ReactIR in Crystallization of Organics

In-situ Monitoring of Solution Concentration by ReactIR

Super-saturation
Growth Kinetics
Solvent Composition
Solubility

The fundamental factors that have impact on crystallography, morphology, filtration rate, and productivity.

- Quantitative data on effects of operating variables.
- Insight into the key parameters for control.
- Process design and optimization.
- Real time monitoring and control during production.

Merck Research Laboratories
API Crystallization
Polymorph Control
Process Monitoring and Design
Growth Kinetics

Application Example by

Merck Research Laboratories


Two polymorphs of API A were isolated from isoT anti-solvent crystallization. Form I is more stable than form II (monotropic).

**Key Process Issues:**
- Difficult to avoid generating Form II (2~10% was typical)
- Very slow growth of Form I (>18 hrs by the old procedure)
- Very slow turnover from Form II to Form I (days in tested solvents)
- Compound decomposes at >40°C (limited to low T)
- Slow filtration rate of isolated form I (<500 L/m2/hr)

**Developmental Objectives:**
- Identify controlling parameters for selective growth of form I.
- Design a robust and efficient process to isolate pure form I.
Kinetic Rationale

**Growth Paths**

- **Form I**: $R_I = R_g + R_n$
- **Form II**: $R_{II} = R_g + R_{n_{II}}$

**Variables**

- Starting Concentration
- Seed Quality & Load
- Aging Time
- Anti-solvent Addition Rate
- Mixing Quality
- Intrinsic Growth Kinetics

**Axes**

- **Solubility (g/L)**
- **vol% of EtOAc in EtOAc/Heptane**

**Equations**

- $R_I = R_g + R_n$
- $R_{II} = R_g + R_{n_{II}}$

**Graph**

- Form I
- Form II
A Path to Pure Form II

No seed, in EtOAc/Heptane at 25°C

\[ \text{dilution} \]

\[ \text{solution concentration by ReactIR} \]

\[ \text{growth rate} \]

- \text{Soly. of II}
- \text{Soly. of I}

\[ R_n^I \ll R_n^{II} \]

\[ C < C^{*}_{II} \] is important.
**A Path to Pure Form I**

Form I seed + controlled anti-solvent addition

- Add 10% Seed
- Start heptane charge
- Start aging

**Solution Concentration**

- Form II Solubility
- Form I Solubility

**Control anti-solvent Addition Rate to maintain C < C_{II}**
Another Path to Pure I

Heel Process (semi-continuous)

Time (hr)

Concentration (g/L)

Addition of Batch and heptane at EtOAc/heptane = 80/20

Solubility of Form I at 23C

Solubility of Form II at 23C

100% I
Robustness and Efficiency Issues

Narrow Metastable Zone of Form II

Problems:
- Poor robustness
- Long time cycle
- Low volume productivity

Way to enhance the growth rate of form I?
How to Enhance Form I Growth Rate?

Seed Loading

Temperature

Already used the right load.  Not much further gain.

\[ \frac{k_{40^\circ C}}{k_{20^\circ C}} \approx 1.3 \]
Effect of $\text{H}_2\text{O}$ on Form I Growth Rate

High $\text{C}_{\text{H}_2\text{O}}$ $=>$ High Growth Rate

$-\ln [\text{C}_-\text{C}^*]/(\text{C}_0-\text{C}^*)$

$K_F = 1462$ mg/L

$K_F = 60$ mg/L

$k_{1462}/k_{60} \approx 22$

($T = 20\sim23^\circ\text{C}$)

High $\text{CH}_2\text{O}$ $=>$ High Growth Rate

97% yield

A seeded batch isothermal rex in EtOAc ($4840K_F$)/n-heptane system at 23°C.
Effect of $H_2O$ on Form I Growth Rate

