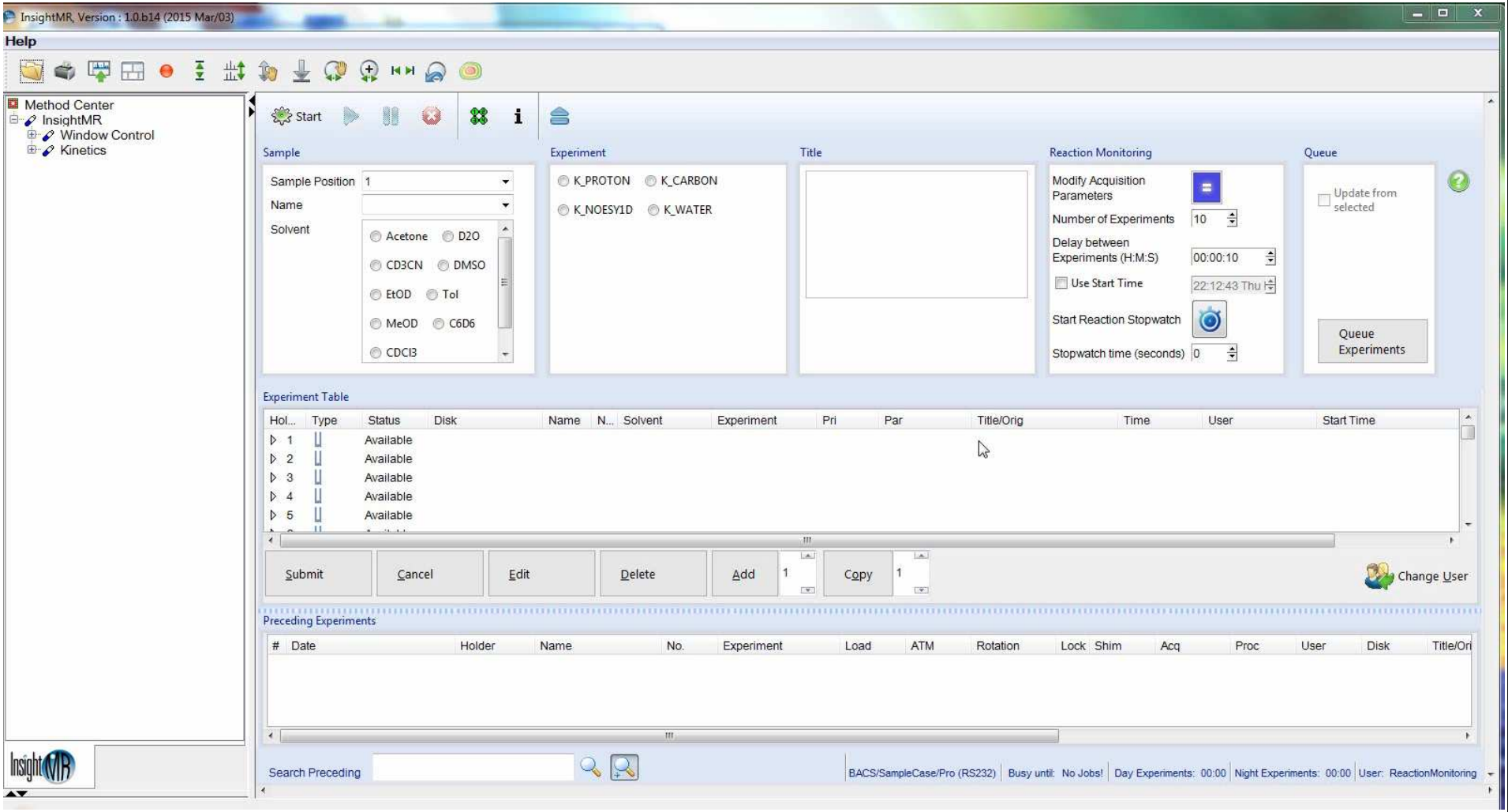
InsightMR Software 1.0

Concentration Profiles



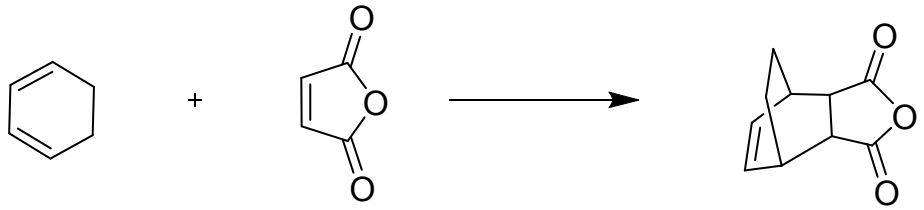


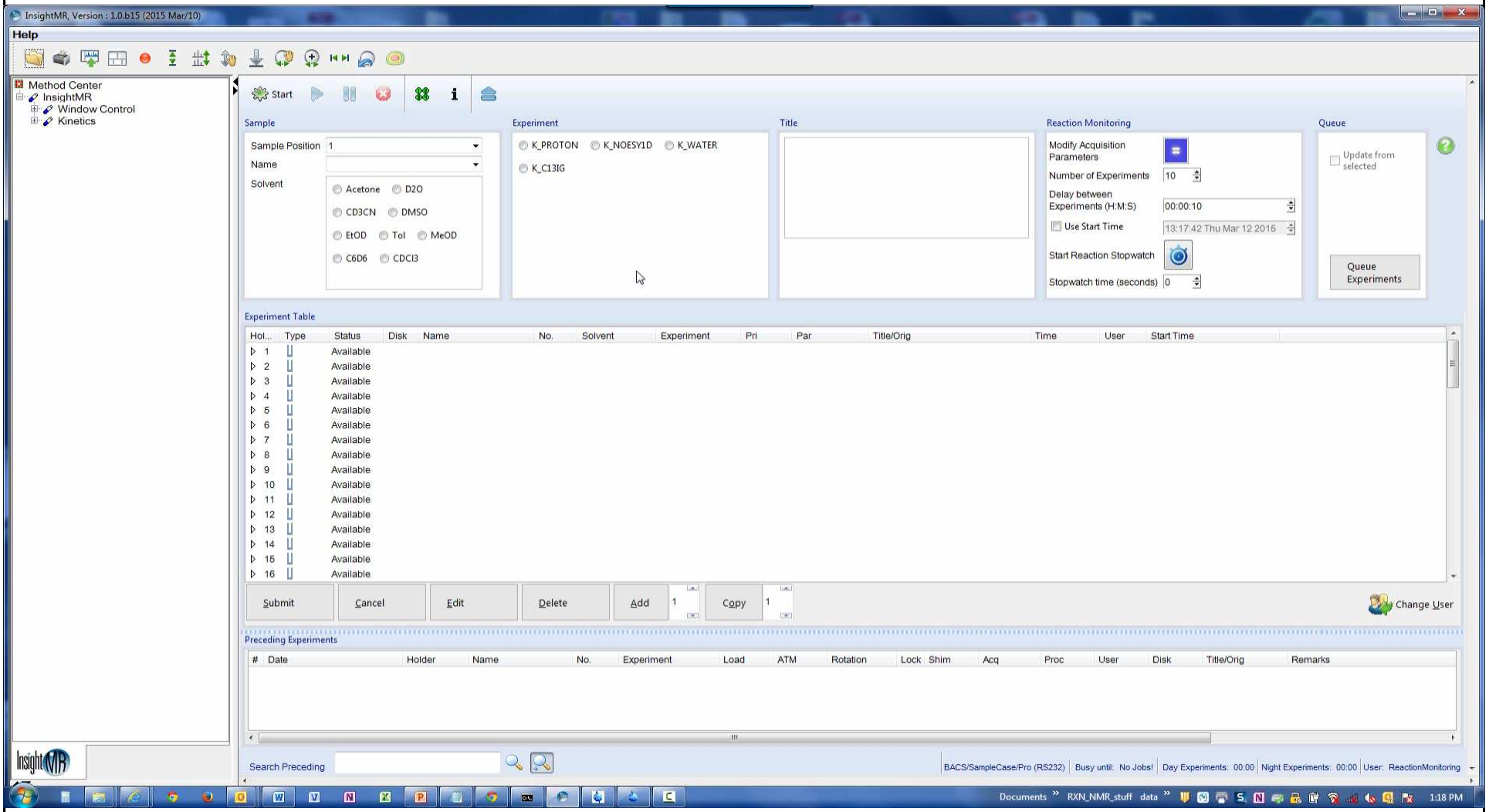
Multiple Samples Run in Parallel



InsightMR *Software* **1.0**

