Glass Microreactors as Promising Tool for High Pressure Reactions

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Outline

- Introduction
- High pressure in a capillary microreactor
- Microreactor fabrication
- Flow phenomena of (m)ethanol/water mixtures
- Reactions in high pressure microreactors
  - Diels-Alder reactions
  - Esterification reaction
    - high pressure
      - supercritical CO$_2$

Conclusions
Introduction

Why high pressure?

It is a very mild and non-destructive activation method for reactions that at atmospheric pressure are either too slow, require too high temperatures, or are hindered by steric or electronic factors.

\[ \Delta G = \Delta H - T \Delta S + p \Delta V \]

Activation volume

\[ \Delta V^\neq = \left( \frac{\partial \Delta G^\neq}{\partial p} \right)_T = \left( - \frac{\partial \ln k_p}{\partial p} \right)_T \cdot RT \]

\[ \Delta V^\neq = \Delta V^\neq_{\text{int}} + \Delta V^\neq_{\text{solv}} \]

The solvation effect is significant when there is a change in the charge or polar character in forming the activated complex.
Introduction
Effect of Pressure

- Pressure benefices reactions with steric hindrance

Menshutkin reaction of methyl iodide with bulky pyridines

\[ \text{Z} \quad \text{Y} \quad \Delta V^\neq / \text{cm}^3 \text{ mol}^{-1} \quad \text{Rel. k} \]

<table>
<thead>
<tr>
<th>Z</th>
<th>Y</th>
<th>$\Delta V^\neq / \text{cm}^3 \text{ mol}^{-1}$</th>
<th>Rel. k</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>-28.2</td>
<td>1</td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>-30.8</td>
<td>28</td>
</tr>
<tr>
<td>t-Bu</td>
<td>Me</td>
<td>-32.5</td>
<td>278</td>
</tr>
</tbody>
</table>

*J. Org. Chem. 1989, 54, 570*
Introduction

Drawbacks of high pressure

Closed systems
- Incorporation of mixers or probes is difficult
- Visualization is done mainly by a view cell
- Difficult and time consuming to clean
- Expensive
- Leakage
Introduction

Why microreactors?

**Small dimensions**

- High surface-to-volume ratio's
- Improved heat and mass transfer rates
- Improved safety conditions:
  - Reduced explosion danger
  - Less amounts of hazardous/toxic chemicals ...
- Inspection/monitoring easy
- Continuous flow operation
- No big machinery and installations
High-Temperature/Pressure Capillary Flow Reactor

Volume: 4, 8, 16 mL
Temperature: up to 350 °C
Pressure: 50-200 bar
Stainless steel coil

Capillary Microreactor

High pressure UV capillary microreactor system:

- High pressure generator (a)
- Six-port valve for injection (b)
- Capillary microreactor (c)
- Optical fiber (d)
- UV/vis light source (e)
- UV/vis detector (f)

Stop flow system
On-line detection technique
3 µL sample
Capillary Microreactor

Nucleophilic aromatic substitution reaction

Strongly accelerated by pressure

Reaction with 1-fluoro-4-nitrobenzene

\[ k = k_{obs}[\text{amine}] \text{ M}^{-1}\text{s}^{-1} \]

- Pyrrolidine
- Piperidine
- Morpholine

\[ R^2 = 0.994 \]

10-fold excess

- a \ X = F \quad a \ Y = -
- b \ X = Cl \quad b \ Y = \text{CH}_2
- c \ X = Br \quad c \ Y = \text{O}
Capillary Microreactor

Nucleophilic aromatic substitution reaction

Activation volume ($\Delta V^*$) calculations

\[
\left( \partial \ln k / \partial p \right)_T = -\Delta V^*/RT
\]

\[\begin{array}{c}
\text{4-Halonitrobenzene/Amine} \\
\text{Cl} \quad \text{Br} \\
\text{F} \\
\text{Cl} \\
\end{array}\]

\[\begin{array}{c}
\text{F} \\
\text{Cl} \\
\text{Br} \\
\end{array}\]

\[\begin{array}{c}
\text{Pyrrolidine} \\
\text{Piperidine} \\
\text{Morpholine} \\
\end{array}\]

\[\begin{array}{c}
\text{Br} \\
\text{Cl} \\
\text{F} \\
\end{array}\]

\[\begin{array}{c}
\text{Br} \\
\text{Cl} \\
\text{F} \\
\end{array}\]

\[\begin{array}{c}
\text{Br} \\
\text{Cl} \\
\text{F} \\
\end{array}\]

\[\begin{array}{c}
\text{Br} \\
\text{Cl} \\
\text{F} \\
\end{array}\]

\[\begin{array}{c}
\text{Br} \\
\text{Cl} \\
\text{F} \\
\end{array}\]
Capillary Microreactor

