Advanced Organic Chemistry/ Organic Synthesis – CH 621

Ultrasound Assisted Organic Synthesis (Sonochemistry)

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Ultrasonics

- Ultrasounds (20-10 000 kHz)
- 1880 Piezoelectricity (Curie brothers)
- 1893 Galton
- 1912 TITANIC
- 1912 Behm (Echo technique)
- 1917 Langevin (Ultrasonic variation, Icebergs, Submarines)
- 1945 Application in chemistry
Ultrasonics/Sonochemistry – Basics

Frequency ranges of sound

- **Human hearing**: 16Hz - 18kHz
- **Conventional power ultrasound**: 20kHz - 100kHz
- **Extended range for sonochemistry**: 20kHz - 2MHz
- **Diagnostic ultrasound**: 5MHz - 10MHz
Sound transmission through a medium
Ultrasonics/Sonochemistry – Acoustic Cavitation

Formation of an acoustic bubble

Bubble size and cavitation dynamics

Transient cavitation
Acoustic cavitation in a homogeneous liquid

Suslick - ~ 4-5000 K
Acoustic cavitation in solid/liquid system

Inrush of liquid from one side of the collapsing bubble produces powerful jet of liquid targeted at surface.

Surface cleaning
destruction of boundary layer
surface activation
improved mass and heat transfer
Acoustic cavitation in solid/liquid system

- **LARGE PARTICLES**: surface cavitation due to defects leading to **fragmentation**
- **SMALL PARTICLES**: collision can lead to **surface erosion** or **fusion**
Acoustic cavitation in liquid/liquid system
Specific ultrasonic effect? Yes and No

No - another internal heating approach

Yes - The temperature dependence of $E_A$ of different reactions could be significantly different – change in selectivities
- Very effective mixing
- Cavitation
- Surface cleaning
1. Acoustic frequency

Increasing frequency – increasing energy

Theory - usually higher reaction rate

Real life – optimum frequency as we have to balance reactivity/selectivity

The effect is different for every reaction and general rule can not be made.
2. Acoustic power

Similar as frequency, however, the extent of increase is limited

Optimum
3. Temperature

Cavitation bubbles – energy of collapse

Pressure inside the bubble

In general lower temperature is better, but again there is an optimum as higher temperature increases the probability of the cavitation
4. External (static) pressure

Not quite clear, but in general higher pressure is better.

Role of particles (ultrafiltration)
5. Gas

Polytrop ratio ($\gamma = \frac{C_p}{C_v}$), thermal conductivity, and solubility

Usually inert gases are the best (noble gases)
6. Solvent

Should be as inert as possible, and stable toward ultrasounds

Sonolysis of the solvent

Usually high boiling point is preferred, but it is controversial as diethylether is a good solvent in many applications.
<table>
<thead>
<tr>
<th>Experimental parameter</th>
<th>Physical parameter</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acoustic frequency</td>
<td>Period of bubble collapse</td>
<td>Change in the size of the bubbles</td>
</tr>
<tr>
<td>Acoustic power</td>
<td>Size of the reaction zone</td>
<td>The number of cavitation phenomena in a unit volume</td>
</tr>
<tr>
<td>Temperature</td>
<td>Vapor pressure of liquid</td>
<td>The content of bubbles, the intensity of collapse</td>
</tr>
<tr>
<td></td>
<td>Thermal activation</td>
<td>Secondary reactions</td>
</tr>
<tr>
<td>Static pressure</td>
<td>Total pressure</td>
<td>Intensity of collapse</td>
</tr>
<tr>
<td></td>
<td>Solubility of gas</td>
<td>The content of bubbles</td>
</tr>
<tr>
<td>Gas</td>
<td>Politrop ratio</td>
<td>Intensity of collapse</td>
</tr>
<tr>
<td></td>
<td>Thermal conductivity</td>
<td>Primer and secondary reactions</td>
</tr>
<tr>
<td></td>
<td>Chemical reactivity</td>
<td>The content of bubbles</td>
</tr>
<tr>
<td>Solvent</td>
<td>Vapor pressure</td>
<td>Intensity of collapse</td>
</tr>
<tr>
<td></td>
<td>Surface tension</td>
<td>Limit of transient cavitation</td>
</tr>
<tr>
<td></td>
<td>Viscosity</td>
<td>Primer and secondary reactions</td>
</tr>
<tr>
<td></td>
<td>Chemical reactivity</td>
<td></td>
</tr>
</tbody>
</table>
Ultrasonics/Sonochemistry – Transducers

