



DBU-Forschungscluster

Novel Process Windows

**“Novel Process Windows in
Chemical Engineering”
- Workshop -**

December 10, 2009

Osnabrück, Germany

**“Process Intensification of the Kolbe-Schmitt-
Synthesis by Using Novel Process Windows”**

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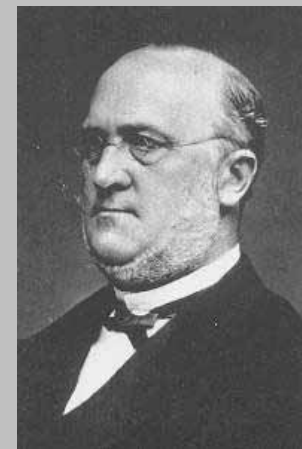
Outlook

- 1. History, motivation, project approach and experimentation**
- 2. Aqueous synthesis using oil bath heating**
- 3. Oil bath heated synthesis using reactive ionic liquids**
- 4. Aqueous synthesis using microwave heating**
- 5. Tailor-made microstructured reactors for microwave heating and direct electrical heating**
- 6. Ecological impact**
- 7. Summary and outlook**

History

Kolbe-Schmitt reaction

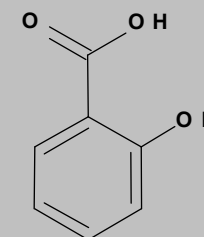
- Developed by A.W. Hermann Kolbe in 1860 for the synthesis of **salicylic acid**
- Improved by Rudolf Schmitt in 1885
- First industrial application in 1874 in Dresden/Radebeul → “start-up company” founded by Friedrich von Heyden (assistant of R. Schmitt)
- **Cradle of the modern API manufacturing**



A.W. Hermann Kolbe
(source: Wikipedia)



“Salicylsäurefabrik Dr. F. von Heyden” in Radebeul



salicylic acid

Motivation

- Kolbe-Schmitt reaction:
Used as standard method for the fabrication of e.g.
 - aromatic hydroxy carboxylic acids (e.g. acetylsalicylic acid = **Aspirin[®]**)
 - p-aminosalicylic acid (PAS)
 - alkyl p-hydroxybenzoate (paraben)
 - Products used as
 - pharmaceuticals
 - antimicrobials
 - fine chemicals
 - Kolbe-Schmitt synthesis is normally carried out **batch wise**
→ long reaction times
- ↳ **Process Intensification** of the industrial relevant Kolbe-Schmitt synthesis
- continuously processed
 - use of Novel Process Windows, e.g. high-p,T, increased concentrations

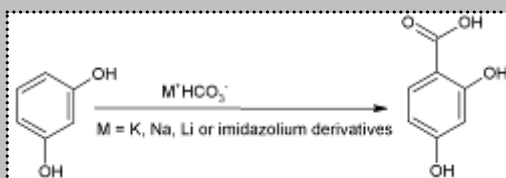


Stirred tank (before 1950)

Project approach

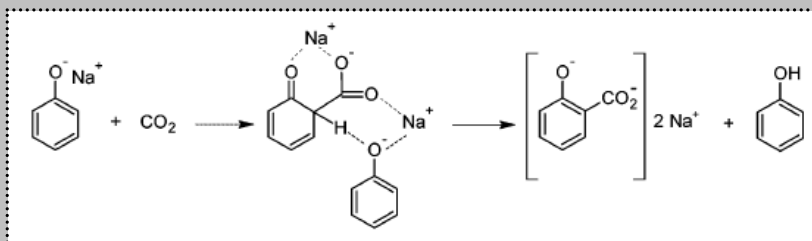
“Combining flow chemistry with alternative solvents, new reagents and advanced reactor engineering”