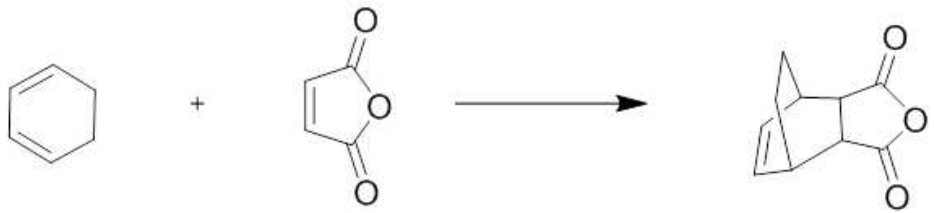
Interleaved Experiments

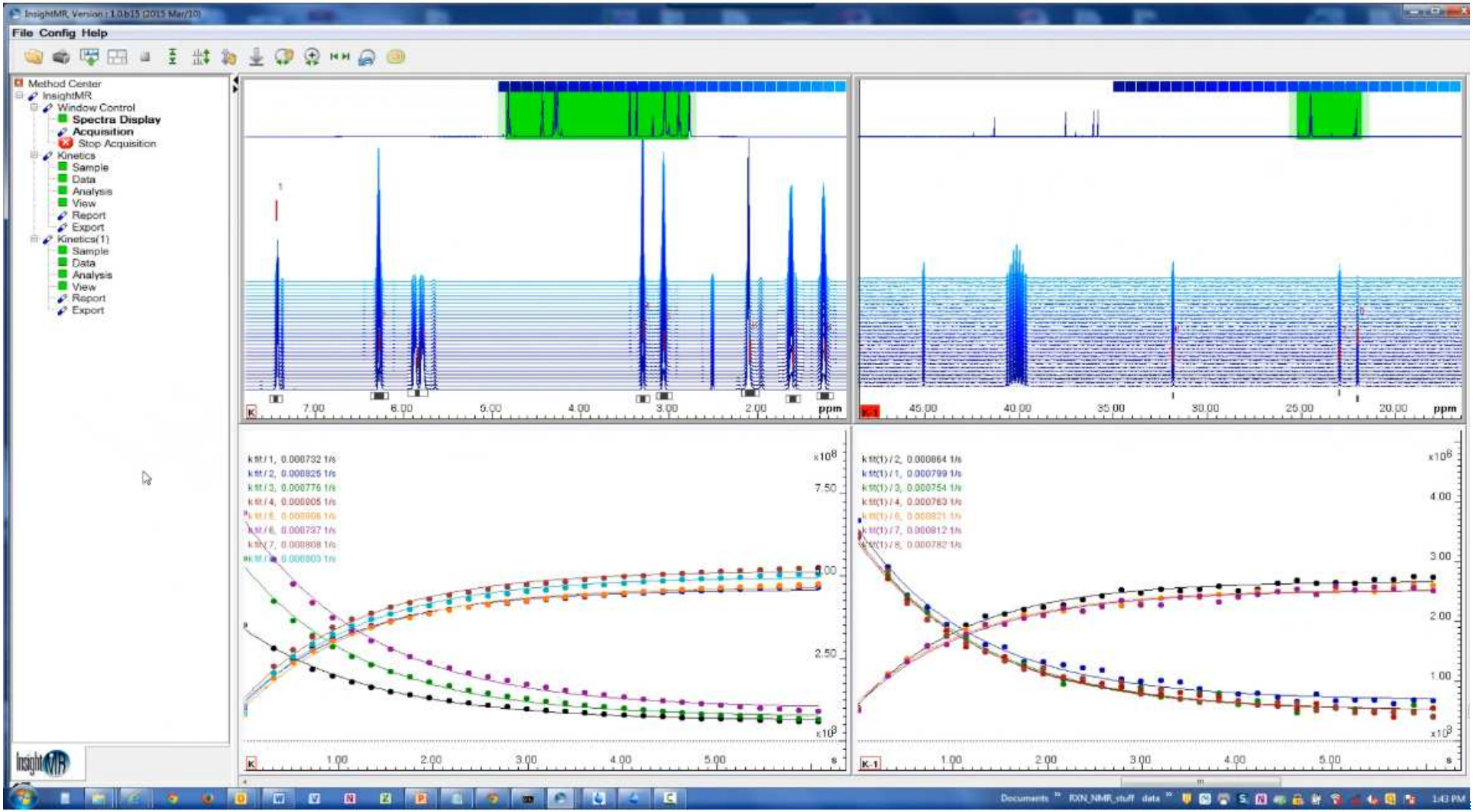




InsightMR Software 1.0

Interleaved Experiments

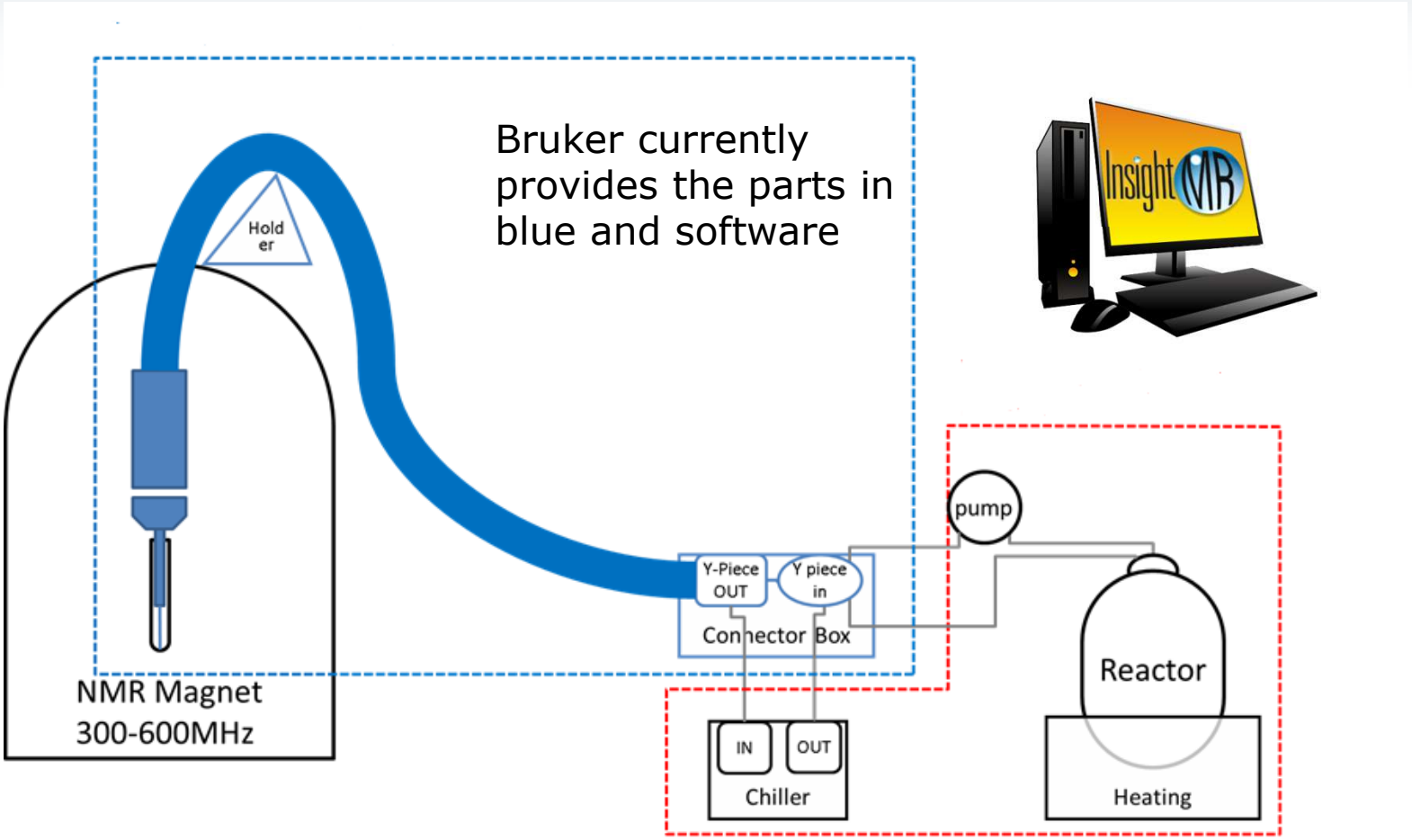




InsightMR Flow Tube

InsightMR hardware part

laboratory setup



InsightMR hardware part

Flow tube features

- Real-time monitoring（实时监测）
- Compatible with Bruker 5 mm probes（与Bruker 5mm 探头兼容）
- **Temperature control** transfer lines（控温传输线）
- Withstand **pressures over 10 bar**（承受压力超过10bar）
- **Interchangeable glass tube**（可更换玻璃管）
- Proven robustness - industry tested（工业测试证明稳定）
- Simultaneous acquisition of：NMR, IR, pH, MS…（可与其它分析仪器同时进行检测）
- Samples closer to the start of the reaction（样品接近反应的开始）