Galton whistle (physical)

Piezoelectric sandwich transducer

Liquid whistle (physical)

Magnetostrictive transducer
- Electronics industry (coating with metals)
- Therapy (surgery with ultrasounds), diagnostics
- Food industry
- Materials (metallurgy)
- Synthesis
- Environmental applications
Applications in Organic Synthesis

1. Homogeneous Sonochemistry
   - Aqueous medium
   - Non-aqueous media

2. Heterogeneous Sonochemistry
   - Phase Transfer Catalysis
   - Reactions with metals
   - Heterogeneous Catalysis

3. Enzyme reactions
1. Homogeneous sonochemistry

1.1. Aqueous sonochemistry

\[
\begin{align*}
\text{H}_2\text{O} & \rightarrow \text{H}^+ + \text{OH}^- \\
\text{H}^+ + \text{OH}^- & \rightarrow \text{H}_2\text{O} \\
2 \text{H}^+ & \rightarrow \text{H}_2 \\
2 \text{OH}^- & \rightarrow \text{H}_2\text{O}_2 \\
2 \text{OH}^- & \rightarrow \text{O}^+ + \text{H}_2\text{O} \\
2 \text{O}^- & \rightarrow \text{O}_2 \\
0.5 \text{O}_2 + 2 \text{H}^+ & \rightarrow \text{H}_2\text{O}
\end{align*}
\]

(2.8)
1. Homogeneous sonochemistry

1.2. Non-Aqueous sonochemistry

**Scheme 1: Rice Radical Chain Mechanism$^a$**

*Initiation:*

\[ \text{C}_{10}\text{H}_{22} \rightarrow 2R^* \quad (1) \]

*Propagation:*

\[ R^* \rightarrow R^* + \text{C}_2\text{H}_4 \quad (2) \]

\[ R^* \rightarrow R + \cdot \text{H} \quad (3) \]

\[ R^* + \text{C}_{10}\text{H}_{22} \rightarrow \text{RH} + R + \cdot \text{R} \quad (4) \]

\[ \cdot \text{H} + \text{C}_{10}\text{H}_{22} \rightarrow \text{H}_2 + \cdot \text{R} + \cdot \text{R} \quad (5) \]

\[ R + \cdot \text{R} \rightarrow R + \cdot \text{R} \quad (6) \]

*Termination:*

\[ R^* + R^* \rightarrow \text{R-R} \quad (7) \]

\[ R^* + \cdot \text{H} \rightarrow \text{RH} \quad (8) \]

\[ \cdot \text{H} + \cdot \text{H} \rightarrow \text{H}_2 \quad (9) \]

$^a$ $R^*$ = terminal radical, $R \cdot \cdot \cdot R$ = internal radical.
1.2. Non-Aqueous sonochemistry

\[ R' + I^- + \text{Cl}_3\text{CCOONa, CH}_3\text{CN} \rightarrow + R \text{CCl}_3 + \text{N} \text{R'} \text{CCl}_3 \quad (2.14) \]

70-100 %

\[ R' + \text{MeOTBuOK} \rightarrow \rightarrow \text{R'NMeCH}_2\text{CCOCH}_3, \text{NaOH} \rightarrow \text{NMeCH}_2\text{CCH}_3O \quad (2.16) \]

91 - 98 %
1.2. Non-Aqueous sonochemistry

\[
\text{H-PO-POEt} + \text{NMe} \xrightarrow{90 \degree C, toluene} \text{EtO-PO-} \text{NMe}
\]

Yield (%)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Stirring</th>
<th>Sonication</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>60</td>
<td>&lt;5</td>
<td>67</td>
</tr>
<tr>
<td>120</td>
<td>37</td>
<td>82</td>
</tr>
</tbody>
</table>
1.2. Non-Aqueous sonochemistry

\[
\begin{align*}
R & \quad R' \quad R'' \\
\text{R} & \quad \text{R'} \quad \text{R''} \\
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{R'} \quad \text{R''} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