Target reaction

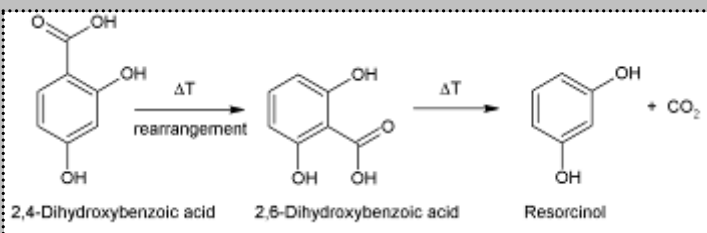


$p=10-40$ bar
 $T=140-200$ °C
 $\tau=10-320$ s

Mechanism

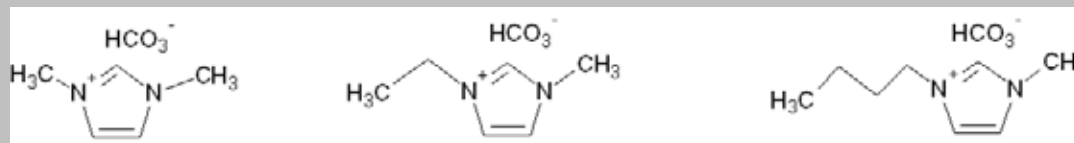


Side and consecutive reactions



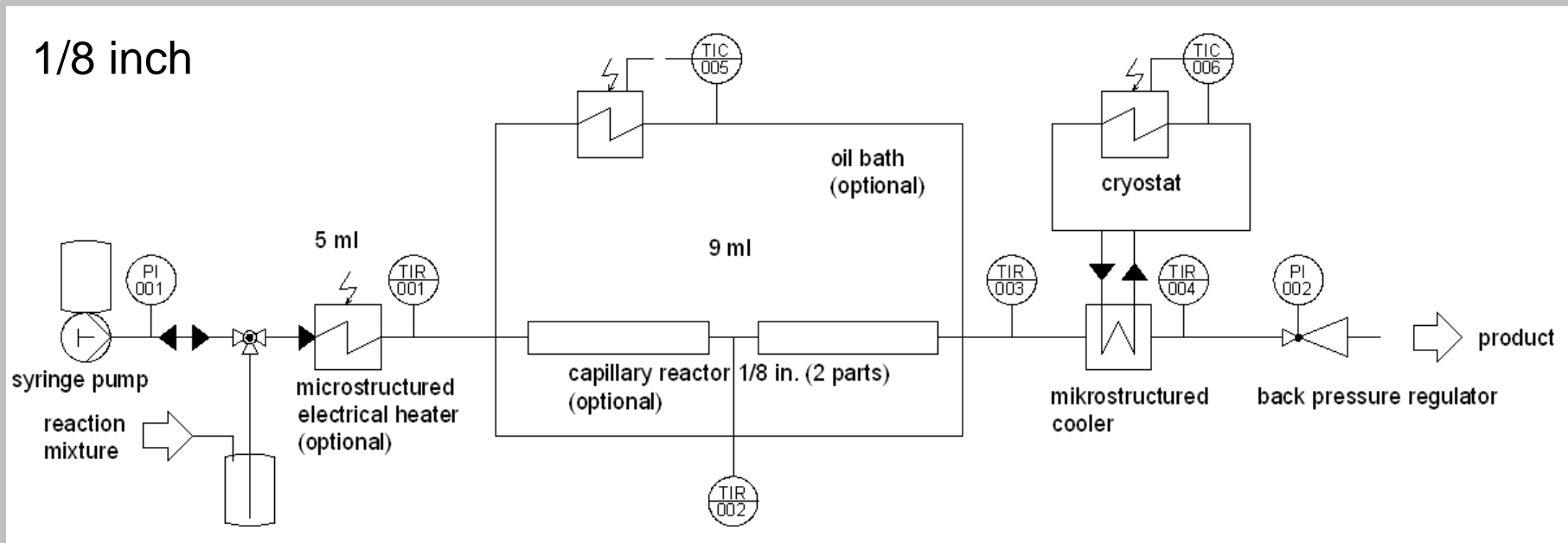
Heating method \ Solvent	Ionic Liquids	Near-critical CO ₂	Aqueous solution
conventionally	CH-IL-KS	CH-A-CO2-KS	CH-A-KS
microwave	M-IL-KS	—	M-A-KS