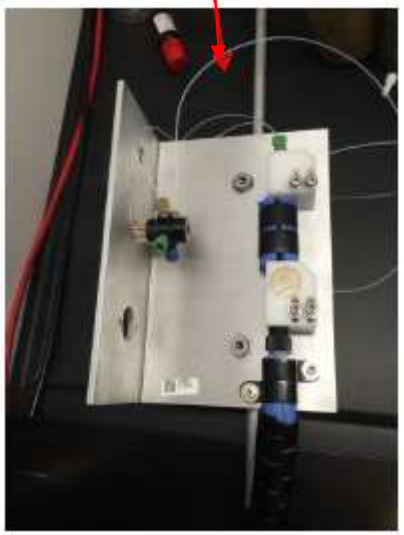
InsightMR hardware part

Demo lab UK

InsightMR hardware part

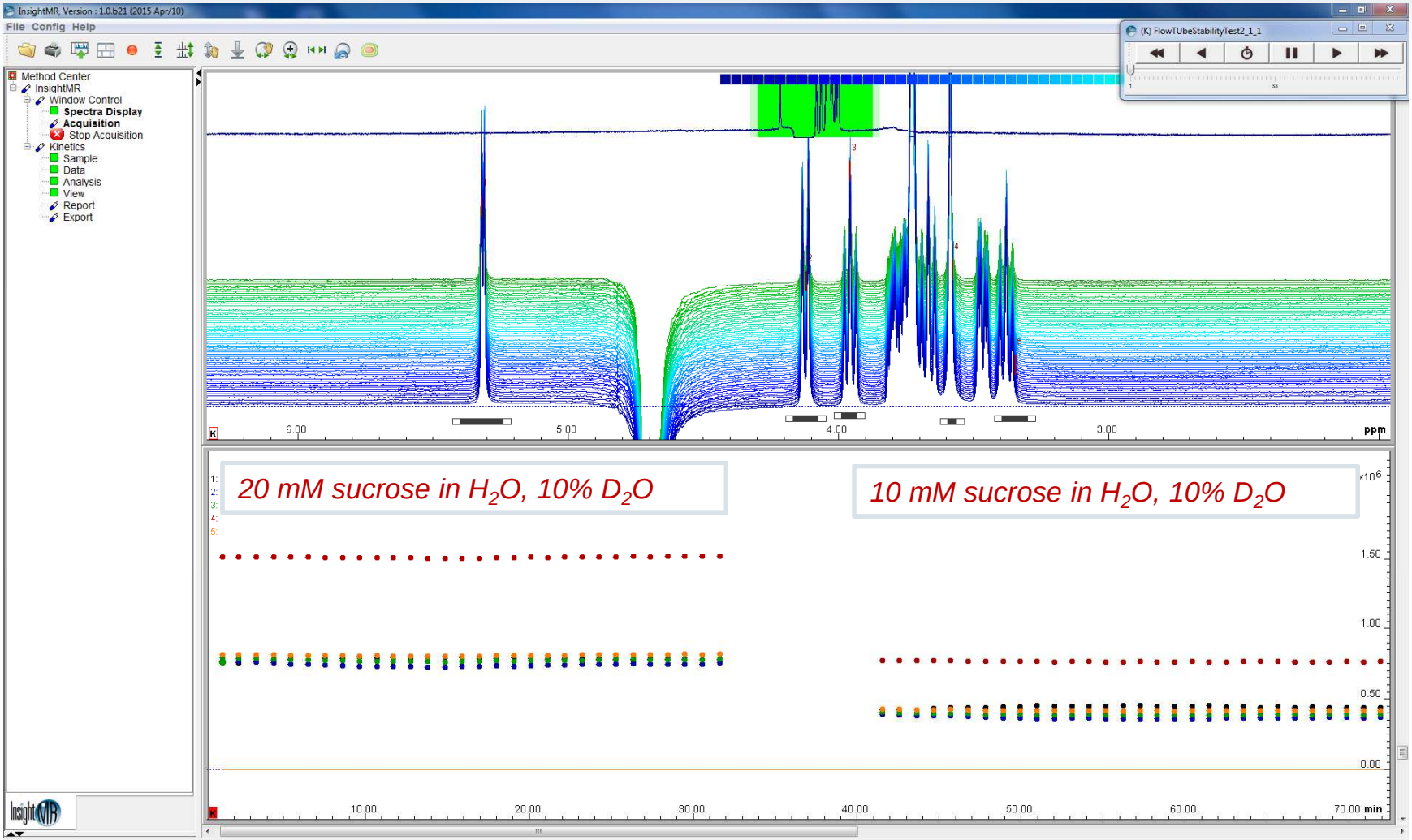
Demo lab UK