Diels–Alder reaction

Kinetic data at high pressure and activation volume ($\Delta V^*$) calculations

<table>
<thead>
<tr>
<th>$p$ /bar</th>
<th>$k_{obs}$ /s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$1.5 \times 10^{-4}$</td>
</tr>
<tr>
<td>100</td>
<td>$1.8 \times 10^{-4}$</td>
</tr>
<tr>
<td>200</td>
<td>$2.2 \times 10^{-4}$</td>
</tr>
<tr>
<td>300</td>
<td>$2.8 \times 10^{-4}$</td>
</tr>
</tbody>
</table>

Danishefsky's diene $\rightarrow$ Dihydro-4-pyridone

$\Delta V^* = -33$ cm$^3$ mol$^{-1}$
High Pressure Microreactor
Microreactor Fabrication

Parameters:

- The fabrication of the inlet/outlet structure
  - Powderblasting
  - Powderblasting and etching with hydrofluoric acid
- The post annealing process
- The manner in which top and bottom wafer are bonded
- The geometry of the inlet/outlet structure
- The way the inlets/outlets develop into the microfluidic channels

a inlet/outlet geometry, b transition area towards microchannel, c microchannel, d glue front (meniscus)
Flow Phenomena of Mixtures

**Chip Layout**

- **Product + CO₂(g)**
- **HP zone** (with and without “herringbone” mixers)

**Expansion zone**

- **Back pressure resistance**
  - CO₂(l)
  - Sample

**Heated zone**
- **COOLED ZONE:** 10 °C
- **HEATED ZONE:** 35 - 95 °C

- **HP zone & inlet channel:** 70 μm wide, 30 μm deep
- **Back pressure resistance:** 20 μm wide, 5 μm deep
Flow Phenomena of Mixtures

Different phase change phenomena
Unique flows

Crossing the bubble line

Methanol/CO₂ mixture
50/50 v/v

100 bar, 61 °C

Liquid CO₂ → Vapour CO₂
Flame-like structure (high p, T-conditions)

70 bar, 39 °C

Liquid CO₂ → Vapour CO₂
Bubble formation (mild p, T-conditions)
Flow Phenomena of Mixtures

Phase diagram construction

Constant pressure and varying temperature

Bubble-point lines for the 50/50 v/v mixtures as derived from literature data
Chemistry in a High Pressure Microreactor

Diels-Alder reaction at high pressure

\[
\text{Cyclohexa-1,3-diene} + \text{maleimide} \xrightarrow{\text{r. t.}} \text{endo product}
\]

- a R = CH$_3$
- b R = Ph
- c R = CH$_2$Ph

Reaction time 8.4 s at 90 bar

Volume 0.26 μL
Chemistry in a High Pressure Microreactor

Conversions in batch experiments at 1 bar

Order of reactivity: \( N \)-phenylmaleimide > \( N \)-methylmaleimide > \( N \)-benzylmaleimide
Chemistry in a High Pressure Microreactor

\[ \begin{align*}
1 + 2 & \xrightarrow{\text{r.t.}, \text{CDCl}_3} 3 \\
\text{a}\ R = \text{CH}_3 \\
\text{b}\ R = \text{Ph} \\
\text{c}\ R = \text{CH}_2\text{Ph}
\end{align*} \]

$\Delta V^\#_{(\text{calculated})}$

<table>
<thead>
<tr>
<th></th>
<th>2</th>
<th>1</th>
<th>k (M$^{-1}$s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>-11.0</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>-12.7</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>-13.4</td>
<td>0.31</td>
<td></td>
</tr>
</tbody>
</table>

Pressure effect:

- $N$-benzylmaleimide > $N$-phenylmaleimide > $N$-methylmaleimide

$\sim 14 \times$ $\sim 2.8 \times$ $\sim 2.0 \times$
Chemistry in a High Pressure Microreactor