HCO₃⁻ donating ionic liquids

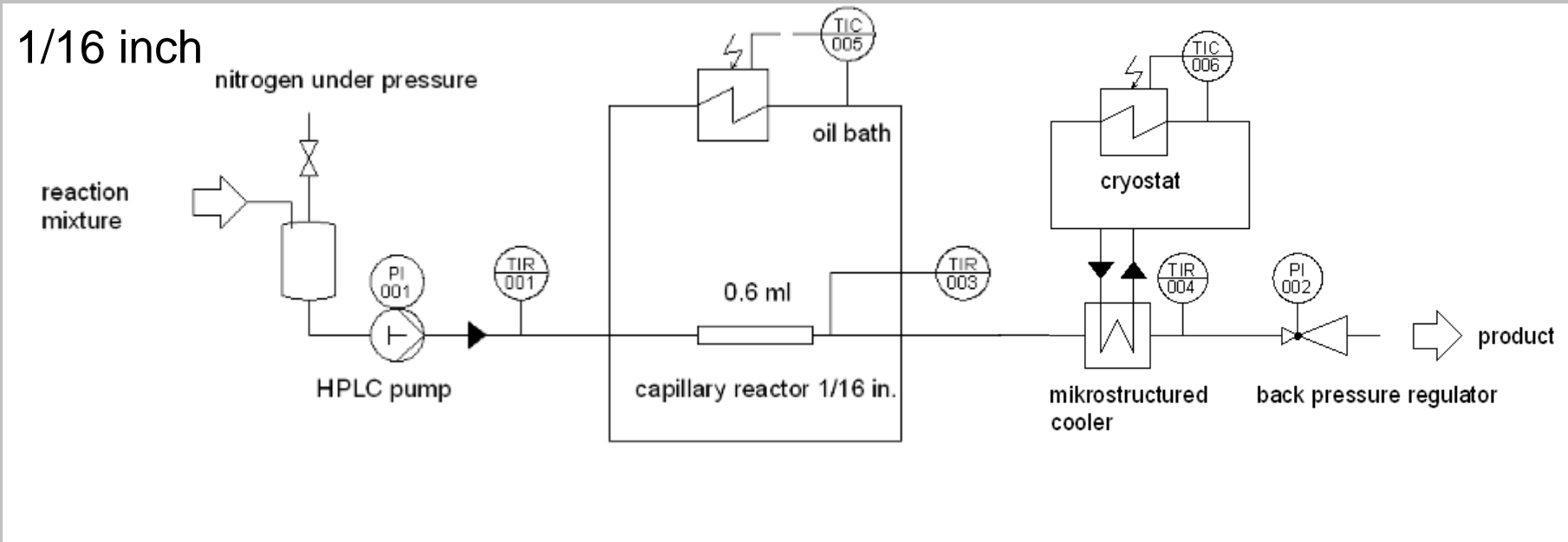


higher temperatures and longer residence times promote side reaction and decomposition