Enabling Parallel Acquisition of Data from Different Techniques

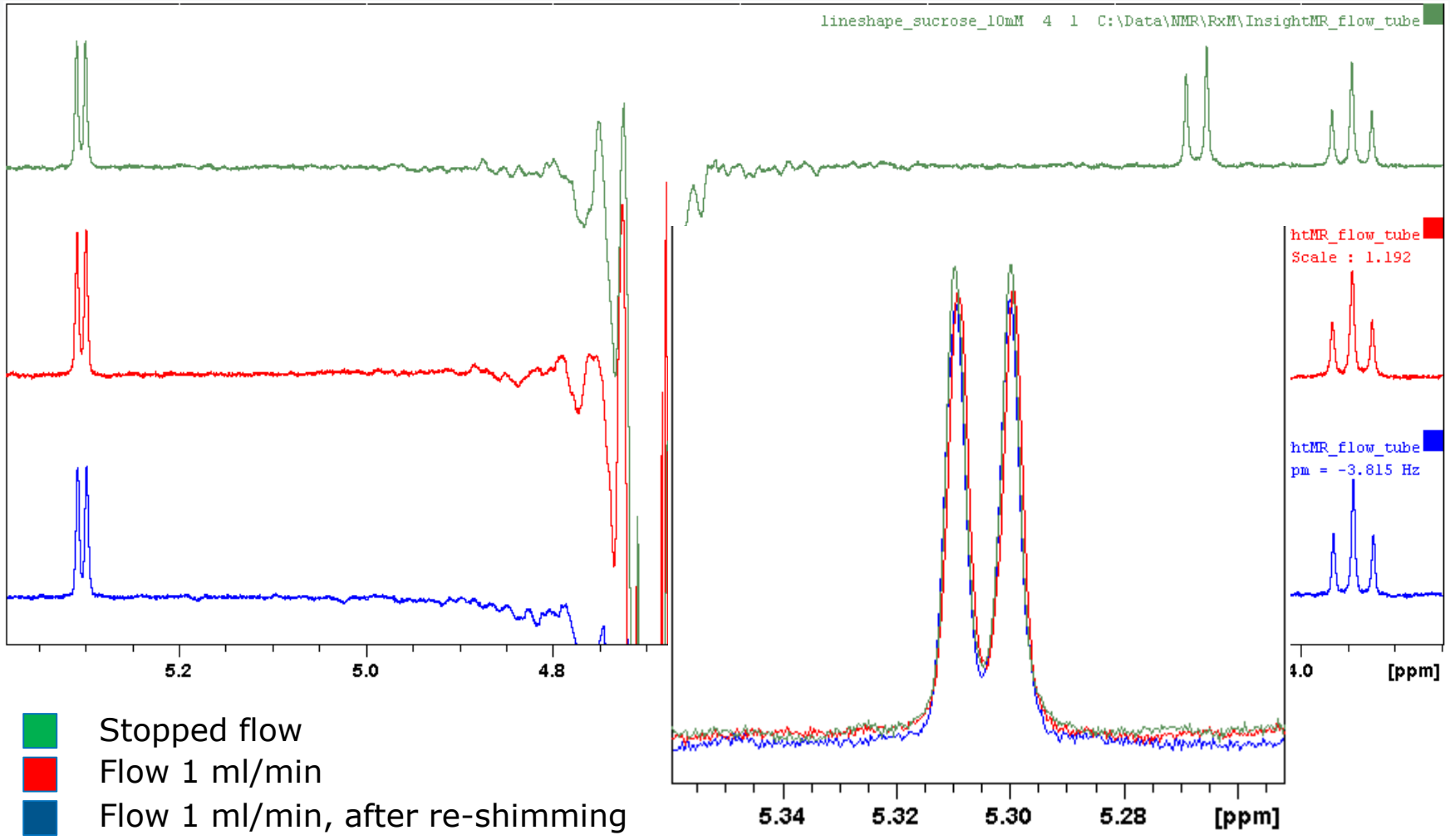


Flow interface

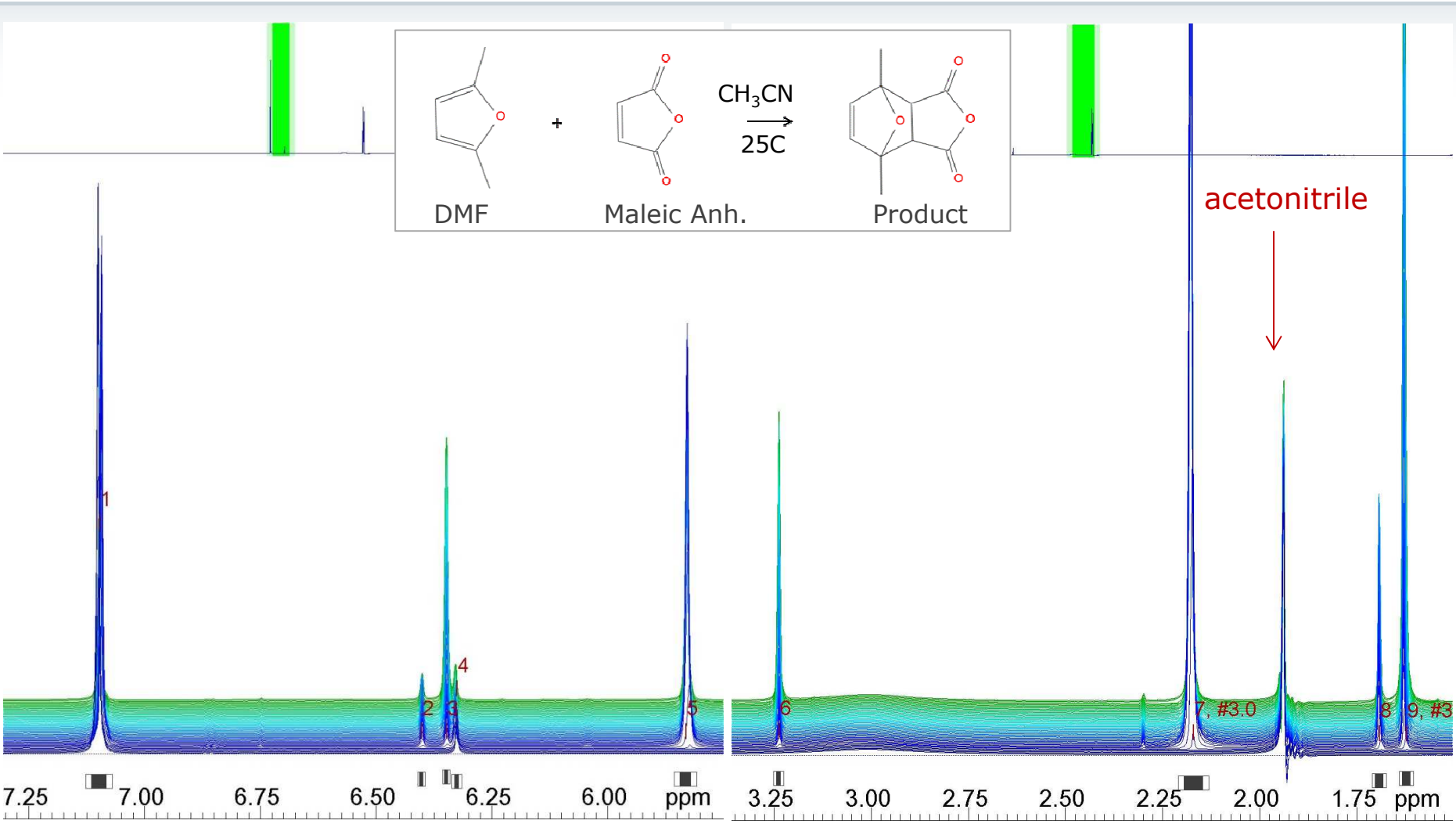
NMR Signal Stability Testing