$\text{Growth rate vs Water Level}$

$R^2 = 0.9948$

$\text{KF1500 (100x)}$

$\text{KF 2800 (200x)}$

$\text{KF<100 (100x)}$
Controlled Crystallization of Form I

**Identified Key Parameters:**

- Anti-solvent Addition Rates
- Solvent Composition (H\textsubscript{2}O)
- Seed Quality and Loading

**Improved Process Features:**

- **Robust isolation of Form I** *(without generating Form II)*
- **Fast crystallization process** *(2~4 hrs vs. 18 hrs)*
- **Fast filtration** *(~4000 L/m\textsuperscript{2}/hr vs. <500 L/m\textsuperscript{2}/hr)*
- **High volume productivity** *(~60 g/L vs. ~20 g/L)*
Operational Safety
Solvent Composition
Compound Concentration

Application Example by

Pfizer Central Research and Process R&D
K. Leeman, P. Ahlijanian, M. Weekly, G. Withbroe,
J. Tucker, S. Kedia, R. Mclaughlin, and A. Serdakowski
Safety Concerns over the API Intermediate

- tested positive for mutagenicity
- a sensitizer

Minimize Exposure & Save Resources by applying ReactIR

- monitor solvent composition in-situ real-time
- monitor compound concentration in-situ real-time
• Isolated FTIR peaks corresponding to H$_2$O, EtOH, and the intermediate.
• Solvent composition can be quantified by ReactIR.
• Intermediate concentration can be quantified by ReactIR.
Concentration of $\text{H}_2\text{O}$, antisolvent, was determined by ReactIR, from lab to pilot plant operation.

Standards generated prior to each run.
C<sub>1</sub> & C<sub>H2O</sub> in Ethanol-H<sub>2</sub>O by ReactIR during antisolvent-addition crystallization

- Quantified both C<sub>1</sub> and C<sub>H2O</sub> in solution.
- ReactIR data agreed well with HPLC analysis.
- Determined ‘the end H<sub>2</sub>O level’ should be 30-35%, at C<sup>*</sup><sub>product</sub> of 2-3 g/l.
ProcessIR in pilot plant
ReactIR was used successfully to

- monitor solvent composition during anti-solvent crystallization
- monitor intermediate concentration during crystallization
- minimize operational exposure to mutagenic compound
- save resources (equipments, manpower, time, …)
pH Swing Crystallization
Solubility vs. pH
Process Monitoring & Control

Application Example by

Michigan State University, Depts. of Chemistry, ChemEng & AgriEng
pH Swing Crystallization of Nicotinic Acid

**Issues:**
- Both solution equilibrium and solubility change with pH.
- Difficult to track contents of chemical species in solution.
- Lack of research works in pH swing crystallization.
- How does solubility change with pH? (=> how to design crystallization?)

**Objectives:**
- Probe/identify key species in H₂O by ReactIR.
- Calibrate ReactIR for solution concentration monitoring.
- Monitor the pH swing crystallization process with ReactIR in-situ.
Identification of Solution Species

**HNic in H₂O (2720 ppm, 30°C)**

- Symmetric stretching of COO⁻ & ring deformation: 1390 cm⁻¹
- Pyridine ring deformation: 1586 cm⁻¹
- N-H deformation: 1640 cm⁻¹

**HNic in D₂O (2720 ppm, 30°C)**

Absorbance peaks at 1390 cm⁻¹, 1586 cm⁻¹, and 1640 cm⁻¹ are highlighted.
pH Swing Crystallization of Nicotinic Acid

Solution Concentrations by ReactIR

Symmetric stretching of COO\(^{-}\) and ring deformation: \(1390 \text{ cm}^{-1}\)

Pyridine ring deformation: \(1586 \text{ cm}^{-1}\)

N-H deformation: \(1640 \text{ cm}^{-1}\)
# pH Swing Crystallization of Nicotinic Acid

## Identification of Solution Species

### HNic in H₂O (2720 ppm, 30°C)

![Graph showing H₂O and HNic in H₂O](image1)

