Principles of Flow Chemistry

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Group Meeting

July 8, 2018
Principles of Flow Chemistry

1. Introduction to Flow Chemistry
2. Mass Transport Phenomena
3. Heat Transfer Phenomena
5. Conclusions
Principles of Flow Chemistry

1. Introduction to Flow Chemistry

2. Mass Transport Phenomena

3. Heat Transfer Phenomena


5. Conclusions
**Batch vs Flow Operations**

**Batch Chemistry**
- Reactants added, reacted, and isolated *discretely*

**Flow Chemistry**
- Reactants added, reacted, and isolated *continuously*
Mixing Units

T-Shaped Mixer  Split and Recombine  Multilaminar

**Reynolds Number**

\[ Re = \frac{\rho D_h \nu}{\mu} = \frac{\text{inertial forces}}{\text{viscous forces}} \]

- \( \rho \) = fluid density
- \( D_h \) = hydraulic diameter
- \( \nu \) = fluid velocity
- \( \mu \) = dynamic viscosity

**Einstein–Smoluchowski Equation**

\[ t_m = \frac{L^2}{D} \]

- \( t_m \) = characteristic mixing time
- \( L \) = diffusion distance
- \( D \) = molecular diffusivity
Types of Reactors

**Chip Reactor**
- Best **heat transfer** properties
- Low throughput

**Coil Reactor**
- **Most widely used** in synthetic chemistry
- Inner diameter 0.01”–1/16”

**Packed Bed Reactor**
- Best for heterogeneous catalysts
- Simulates **high effective molarity** of catalyst
Laminar Flow

Slug Flow

Taylor Flow

Thin Film

transverse interfaces

longitudinal interface

Key Parameters

![Diagram showing the flow of reagents and product]

- Reagent A
  - $c_1$
  - $\nu_1$
- Reagent B
  - $c_2$
  - $\nu_2$
- Product C
  - $V,T$
  - $P$
  - Quench

**Molar Flow Rates**

$n = c\nu$

**Residence Time**

$\tau = \frac{V}{\nu}$

- Parabolic reaction profile results in residence time distribution

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Damköhler Number

\[ \text{Da} = \frac{\chi D_{t}^{2}}{4\pi D} = \frac{\text{characteristic mixing time}}{\text{reaction time}} \]

\( \chi = \text{kinetic coefficient} \)

\( D_{t}^{2} = \text{channel diameter} \)

\( \tau = \text{residence time} \)

\( D = \text{diffusivity} \)

For \( \text{Da} > 1 \): Reaction faster than mixing

For \( \text{Da} < 1 \): Mixing faster than reaction

What happens when the reaction rate outpaces the rate of mixing?
• C primarily is formed

• Significant side products as C reacts with B

**Damköhler Number**

\[ Da = \frac{\text{characteristic mixing time}}{\text{reaction time}} \]
Manipulation of the Damköhler Number

• Batch Strategy: Slow down reaction rate

**Damköhler Number**
\[ Da = \frac{\text{characteristic mixing time}}{\text{reaction time}} \]

**Arrhenius Rate Law**
\[ k = Ae^{-\frac{E_a}{RT}} \]

**Eyring Equation**
\[ k = \frac{k_B T}{h} e^{-\frac{\Delta G^\ddagger}{RT}} \]

• Expensive to cool large reactors to cryogenic temperatures

• Small temperature gradients can degrade selectivity for highly exothermic reactions

• Longer overall operation time
Manipulation of the Damköhler Number

• Flow Strategy: Accelerate mixing rate

T-Shaped Mixer

Split and Recombine

Multilaminar
Manipulation of the Damköhler Number

• Flow Strategy: Accelerate mixing rate

\[ A + B \rightarrow C + B \rightarrow S \]

\[ Da > 1 \]  \hspace{1cm} \[ Da < 1 \]
Manipulation of the Damköhler Number

• Flow Strategy: Accelerate mixing rate

\[ \text{OMe} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \]
\[ \text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \]

\[ \text{Bu} \quad \text{N} \quad \text{CO}_2\text{Me} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \]

\[ \text{MeO} \quad \text{N} \quad \text{Bu} \quad \text{MeO} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \]

\[ \text{OMe} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \]

\[ \text{Bu} \quad \text{N} \quad \text{CO}_2\text{Me} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \]

\[ \text{MeO} \quad \text{N} \quad \text{Bu} \quad \text{MeO} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \]

\[ \text{OMe} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \]