Line Shape Test – 10 mM sucrose

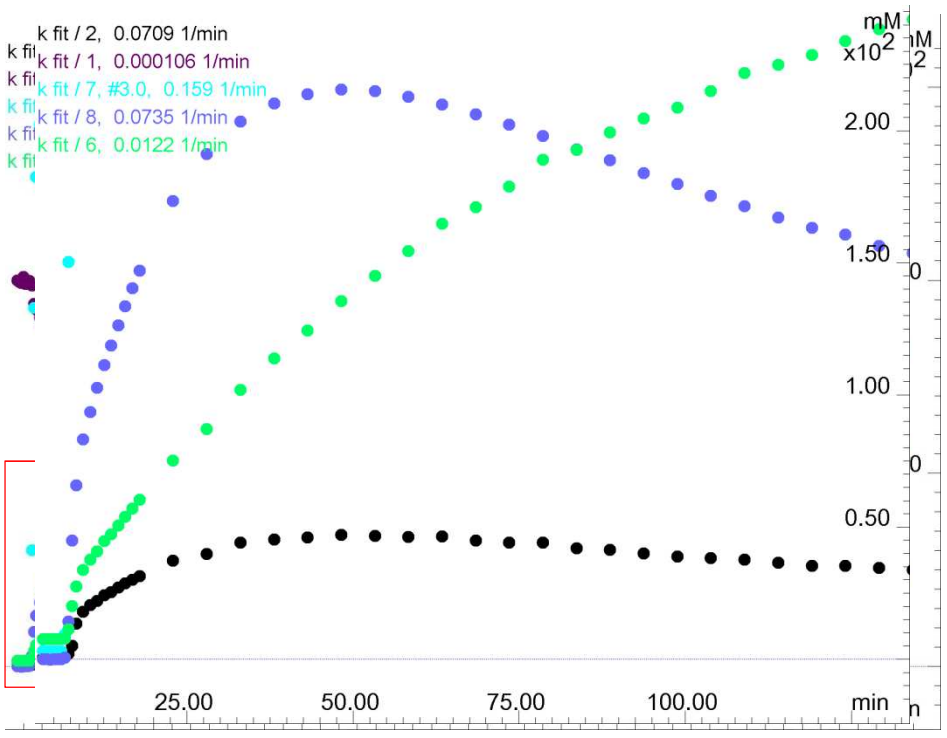


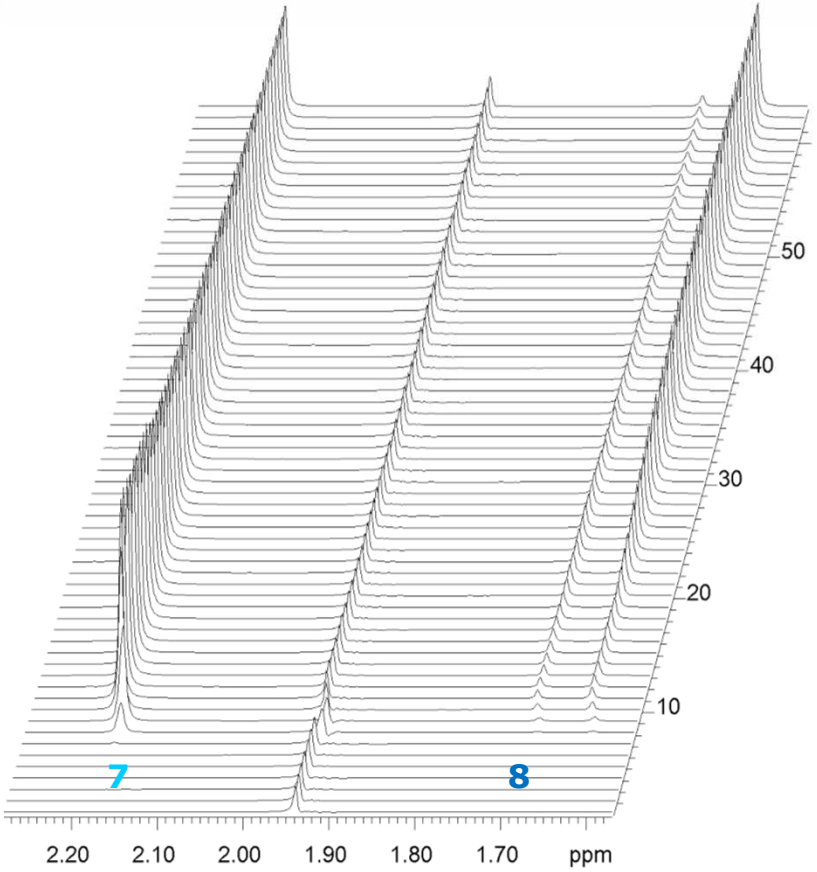
Diels Alder Chemistry, NON-Deuterated Solvent