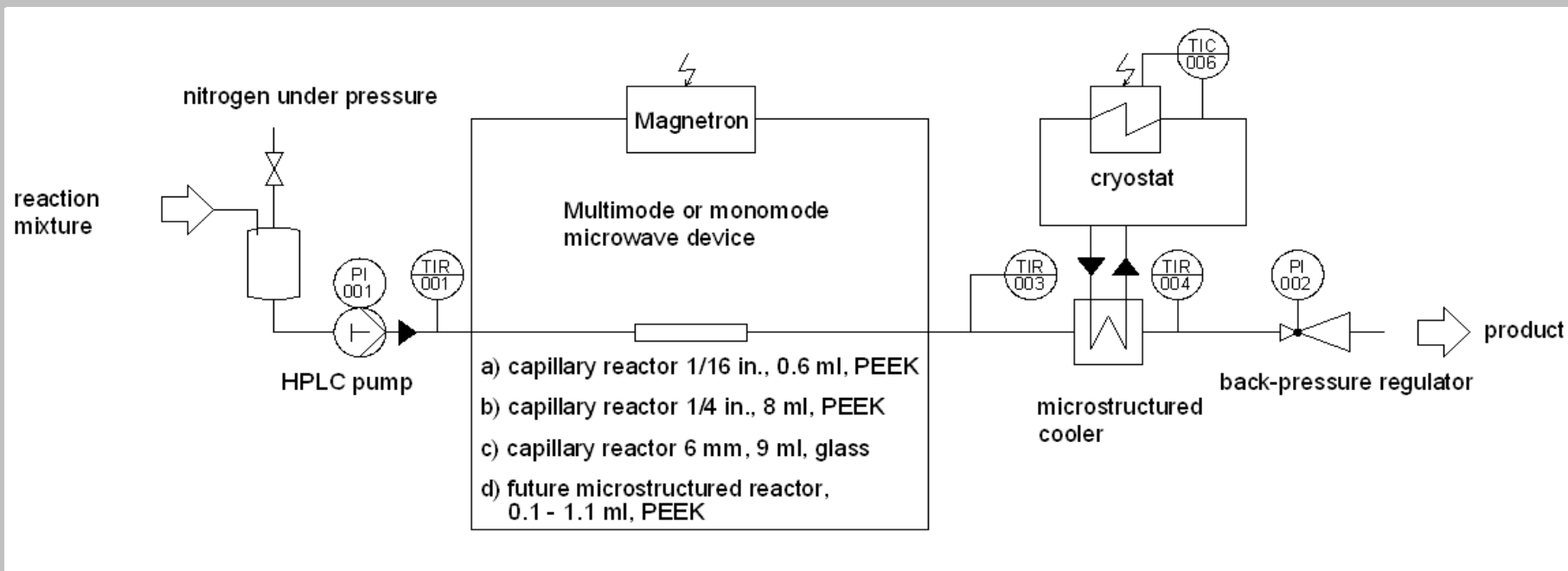
Experimental set-ups



Experimental set-ups



Experimental set-ups

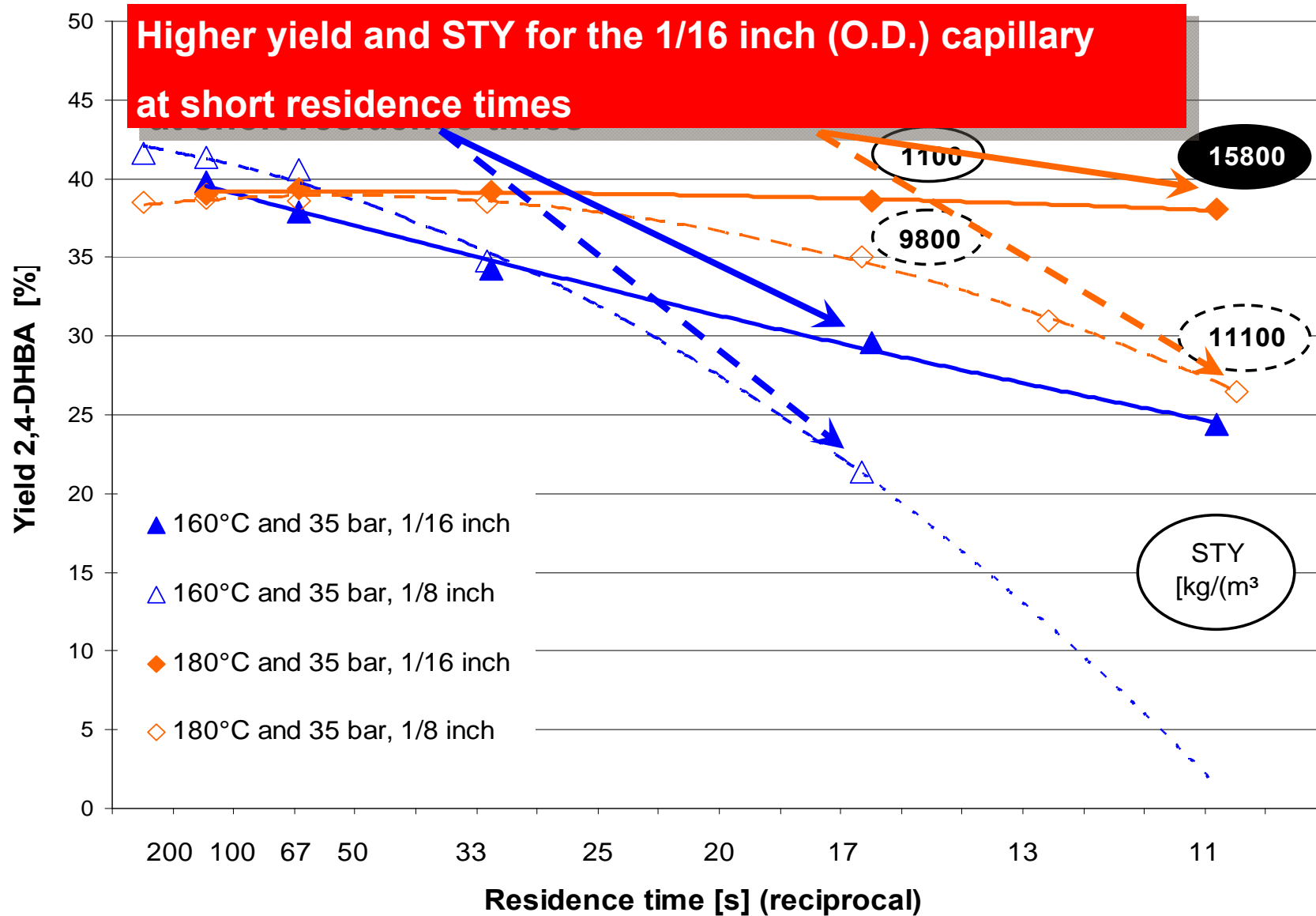


Analytics

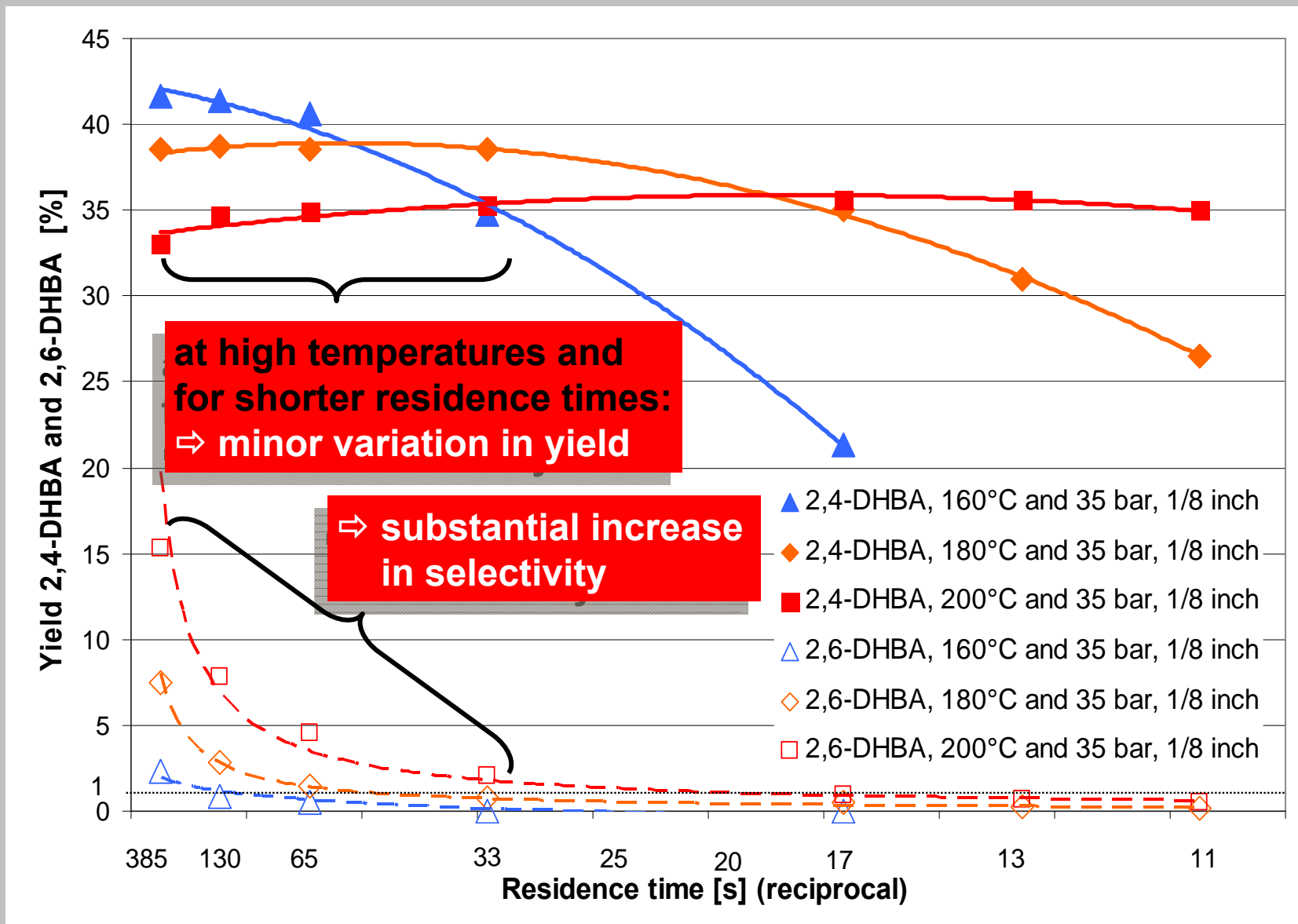
- HPLC (Shimadzu VP series)
- UV detection at 220 and 260 nm
- Reported data received when using 220 nm
↳ better detection of resorcinol
- Acidic eluent to avoid deprotonation of the acidic sites
- Eluent is a mixture of acetonitrile, water and potassium dihydrogen phosphate as buffer

