Scalability of Microwave-Assisted Organic Synthesis. From Single-Mode to Multimode Parallel Batch Reactors

Alexander Stadler, Behrooz H. Yousefi, Doris Dallinger, Peter Walla, Erik Van der Eycken, Nadya Kaval, and C. Oliver Kappe

Institute of Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria
Microwave Theory

**Microwaves**
- Between IR and Radio wave: 0.3 - 300GHz
- In use 2.45GHz (cooking and chemistry)

**Microwave heating**
- Dipolar polarization - rxn mixture must have some polar species (solvent, reactants, additives)
- Conduction

*DDT 2002, 7, 373*
Dielectric heating

- For a substance in MW to generate heat it must have dipole moment.
- In liquids alignment is affected by viscosity and frequency.
- The dipole reorients to align itself with electric field, the field is already changing and phase difference is generated, causing energy to be lost by molecular friction and collisions giving rise to dielectric heating.

Tetrahedron 2001, 57, 9225
Conductivity heating

- Ions in the solution follow the electric field resulting in expenditure of energy due to increased collision rate, converting kinetic energy to heat.
- This mechanism gives much stronger heating than dipolar.

Tetrahedron 2001, 57, 9225
Loss angle

- The reorientation of dipoles and displacement of charge are equivalent to an electric current. This displacement is 90° when the dielectric follows precisely the field. That is not the case, therefore the resulting phase displacement, \( \delta \) produces a component \( I \sin \delta \) in phase with electric field. This causes the energy to be absorbed from the electric field which is converted to heat - dielectric loss.

(A) A phase displacement which results when energy is converted to heat. (B) The relationship between \( \varepsilon' \) and \( \varepsilon'' \), \( \tan \delta = \varepsilon''/\varepsilon' \).

Tetrahedron 2001, 57, 9225
## Solvents

### Table 1. Values of solvent loss tangents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Dielectric constant ($\varepsilon_r$)</th>
<th>Loss tangent (tan(\delta))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexane</td>
<td>1.9</td>
<td>–</td>
</tr>
<tr>
<td>Benzene</td>
<td>2.3</td>
<td>–</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>2.2</td>
<td>–</td>
</tr>
<tr>
<td>Chloroform</td>
<td>4.8</td>
<td>0.091</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>6.1</td>
<td>0.174</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>6.2</td>
<td>0.059</td>
</tr>
<tr>
<td>THF</td>
<td>7.6</td>
<td>0.047</td>
</tr>
<tr>
<td>Methylene chloride</td>
<td>9.1</td>
<td>0.042</td>
</tr>
<tr>
<td>Acetone</td>
<td>20.6</td>
<td>0.054</td>
</tr>
<tr>
<td>Ethanol</td>
<td>24.6</td>
<td>0.941</td>
</tr>
<tr>
<td>Methanol</td>
<td>32.7</td>
<td>0.659</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>36.0</td>
<td>0.062</td>
</tr>
<tr>
<td>Dimethyl formamide</td>
<td>36.7</td>
<td>0.161</td>
</tr>
<tr>
<td>Dimethyl sulfoxide</td>
<td>47.0</td>
<td>0.825</td>
</tr>
<tr>
<td>Formic acid</td>
<td>58.0</td>
<td>0.722</td>
</tr>
<tr>
<td>Water</td>
<td>80.4</td>
<td>0.123</td>
</tr>
</tbody>
</table>

*a* The dielectric constant, $\varepsilon_r$, equals the relative permittivity, $\varepsilon'$, at room temperature under the influence of a static electric field.

*b* Values determined at 2.45 GHz and room temperature.  
Abbreviation: THF, tetrahydrofuran.
Terminology to remember

- **Magnetron** – an electromagenetic device that generates microwaves at fixed frequency (2.45GHz).

- **Multi-mode cavity** – domestic and large chamber microwaves – large enough to propagate multiple modes of microwave energy (20-30) which interact with each other constructively and destructively and create “hot spots” and “cold spots”. To get uniform heating simple stirring (mode stirrer- moving metal vane that continuously changes the instantaneous field pattern inside the cavity) is used or rotation. Field intensity is homogeneous in all directions and all locations throughout the entire cavity.

- **Mono-mode cavity** – a small chamber that allows the propagation of one mode of microwaves. This allows a more homogenous energy distribution and higher power density then multimode cavities. The essential characteristic of single-mode cavities is the deliberate creation of a standing wave pattern inside the cavity.

*Microwave synthesis, B.L. Hynes, CEM*

http://www.milestonesci.com/synth-fund.php
Why do the microwaves speed up reactions?

\[ K = A \, e^{-\frac{\Delta G}{RT}} \]

- \( A \) describes molecular mobility
- \( \Delta G \) - free energy of activation
- \( T \) - temperature (the key!)

*No magic!* *More efficient heating!*

Superheating and hot spots.
Microwave chemistry is a hot spot!

Supercharged
Most experts now believe that the mysterious effect is the result of nothing more than microwaves' ability to superheat solvents way beyond their normal boiling points — because the even spread of heat through the liquid allows it to reach a higher temperature before bubbles form. Water, for example, reaches 105 °C before boiling in a microwave oven; whereas the solvent acetonitrile boils at 120 °C instead of its usual 82 °C. “There are
designer microwave ovens that can heat reactants in record time are heralding a quiet revolution in chemical synthesis. David Adam feels the heat.
What reactions can be done in microwave?

- Almost any reaction that requires heat, but not limited to these...