Manipulation of the Damköhler Number

- Flow Strategy: Accelerate mixing rate

\[
\begin{align*}
\text{OMe} & \quad \text{OMe} & \quad \text{OMe} \\
\text{MeO} & \quad \text{MeO} & \quad \text{MeO} \\
\text{Bu} & \quad \text{Bu} & \quad \text{Bu} \\
\text{N} & \quad \text{N} & \quad \text{N} \\
\text{CO}_2 \text{Me} & \quad \text{CO}_2 \text{Me} & \quad \text{CO}_2 \text{Me} \\
-78^\circ \text{C} & \quad & \\
\text{OMe} & \quad \text{OMe} & \quad \text{OMe} \\
\text{MeO} & \quad \text{MeO} & \quad \text{MeO} \\
\text{Bu} & \quad \text{Bu} & \quad \text{Bu} \\
\text{N} & \quad \text{N} & \quad \text{N} \\
\text{CO}_2 \text{Me} & \quad \text{CO}_2 \text{Me} & \quad \text{CO}_2 \text{Me} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Mixer</th>
<th>% Mono-alkylated</th>
<th>% Di-alkylated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td>T-Shaped</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td>SAR-type</td>
<td>50</td>
<td>14</td>
</tr>
<tr>
<td>Multilamination type</td>
<td>92</td>
<td>4</td>
</tr>
</tbody>
</table>

Synthesis of Verubecestat

• Both lithiated A and C are capable of deprotonating B

• True kinetic selectivity of nucleophilic addition masked by inefficient mixing in batch

• Authors hypothesized that increased rate of mixing in flow may contribute to higher conversions and yield

Synthesis of Verubecestat

Hypothetical Side Reactions

- Starting Material → Intermediate
- Intermediate → Product
- Intermediate → Decomposition
- Intermediate → Intramolecular Reaction
Outpacing Intermediate Decomposition

\[ \alpha\text{-Elimination} \quad \text{MeLi} \quad \text{Cl}_2 \text{equiv} \quad \text{OH} \quad 310 \text{ ms} \quad -40^\circ \text{C} \]

Outpacing Intermediate Decomposition

\[ \text{\(\alpha\)-Elimination} \quad \text{LiX} + \text{H}_2 \quad \rightarrow \quad \text{Productive Chemistry} \]

- 1 equiv of benzaldehyde
- 2 equiv of MeLi
- 2 equiv of ICl

310 ms at -40\(^\circ\)C

Outpacing Intramolecular Reactions

Anionic Fries Rearrangement

Outpacing Intramolecular Reactions

Anionic Fries Rearrangement

<table>
<thead>
<tr>
<th>Residence Time (ms)</th>
<th>Unrearranged</th>
<th>Rearranged</th>
</tr>
</thead>
<tbody>
<tr>
<td>628</td>
<td>0</td>
<td>91</td>
</tr>
<tr>
<td>377</td>
<td>20</td>
<td>74</td>
</tr>
<tr>
<td>220</td>
<td>45</td>
<td>51</td>
</tr>
<tr>
<td>55</td>
<td>73</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>87</td>
<td>4</td>
</tr>
<tr>
<td>0.33</td>
<td>91</td>
<td>0</td>
</tr>
</tbody>
</table>

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Temperature Gradients

Adiabatic Temperature Rise

\[ \Delta T_{ad} = \frac{c_{s,0}(\Delta H_R)}{\rho C_p} \]

"worst case scenario"

\[ c_{s,0} = \text{inlet concentration} \quad \rho = \text{fluid density} \]
\[ \Delta H_R = \text{reaction enthalpy} \quad C_p = \text{specific heat} \]

Ratio of Heat Exchange

\[ \beta = \frac{-r\Delta H_R d_h}{6h_{in} \Delta T_{ad}} = \frac{\text{heat generation rate}}{\text{heat removal rate}} \]

\[ \Delta H_R = \text{reaction enthalpy} \quad h_{in} = \text{heat-transfer coefficient} \]
\[ d_h = \text{diameter} \quad \Delta T_{ad} = \text{adiabatic temperature rise} \]