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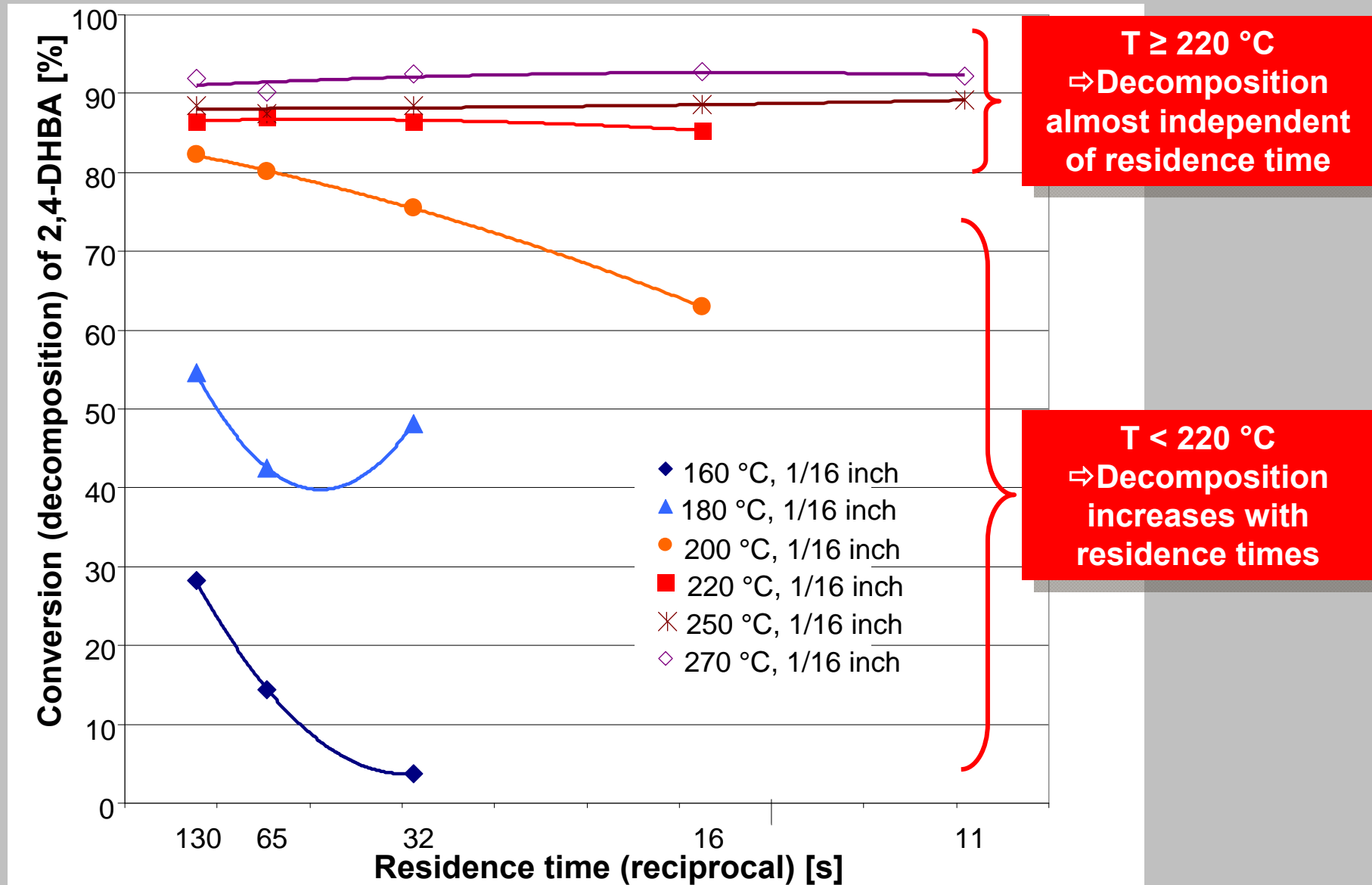
CH-A-KS: Dependency of yield and STY on the capillary dimension



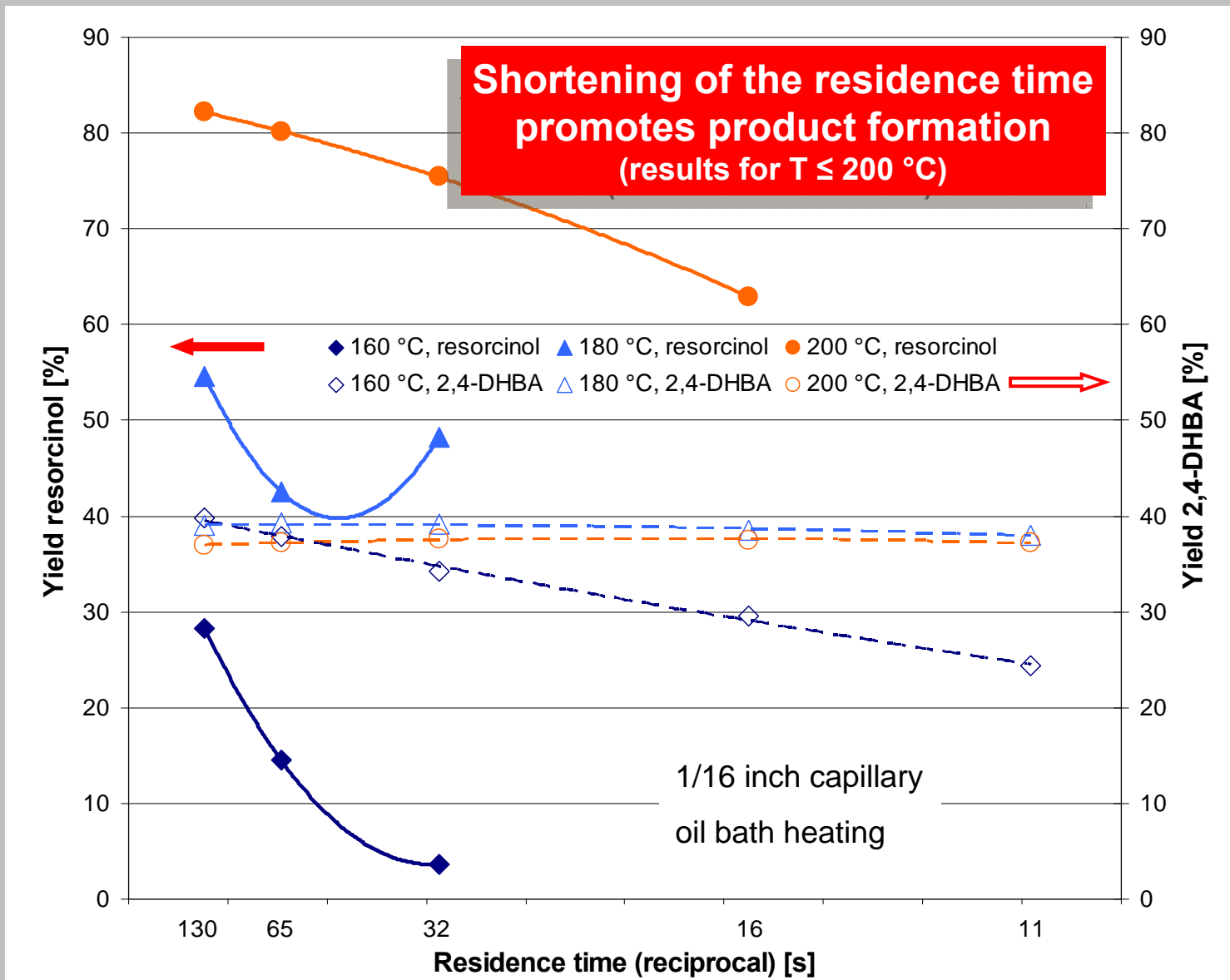
CH-A-KS: Selectivity improvements for short residence times