Diels Alder Chemistry, NON-Deuterated Solvent

Process Understanding – Structural Information of Intermediates



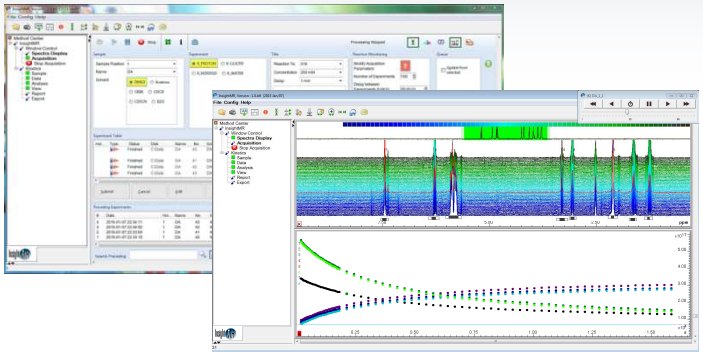


Conclusions

- Answers to key chemical questions: reaction yield, reaction kinetics
- Reactiong understanding, identification of reaction intermediates and mechanistic information
- Rapid and straightforward generation of data to build kinetic models
- Intuitive – straightforward acquisition and processing workflow - makes NMR an accessible PAT tool for all audiences (no NMR experience required)
- Enables the facile use of NMR data to make strategic process chemistry decisions, ultimately leading to **cost savings**

Conclusions

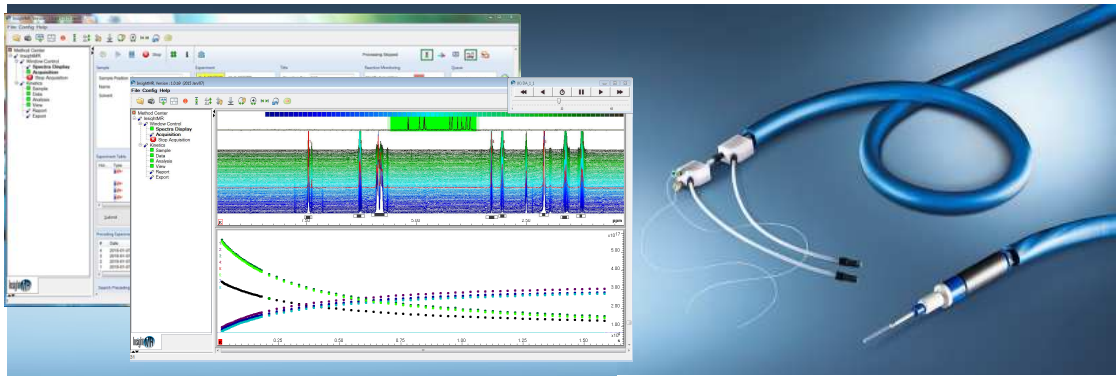
1. InsightMR Software

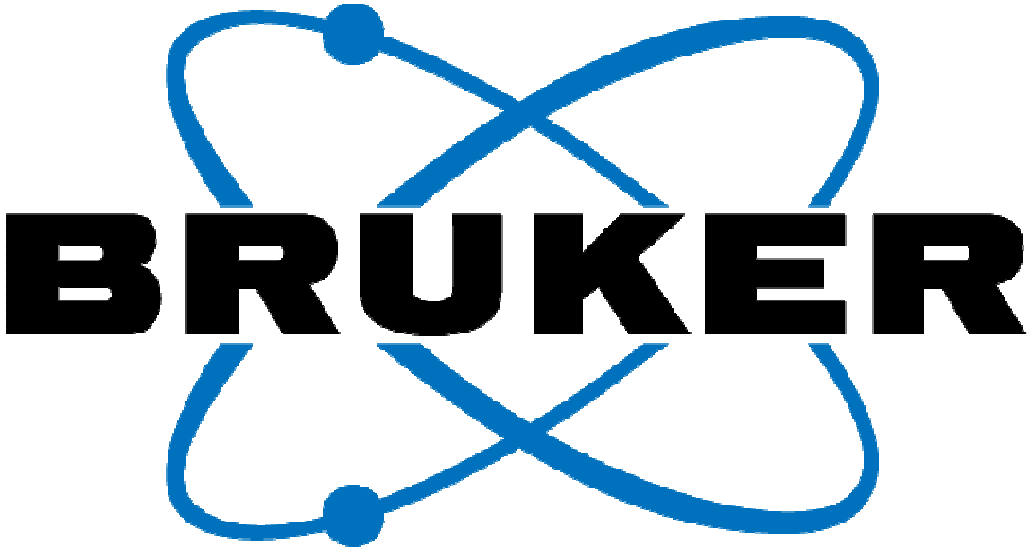


- Download:
https://www.bruker.com/service/support-upgrades/software-downloads/nmr.html

- 3 months demo:
https://www.bruker.com/service/support-upgrades/license-requests/insightmr-license-request-form.html

2. InsightMR (Flow Tube + Software)





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Q & A

- 是否有问题？
- 请您在Q&A面板中提交您的问题
- 我们做的如何？
- 当您退出webinar的时候，请填写您对此次webinar的评价，我们非常感谢您的反馈。

- 非常感谢！

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