Yield (%)

- stirring: 10-53
- sonication: 57-93
1.2. Non-Aqueous sonochemistry

\[
\begin{align*}
\text{H}_2 & \xrightarrow{\text{Ultrasonics}} \text{H}_2 + \text{H}^+ \\
\text{H}_2 & + \text{O}_2 \rightarrow \text{H}_2\text{O}_2^+ \\
\text{H}_2\text{O}_2^+ & + \text{CH}_2\text{CH}_2\text{O} \rightarrow \text{CH}_2\text{CH}_2\text{OOH} + \text{H}_2\text{O} \\
\text{CH}_2\text{CH}_2\text{OOH} & + \text{CH}_2\text{CH}_2\text{O} \xrightarrow{\text{Mo(CO)}_6} \text{CH}_2\text{CH}_2\text{OH} + \text{H}_2\text{O}
\end{align*}
\]
2. Heterogeneous sonochemistry

2.1. Phase transfer catalysis

Organic Phase

\[ Q^+X^- + R-Y \rightarrow R-X + Q^+Y^- \]

Aqueous Phase

\[ Q^+X^- + Y^- \rightleftharpoons X^- + Q^+Y^- \]

\[ M^+ \]

\[ M^+ \]
2.1. Phase transfer catalysis

NaOH + CHCl₃ \rightarrow [:::CCl₂] + CHCl₃

stirring 9 h 15%
sonication, 3 h 83%
2.1. Phase transfer catalysis
2.2. Reactions with metals

\[
\text{R}_1\text{R}_2\text{O} + \text{R}''\text{-Cl} \xrightarrow{\text{Li}} \text{R}_1\text{R}_2\text{OH}
\]

10-40 min 68-99%

\[
\text{R}_3\text{O}\text{Li} + \text{R}'\text{-Cl} \xrightarrow{\text{Li, THF}} \text{R}_3\text{O}
\]

72-99%
2.2. Reactions with metals

\[
\text{EtOOC} - \text{COOEt} \xrightarrow{\text{K, toluene, 5 min}} \text{COOEt}
\]

\[
\text{RF-X} + \text{CO}_2 \xrightarrow{\text{Zn, DMF, 10 min}} \text{RF-COOH}
\]

\[
\text{Me} \quad \text{Me} \quad \text{C}_8\text{H}_{17} \quad \text{Me} \quad \text{Me} \quad \text{C}_8\text{H}_{17}
\]

\[
\text{Zn, AcOH, 10 min}
\]

32
2.3. Heterogeneous catalysis

Catalytic system: Raney Ni (presonicated)
(R, R)-tartaric acid-NaBr

\[
\begin{align*}
\text{OH} & \quad \text{OMe} \\
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{R} \\
\text{OH} & \quad \text{OMe}
\end{align*}
\]

\text{ee: up to 98% (S)}

\[
\begin{align*}
\text{OH} & \quad \text{OMe} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OMe}
\end{align*}
\]

\text{ee: up to 98% (R)}

\text{yield: 52% 52%}
\text{ee}_{\text{max}}: 85% 90%
2.3. Heterogeneous catalysis

Fig. 1. Effect of ultrasound frequency on the optical yield sonochemical hydrogenation of ethyl pyruvate over cinchonidine modified Pt/Al₂O₃ catalyst (● – 20 kHz, ■ – 35 kHz, ▲ – 47 kHz). The ee values were determined at 100% conversion.
2.3. Heterogeneous catalysis

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Modifier</th>
<th>Catalyst</th>
<th>Hydrogen pressure (bar)</th>
<th>Solvent</th>
<th>Major product</th>
<th>Optical yield (ee%)</th>
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<td>CD</td>
<td>E4759</td>
<td>10</td>
<td>AcOH</td>
<td>R</td>
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<td>Toluene</td>
<td>S</td>
<td>50 62</td>
</tr>
</tbody>
</table>

DCB – 1,2-dichlorobenzene.
Microwaves/Sonochemistry – References

- Mason, T. J., Sonochemistry: Current Uses and Future Prospect in Chemical and Industrial Processing, RSC, 1999