(phthalic anhydride) + MeOH $\rightleftharpoons$ High-Pressure

UV/ Vis

- Batch scale reaction
- Reaction under pressure
- Reaction under supercritical CO$_2$ conditions
Chemistry in a High Pressure Microreactor

**Batch Scale**

<table>
<thead>
<tr>
<th>T/°C</th>
<th>k/M⁻¹s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.45 x 10⁻⁶</td>
</tr>
<tr>
<td>25</td>
<td>1.46 x 10⁻⁶</td>
</tr>
<tr>
<td>50</td>
<td>4.56 x 10⁻⁶</td>
</tr>
<tr>
<td>60</td>
<td>5.66 x 10⁻⁶</td>
</tr>
</tbody>
</table>

**Stainless steel loop (0 °C)**

<table>
<thead>
<tr>
<th>P/bar</th>
<th>k/M⁻¹s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>2.43 x 10⁻⁶</td>
</tr>
<tr>
<td>110</td>
<td>2.43 x 10⁻⁶</td>
</tr>
</tbody>
</table>

**NO PRESSURE EFFECT**
Chemistry in a High Pressure Microreactor

Set-up microreactor

Pressures of 90 and 110 bar and scCO₂ conditions

Pressure up to 10 bar

Reactants T: 0°C

Close valve

Cooled zone

Heated zone

Product T: 0°C

Valve 8

Loop 7

High Pressure Pump

Valve 10

Open/Close

Valve 9

CO₂

$p > 70$ bar

1

2

3

4

5

6

PO: back pressure resistance

5: expansion zone
Chemistry in a High Pressure Microreactor

Microreactor results up to 10 bar

\[ \frac{k_{\text{microreactor}}}{k_{\text{batch}}} \text{ (up to 10 bar)} = 1.5 - 1.9 \]

Depending on temperature
Chemistry in a High Pressure Microreactor

Microreactor results at 90 and 110 bar

<table>
<thead>
<tr>
<th>TEMPERATURE /°C</th>
<th>$k_{90 \text{ bar}}/k_{1 \text{ bar}}$</th>
<th>$k_{110 \text{ bar}}/k_{1 \text{ bar}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>17</td>
<td>32</td>
</tr>
<tr>
<td>40</td>
<td>21</td>
<td>40</td>
</tr>
<tr>
<td>60</td>
<td>29</td>
<td>54</td>
</tr>
</tbody>
</table>
Chemistry in a High Pressure Microreactor

Microreactor results at 90 and 110 bar and scCO₂ conditions

<table>
<thead>
<tr>
<th>TEMPERATURE / °C</th>
<th>$k_{90 \text{ bar} \text{ SC}} / k_{90 \text{ bar}}$</th>
<th>$k_{110 \text{ bar} \text{ SC}} / k_{110 \text{ bar}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>161</td>
<td>1428</td>
</tr>
<tr>
<td>60</td>
<td>109</td>
<td>100</td>
</tr>
<tr>
<td>80</td>
<td>77</td>
<td>72</td>
</tr>
</tbody>
</table>
Chemistry in a High Pressure Microreactor

- Catalytic effect (silanol groups)
- Continuous flow
- Pressure effect (increase of collisions)
- Supercritical conditions (Clusters of phthalic anhydride and MeOH)

<table>
<thead>
<tr>
<th>Experiment</th>
<th>$E_a$ /kJ mol$^{-1}$</th>
<th>$A /M^{-1} s^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch-scale</td>
<td>40.1</td>
<td>128.1</td>
</tr>
<tr>
<td>Microreactor $&lt; 10$ bar</td>
<td>38.8</td>
<td>142.6</td>
</tr>
<tr>
<td>Microreactor 90 bar</td>
<td>34.6</td>
<td>468.7</td>
</tr>
<tr>
<td>Microreactor 110 bar</td>
<td>33.9</td>
<td>690.9</td>
</tr>
<tr>
<td>Microreactor 90 bar + $scCO_2$</td>
<td>18.0</td>
<td>120.1</td>
</tr>
<tr>
<td>Microreactor 110 bar + $scCO_2$</td>
<td>19.9</td>
<td>411.6</td>
</tr>
</tbody>
</table>
Conclusions

. Microreactors are excellent platforms to study organic reactions under pressure

. The combination of a microreactor and pressure gives rise to significant rate enhancements

Limitations:
. Pressures up to 600 bar
. Short reaction times

Challenge:
. What is the reason of the huge rate enhancements?
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                            STW