- Symmetric stretching of COO⁻ and ring deformation
- Asymmetric stretching of COO⁻
- Pyridine ring deformation
- N-H deformation

### NaNic in H₂O (2720 ppm, 30°C)

![Graph showing NaNic in H₂O](image2)

### Wave Numbers

<table>
<thead>
<tr>
<th>Species</th>
<th>Wave Number</th>
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<tr>
<td>HNic</td>
<td>1390 cm⁻¹</td>
</tr>
<tr>
<td>NaNic</td>
<td>1556 cm⁻¹</td>
</tr>
</tbody>
</table>

### Additional Notations

- ex. weak
- 1586 cm⁻¹
- 1605 cm⁻¹
- 1640 cm⁻¹
- -
pH Swing Crystallization of Nicotinic Acid

Solution Concentrations by ReactIR

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<td>-</td>
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</table>

\[ C_{(NHNic)} = C_{(HNic + NaNic)} - C_{(NaNic)} \]

- Symmetric stretching of COO⁻ and ring deformation
- Asymmetric stretching of COO⁻: ex. weak
- Pyridine ring deformation: 1586 cm⁻¹ - 1605 cm⁻¹ (overlap with H₂O)
- N-H deformation: 1640 cm⁻¹

Chemical structures and IR data points:

- Symmetric stretching of COO⁻ at 1390 cm⁻¹
- Asymmetric stretching of COO⁻ at 1556 cm⁻¹
- Pyridine ring deformation at 1586 cm⁻¹ - 1605 cm⁻¹
- N-H deformation at 1640 cm⁻¹

Chemical reactions:

\[ H^+ + OH^- \leftrightarrow H_2O \]

Nicotinic acid (HNic) and sodium nicotinate (NaNic) interactions with H⁺ and OH⁻.
pH Swing Crystallization of Nicotinic Acid

Monitor Crystallization by ReactIR

Crystallization

HCl (1M) added to aqueous NaNic solution (8140 ppm) at 1 ml/min, 30°C.

I: under-supersaturated
II: supersaturated, w/o nucleation
III: rapid de-supersaturation with nucleation + growth
IV: stay saturated with rapid growth
A pH swing crystallization, the least studied type, was found possible to be monitored by ReactIR.

The fundamental data of solubility vs. pH were obtained via ReactIR.

The solution concentration change during a crystallization process was monitored to gain insight and control of the process.
### Real-Time Analytics for Crystallization of Organics

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<th>Measures in Real-Time In-Situ</th>
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<td>ReactIR, NIR</td>
<td>Solution Concentration, Growth/Nucleation Kinetics</td>
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<tr>
<td>FBRM</td>
<td>Chord Length Distribution, CSD</td>
</tr>
<tr>
<td>PVM</td>
<td>Morphology, Size, CSD</td>
</tr>
<tr>
<td>Raman</td>
<td>Crystal Structure Difference, Polymorphs</td>
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</table>

![Image of equipment setup with FTIR, FBRM, Raman, and T-controlled Reactor]
Real-Time Analytics for Crystallization of Organics

\[ V_{\text{batch}} = 10\sim100 \text{ ml} \]
Real-Time Analytics for Crystallization of Organics

**Instrument**  
RIR, NIR  
FBRM  
PVM  
Raman

**Measures in Real-Time In-Situ**  
Solution Concentration, Growth/Nucleation Kinetics  
Chord Length Distribution, CSD  
Morphology, Size, CSD  
Crystal Structure Difference, Polymorphs
ReactIR™ Applications in Crystallization of Organics

Continuous Data Acquisition and Display of

- Solution concentrations (compounds in solution)
- Super-saturation during crystallization
- Solvent composition during crystallization
  - Nucleation and growth kinetics of crystallization (fundamentals)
- Critical parameters for process control
  - Operational safety
- Process efficiency and robustness