Decomposition of the product 2,4-DHBA

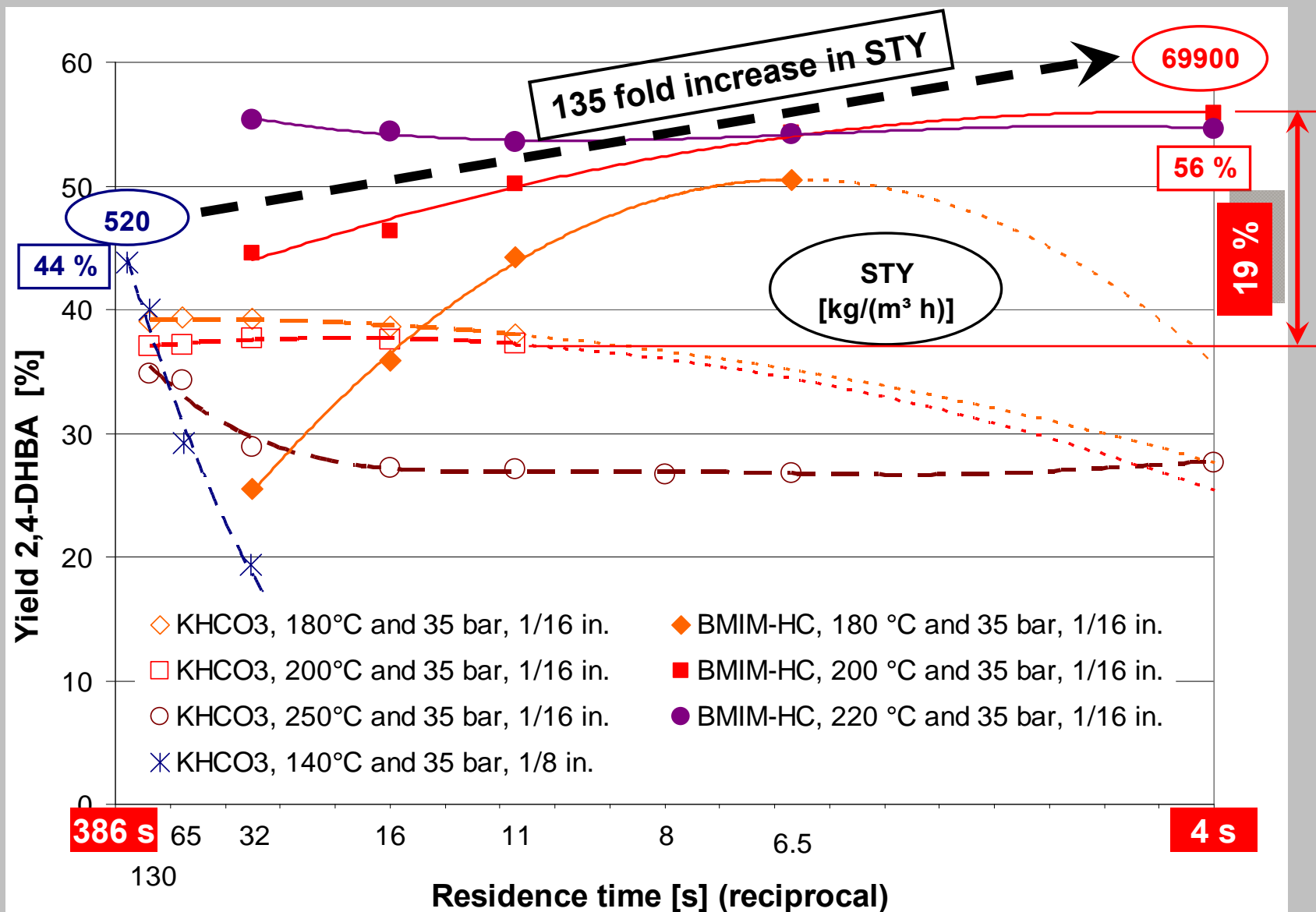


Comparison of product formation and decomposition