Heat Exchange in Flow

**Ratio of Heat Exchange**

\[ \beta = \frac{-r\Delta H_R d_h}{6h_{in}\Delta T_{ad}} = \frac{\text{heat generation rate}}{\text{heat removal rate}} \]

- \( \Delta H_R \) = reaction enthalpy
- \( h_{in} \) = heat-transfer coefficient
- \( d_h \) = diameter
- \( \Delta T_{ad} \) = adiabatic temperature rise

- Increasing **surface area to volume ratio** increases heat exchange efficiency

Consequences of Temperature Gradients

What are the consequences of temperature gradients?
Consequences of Temperature Gradients

Curtin-Hammett Selectivity

Degradation of Selectivity

Product Formation/Degradation

Degradation of Product

Energy

P1

I1

I2

P2

SM

SP

$\Delta \Delta G^\ddagger$

$\Delta G^\ddagger_1$

$\Delta G^\ddagger_2$

$\Delta G^\ddagger$

$\Delta G^\ddagger_1$

$\Delta G^\ddagger_2$
Intermediate Degradation

$\beta_B = 6.3$ (exotherm faster than heat transfer)

$\beta_F = 0.2$ (heat removed effectively)

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**Temperature vs Reaction Rate**

<table>
<thead>
<tr>
<th>T (°C)</th>
<th>times (hour/minute/second/millisecond)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1 4 12 48 172</td>
</tr>
<tr>
<td>40</td>
<td>15 1 3 12 86</td>
</tr>
<tr>
<td>60</td>
<td>4 15 45 3 11</td>
</tr>
<tr>
<td>80</td>
<td>56 2 11 45 3</td>
</tr>
<tr>
<td>100</td>
<td>14 56 3 11 40</td>
</tr>
<tr>
<td>120</td>
<td>4 14 42 3 10</td>
</tr>
<tr>
<td>140</td>
<td>53 4 11 42 3</td>
</tr>
<tr>
<td>160</td>
<td>13 53 3 11 38</td>
</tr>
</tbody>
</table>

**Arrhenius Rate Law**

\[ k = Ae^{-\frac{E_a}{(RT)}} \]

**Eyring Equation**

\[ k = \frac{k_BT}{h}e^{-\frac{\Delta G^\ddagger}{(RT)}} \]

- When reactions are **prohibitively slow**, heating will accelerate the rate.
- Frequently reactions can be heated in batch to a temperature that allows for a reasonable reaction time.

# Boiling Points of Common Solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Boiling Point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetonitrile</td>
<td>82</td>
</tr>
<tr>
<td>1-butanol</td>
<td>118</td>
</tr>
<tr>
<td>chloroform</td>
<td>61</td>
</tr>
<tr>
<td>dimethylformamide</td>
<td>153</td>
</tr>
<tr>
<td>1,4-dioxane</td>
<td>101</td>
</tr>
<tr>
<td>ethanol</td>
<td>79</td>
</tr>
<tr>
<td>ethyl acetate</td>
<td>77</td>
</tr>
<tr>
<td>methanol</td>
<td>65</td>
</tr>
<tr>
<td>methylene chloride</td>
<td>40</td>
</tr>
<tr>
<td>N-methyl-2-pyrrolidinone</td>
<td>202</td>
</tr>
<tr>
<td>2-propanol</td>
<td>82</td>
</tr>
<tr>
<td>tetrahydrofuran</td>
<td>65</td>
</tr>
<tr>
<td>toluene</td>
<td>111</td>
</tr>
<tr>
<td>water</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reaction Vessel</th>
<th>Pressure Rating (bar)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mL screw-cap vial</td>
<td>10</td>
</tr>
<tr>
<td>0.2–30 mL microwave tubes</td>
<td>30</td>
</tr>
<tr>
<td>250 mL screw-cap flask</td>
<td>~4</td>
</tr>
<tr>
<td>polymer-based tubing</td>
<td>~10</td>
</tr>
<tr>
<td>stainless steel tubing</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

