Reaction Monitoring with NMR

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Reaction Monitoring
What is it and Why are we Doing it?

Purpose:
- Reaction completion determination
- *In-situ* yield determination
- Reaction understanding: mechanistic information
- Extracting kinetic parameters from the time course data: activation energy, rate constant
- Stability, degradation studies
- Dissolution
- Bio transformations
- ...
Techniques for Reaction Monitoring

- Calorimetry
- LC-UV
- MS, GC, GC-MS
- IR
- **NMR**
  - Quantitative by default: ‘no need to calculate response factors’!
  - **Information rich**: possible to elucidate the structure of starting materials, products, and intermediates.

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

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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 about reaction components in solution. These two characteristics give NMR a distinct advantage over other analytical techniques 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.\textsuperscript{[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 feature that both NMR tube and online reaction monitoring cannot provide because of the time required to mix and get reagents to
Some Available Options

1. A single interface for on-the-fly acquisition control, based on real-time data processing and analysis.
2. Hardware for online monitoring in real-time under real conditions.
InsightMR
The Solution to Enhance Process Understanding

*InsightMR flow tube*

*InsightMR software*
InsightMR Flow Tube
Laboratory Setup for Chemical Applications

Bruker: InsightMR = Flow Unit + Software

User: Reactor, pump, Chiller

NMR Magnet 300-700MHz
Bruker’s Current Offering

Bruker: InsightMR + pump + chiller

NMR system 300-950 MHz

Flow Interface

Chiller

Reactor

Heater
InsightMR Laboratory Setup
NMR Signal Stability Testing

20 mM sucrose in H$_2$O, 10% D$_2$O

10 mM sucrose in H$_2$O, 10% D$_2$O
Flow Behaviour

Delay of Transfer
(a) Integral corresponds to 15 mM composition
(b) @27.75 min Composition in pump was changed to 100%
(c) After 1 min @ 28.75 min change visible in NMR
(d) After 1.75 min @ 29.5 min 90% of target composition reached
(e) After ~3 min @ 30.5 min ~100% target composition reached

• <1-2 min is possible by adjusting the flow rate to 2-3ml/min
• Adjustment of hardware (length diameter) also possible.
• (4 m length, 1 ml/min flow, 0.5 mm i.d. capillaries)

Pump contributes ~100 ul to delay of concentration step propagation.
Line Shape Test – 10 mM sucrose

- Stopped flow, 16%
- Flow 1 ml/min, 17%
- Flow 1 ml/min, after re-shimming, 15%
Diels Alder Chemistry, NON-Deuterated Solvent

DMF + Maleic Anh. → Product

CH₃CN
25°C

acetonitrile
Diels Alder Chemistry, NON-Deuterated Solvent
InsightMR Software
Integration Acquisition - Analysis

Click Acquisition
Answers to Chemical Questions
Concentration Profiles

DMF + Maleic Anh. → Product

Visual, immediate chemical information!!
Key Benefits

- Online reaction monitoring in real-time under real condition
- Compatible with Bruker 5 mm probes
- Complete temperature control from vessel to probe

- A single interface for automated acquisition control, and interactive processing and analysis
- On-the-fly acquisition changes as needed based on real-time kinetic data
- Rapid and effortless handling of hundreds of stacked spectra
Are we Fast Enough?

Transfer times in the order of minutes

Standard NMR tubes

Online – InsightMR
(with batch reactor)
When do we Need to go Faster?

1. Repeating the reaction varying conditions
   - Labour-intensive
   - Time consuming

2. Fast Reactions (seconds)

![Graph showing conversion, [reagent], [cat], and Temp with t1/2 ≈ 5 s]
InsightXpress
Automated in-situ Monitoring

The Solution for Fast Reaction Monitoring and Optimisation

1. Flow Unit
2. High speed delivery pumps
3. NMR system
InsightXpress
Automated in-situ Monitoring
Stop-Flow with added Flexibility

- unlimited ‘shots’
- variable conc.
- variable reagents
- temp. control
- fast
- reproducible
AYAW FROM MAGNET (e.g. in fume hood)

RESERVOIRS

ON TOP OF MAGNET

PRE-CONDITIONER (temp, magnetisation)

130 msec deadtime

SOLVENT FLUSH (n x 1ml)

shot signal

CONTROL SOFTWARE

i) \( V_{TOT} \)

ii) velocity (ml/sec)

iii) fractions A, B, and C

trigger

variable delay (\( D_1 \)), pulse, FID variable delay (\( D_2 \)) cycle

SPECTROMETER CONSOLE

thermostatted by spectrometer

thermostatted by Reaction Express

WASTE

300 uL

300 uL shot

600 uL shot

130 msec deadtime

Flow cell

IN MAGNET

IN MAGNET
4. attached flow lines to reagent reservoirs A, B, C, W
4. attached flow lines to reagent reservoirs

5. connect to thermostatic circulator

A, B, C, W
4. attached flow lines to reagent reservoirs

5. connect to thermostatic circulator
Suzuki-Miyaura coupling reaction

\[
\begin{align*}
\text{BOH} & \quad \text{Pd catalyst} \quad \text{Base} \\
\text{OH} & \quad \text{H}_2\text{O/THF}
\end{align*}
\]

Protodeboronation

\[
\begin{align*}
\text{Boronic acid} & \quad \text{FAST} \\
\text{OH} & \quad \text{H}_2\text{O} \\
& \quad (\text{H}^+ \text{ or } \text{HO}^-) \\
\text{Boric acid} & \quad \text{OH} \quad \text{OH}
\end{align*}
\]
Manual Sample Preparation

14 Kobs (rate) values
X 20 data points = 280 NMR tubes

~ 1-2 weeks work

In-situ stop flow monitoring

0.0005
0.001
0.0015
0.002
0.0025
0.003
0.0035

0 0.5 1 1.5 2
equiv OH

14 Kobs (rate) values
3 h

Professor Guy Lloyd-Jones, FRS
$t_{\frac{1}{2}} \approx 1$ second


InsightXpress
Features at a Glance

- Used when needed seats on SampleXpress base
- Simple install 10-15 min
- Low sample vol a+b+c ≤ 600 uL / shot
- Time efficiency unlimited shots
- Variable ratios explore
- Temp. control detailed kinetics
- Pre-magnetisation quantitative
- Precise timing triggered pulse trains
- Reproducible stable measured vol.
- fast reactions <150 ms dead-time
- In-situ clean solvent flush line
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In-situ Fast RxM

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