**Figure 1.** Growth in the number of published papers on microwave-assisted inorganic and organic chemistry. Accumulated number of papers (red) compared with the number of papers on organic synthesis (green).
Microwaves in combinatorial synthesis, medicinal chemistry and drug discovery

Organic Process Research & Development 2003, 7, 707-716

DDT 2002, 7, 373

Sonogashira Coupling of Arylacetylenes on Iodophenyl and Bromophenyl Resins

\[
\text{Pd(PPh}_3\text{)}_2\text{Cl}_2, \text{ Cul, (CH}_3\text{CH}_2\text{)}_2\text{NH, DMF, t=15-25 min} \rightarrow \text{86-98%}
\]

<table>
<thead>
<tr>
<th>R-C≡CH</th>
<th>3-iodophenyl resin</th>
<th>3-bromophenyl resin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^c)</td>
<td>Me(_3)Si-C≡H</td>
<td>94%</td>
</tr>
<tr>
<td>2</td>
<td>Ph-C≡H</td>
<td>89%</td>
</tr>
<tr>
<td>3</td>
<td>Ph-C≡H</td>
<td>92%</td>
</tr>
<tr>
<td>4(^c)</td>
<td>Fmoc-N-C≡H</td>
<td>-</td>
</tr>
<tr>
<td>5(^c)</td>
<td>Boc-N-C≡H</td>
<td>98%</td>
</tr>
</tbody>
</table>

\(^a\) yield \(^b\) yield

*Method A, 120 °C, 15 min, 5% Pd, 10% Cu.*
*Method B, 120 °C, 25 min, 10% Pd, 20% Cu, 20% PPh3.*

*J. Org. Chem. 2003, 68, 6431-6434*
Small scale gets big!

Major concerns:
Restricted penetration depth of microwave irradiation into reaction mixtures. At the typical operating frequency of most microwave reactors of 2.45 GHz, the penetration depth is generally in the order of a few centimeters, depending on the dielectric properties of the medium.
Prototype multimode batch reactor
(Anton Paar GmbH, Graz)

- operating at a frequency of 2.45 GHz with continuous microwave output power from 0 to 1400 W.
- dimensions: W D H, 45 42 35 cm
- eight-vessel rotor, employing either 100mL PTFE-TFM or 80 mL quartz glass vessels (max filling volume ca. 50-60 mL), both types dedicated for reactions at high pressure (60 or 80 bar controlled pressure) and temperatures (260 and 300 °C).
- PTFE-TFM vessels are inserted into a ceramic vessel jacket, which provides structural strength and dimensional stability.
- vessels are placed in the corresponding rotor
- temperature of all vessels can be monitored by IR
- After irradiation, the rotor is cooled to approximately 40 °C within 20 min by venting air through cooling gaps which are surrounding the reaction vessels.

*Organic Process Research & Development 2003, 7, 707-716*
Scaled up reactions using 8 vessel rotor system
Biginelli condensation

Monomode rxn
4.0 mmol scale in AcOH/EtOH 3:1 at 120 °C within 10 min
88 % yield (>98% purity)

Multimode scale up
80 mmol of reagents each (0.32 mol in total) at 120 °C within 10 min
ramp time was programmed for the large-scale run (3 min to 120 °C)
individual 4 vessels -(70-74%)
yields almost identical.

Organic Process Research & Development 2003, 7, 707–716
Temperature control

The magnetron power of the reactor (1400 W) sufficient to allow the linear heating from room temperature to 120 °C within 3 min (ramp) of all eight vessels, even when filled with ca. 50 mL each (total of 400 mL) of reaction mixture.
### Kindler Reaction

**Monomode rxn – sealed vessel**
- 4.0 mmol scale
- at 140 °C within 10 min
- 95 % yield

**Multimode scale up**
- 40 mmol of reagents each
- at 140 °C within 10 min
- ramp time was programmed for the large-scale run (3 min to 140 °C)
- individual 8 vessels – 90% yield

---

**Heck reaction**

\[
\begin{align*}
\text{NC-} & \quad \text{Br} \quad + \quad \text{\textit{CO}_2\textit{H}} \\
\text{MW, 180°C, 15 min} & \quad \Rightarrow \\
\text{NC-} & \quad \text{\textit{CO}_2\textit{H}}
\end{align*}
\]

Monomode rxn – sealed vessel

<table>
<thead>
<tr>
<th>2.0 mmol scale</th>
<th>4 x 20 mmol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mol %</td>
<td>at 180 °C within 15 min</td>
</tr>
<tr>
<td>Pd(OAc)₂/tri(otolyl)phosphine</td>
<td>Overall yield 3a (77%), 3b (56%)</td>
</tr>
<tr>
<td>triethylamine (TEA) as base, at 180 °C within 15 min</td>
<td></td>
</tr>
<tr>
<td>3a (82%), 3b (55%)</td>
<td></td>
</tr>
</tbody>
</table>

**Multimode scale up**
Negishi Reactions.

The large-scale synthesis was carried out in two vessels on a 2 x 20 mmol scale under an argon atmosphere in the multimode batch reactor. The reaction was heated to 160°C, employing a heating ramp of 2 min, and kept at 160 °C for an additional minute - 77% isolated yield.
Are there reactors for scale ups?

Milestone's MRS Batch Reactors, designed to work with the MicroSYNTH Labstation, are inserted into the multimode cavity through the top of the labstation.

The First Prototype of the Batch Reactor

Specifications
- 350 ml
- 260°C
- 100 Bar
- 100-1200W
- Overshoot <3°C
- Stability <0.5°C
- Safety valves, Safety Interlocks
Conclusions

- Microwave heating becomes more and more popular.
- Major problems with scaling up reactions are being solved.
- Scale up in monomode cavity is still an issue.
- Multimode cavity reactors with mode stirrers do provide homogenous field and high control and allow successful scale up.