- Batch reactors are limited by the **boiling point** of the solvent.
- Microwave tubes **cannot be scaled** beyond 30 mL.
- With **stainless steel tubing**, virtually any temperature with any solvent can be achieved.
Examples of High Temperature Reactions

Diels-Alder Reaction

\[
\text{Me} = \text{CN} \quad \xrightarrow{\text{Toluene (2.0 M)}} \quad \text{Me} = \text{CN}
\]

\[
\text{Toluene (2.0 M)} \quad 250^\circ\text{C}, 60\text{ bar} \quad 0.8\text{ mL/min}
\]

Nucleophilic Aromatic Substitution

\[
\begin{align*}
\text{N}=\text{Cl} & \quad \xrightarrow{\text{Toluene (2.0 M)}} \quad \text{N}^\text{2} & \quad \text{MeO} & \quad \text{S} & \quad \text{O} & \quad \text{MeO} & \quad \text{S} & \quad \text{NMe}^\text{2} \\
\text{Toluene (2.0 M)} & \quad 250^\circ\text{C}, 60\text{ bar} \quad 0.8\text{ mL/min}
\end{align*}
\]

Claisen Rearrangement

\[
\text{O} \quad \xrightarrow{\text{Toluene (0.1 M)}} \quad \text{OH}
\]

\[
\text{Toluene (0.1 M)} \quad 240^\circ\text{C}, 100\text{ bar} \quad 1.0\text{ mL/min}
\]

Fisher Indole Synthesis

\[
\begin{align*}
\text{N} & \quad \text{NH} & \quad \text{Am} & \quad \text{NH}_2 & \quad \text{AcOH/IPA (0.5 M)} & \quad 200^\circ\text{C}, 75\text{ bar} \quad 5.0\text{ mL/min} \quad \text{N} & \quad \text{NH} & \quad \text{N} & \quad \text{H}
\end{align*}
\]

Newman-Kwart Rearrangement

\[
\begin{align*}
\text{N} & \quad \text{Cl} & \quad \text{N} & \quad \text{O} & \quad \text{N} & \quad \text{Cl} & \quad \text{N} \\
\text{DME (0.15 M)} & \quad 300^\circ\text{C}, 80\text{ bar} \quad 1.0\text{ mL/min} \quad \text{N} & \quad \text{N} & \quad \text{O} & \quad \text{N} & \quad \text{H}
\end{align*}
\]

Gaseous Reagents in Flow

For many gas-liquid reactions, mass transfer is rate-determining.

Henry’s Law

\[ p = k_H c \]

- \( p \) = partial pressure
- \( c \) = concentration
- \( k_H \) = temperature-dependent constant

Gaseous Reagents in Flow

**Mass Transfer Efficiency**

$$k_L a$$

- $k_L$ = mass transfer coefficient
- $a$ = interfacial area

<table>
<thead>
<tr>
<th>type of reactor</th>
<th>interfacial area (m$^2$/m$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mL RB Flask</td>
<td>141</td>
</tr>
<tr>
<td>50 mL RB Flask</td>
<td>66</td>
</tr>
<tr>
<td>250 mL RB Flask</td>
<td>38</td>
</tr>
<tr>
<td>tube reactors</td>
<td>50–700</td>
</tr>
<tr>
<td>gas–liquid microchannel</td>
<td>3400–18000</td>
</tr>
</tbody>
</table>

**Henry’s Law**

$$p = k_H c$$

- $p$ = partial pressure
- $c$ = concentration
- $k_H$ = temperature-dependent constant

For many gas-liquid reactions, **mass transfer** is rate-determining

**Gas Phase**

**Liquid Phase**

---

## Biphasic Mass Transfer

![Chemical reaction](attachment:chemical_diagram.png)

KOH (aq), 80°C, 9.8 min

<table>
<thead>
<tr>
<th>Aqueous:Organic (v/v)</th>
<th>Organic Slug Length (µm)</th>
<th>Interfacial Area (m²/m³)</th>
<th>( k_L \alpha )</th>
<th>% Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>467</td>
<td>3000</td>
<td>0.24</td>
<td>40</td>
</tr>
<tr>
<td>2.3</td>
<td>330</td>
<td>4500</td>
<td>0.36</td>
<td>74</td>
</tr>
<tr>
<td>4.0</td>
<td>295</td>
<td>5100</td>
<td>0.41</td>
<td>92</td>
</tr>
<tr>
<td>6.1</td>
<td>265</td>
<td>5900</td>
<td>0.47</td>
<td>99</td>
</tr>
</tbody>
</table>

Gas Diffusion vs Reaction Rate

Hatta Number

\[ Ha = \sqrt{\frac{2}{m+1} \frac{k_{m,n}(c_{A,i})^{m-1}(c_{B,bulk})^{n}D_{A}}{k_{L}}} \]

Compared to the rate of diffusion through the film

- Instantaneous reaction happens at interface when \( Ha > 3 \)
- Slow reaction happens in bulk phase when \( Ha < 0.3 \)

Photon Transport Phenomenon

Beer–Lambert Law

\[ A = \varepsilon cl \]

- \( A \) = absorbance
- \( \varepsilon \) = extinction coefficient
- \( c \) = concentration
- \( l \) = path length

Handling of Hazardous Reagents

- **Generate and consume** hazardous reagents instantaneously
- **Minimize total concentration** of hazardous reagents

<table>
<thead>
<tr>
<th>Fluorine</th>
<th>Chlorine</th>
<th>Diazomethane</th>
<th>Phosgene</th>
</tr>
</thead>
<tbody>
<tr>
<td>F=F</td>
<td>Cl-Cl</td>
<td>H₂C≡N=O⁻</td>
<td>Cl₂Cl₂</td>
</tr>
</tbody>
</table>

- **Precursor**
- **Activator**
- **Substrate**
- **Hazardous Reagent**
- **Product**
Handling of Diazomethane

Methylation  [2+3] Cycloaddition  Cyclopropanation  Homologation

\[
\begin{align*}
\text{Diazomethane} \quad &\quad \text{Acetic Acid} \\
\text{KOH} &\quad \text{PMDS membrane reactor}
\end{align*}
\]

Handling of Phosgene

- Epimerization is reduced by reducing residence time

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### Flask vs Flow

**Flask Conditions**

\[
\text{RCHO} + \text{Ph-NO}_2 + \text{Pyrrrole} \quad \text{DMSO, RT} \quad \text{5 mol\%} \quad \text{40 hours} \\
\text{77\% yield, 74\% ee}
\]

**Flow Conditions**

\[
\text{RCHO} + \text{Ph-NO}_2 + \text{Pyrrrole} \quad \text{DMSO, 60\°C} \quad \text{5 mol\%} \\
\text{20 min} \\
\text{79\% yield, 75\% ee}
\]

---

Flask vs Flow

“It may simply be a case of comparing apples with oranges, combined with the dangers inherent in inferring conclusions based on simple end-point analysis in the absence of time-course data.”

Conclusions

• Flow chemistry has emerged as a tool for synthetic organic chemists

• The decision to implement a flow vs batch process is highly context specific

• Flow can potentially provide higher yield and selectivity by reducing concentration and temperature gradients

• Flow setups allow chemists to reach novel process windows with regards to temperature, pressure, and photon flux, potentially accelerating reaction rates

• Flow chemistry does not improve every process!
Is flow chemistry the answer to the ultimate questions of life, the universe, and whether or not Rob can actually dunk?

- **unfortunately not**

  - **no** Is the reaction safe in batch?
    - **yes** Is the reaction reported in batch at an acceptable level with respect to yield, scale, and reaction time?
      - **yes**
      - **no** Is one of the reagents a gas?
        - **no** Does a precipitate drive the equilibrium in the desired direction?
          - **yes**
          - **no** Is one reagent/catalyst a solid?
            - **yes** Is the reaction fast (<1 min)?
              - **yes** Is selectivity affected by temperature?
                - **yes** Does the reaction need to be high heat in order to achieve a reasonable reaction rate?
                  - **yes** Is the reaction photochemically driven?
                    - **no**
    - **no**

Additional Reading

The Hitchhiker’s Guide to Flow Chemistry

Beyond Organometallic Flow Chemistry: The Principles Behind the Use of Continuous-Flow Reactors for Synthesis

Deciding Whether to Go with the Flow: Evaluating the Merits of Flow Reactors for Synthesis