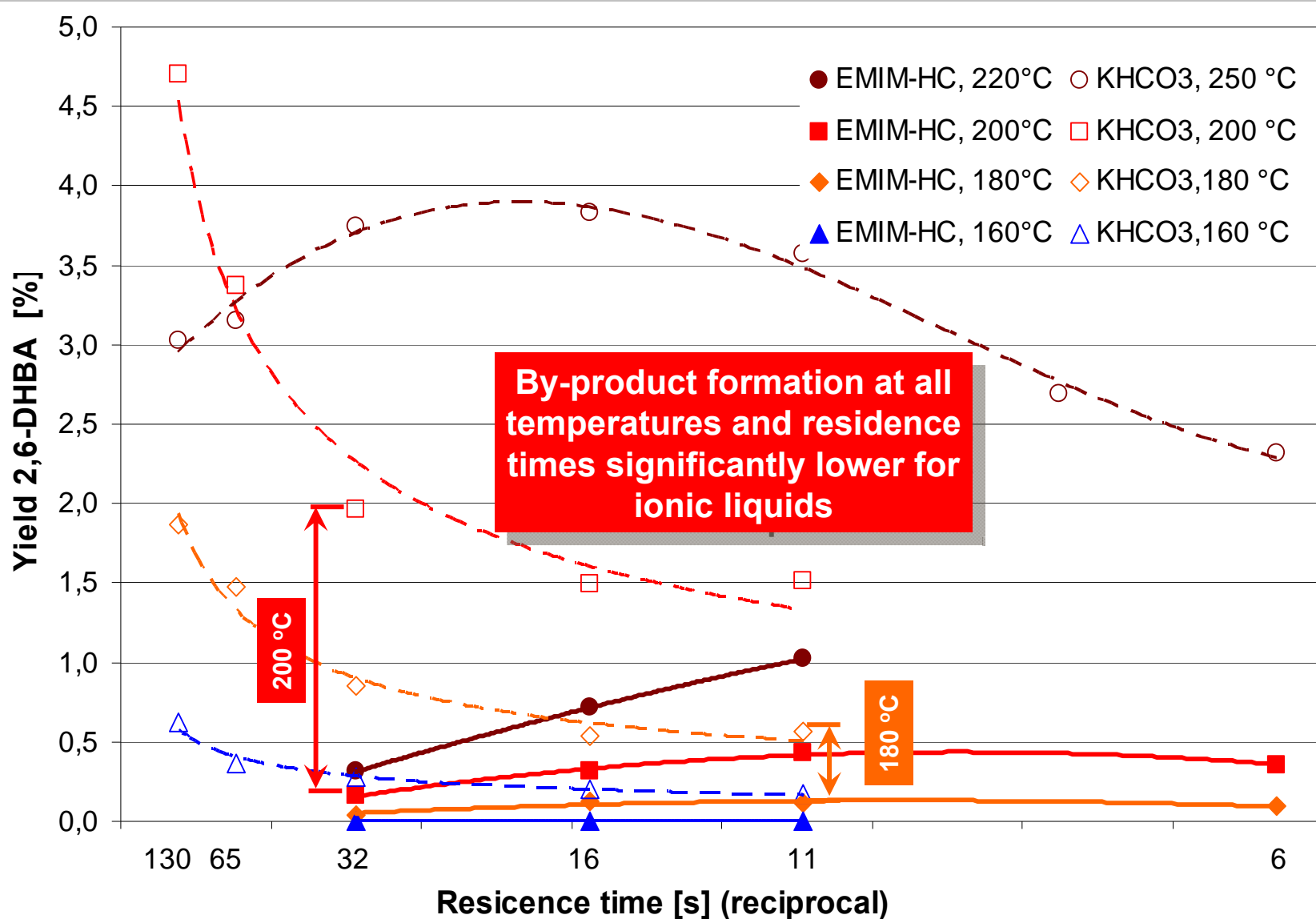


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CH-IL-KS: Enhancements in yield and space-time yield

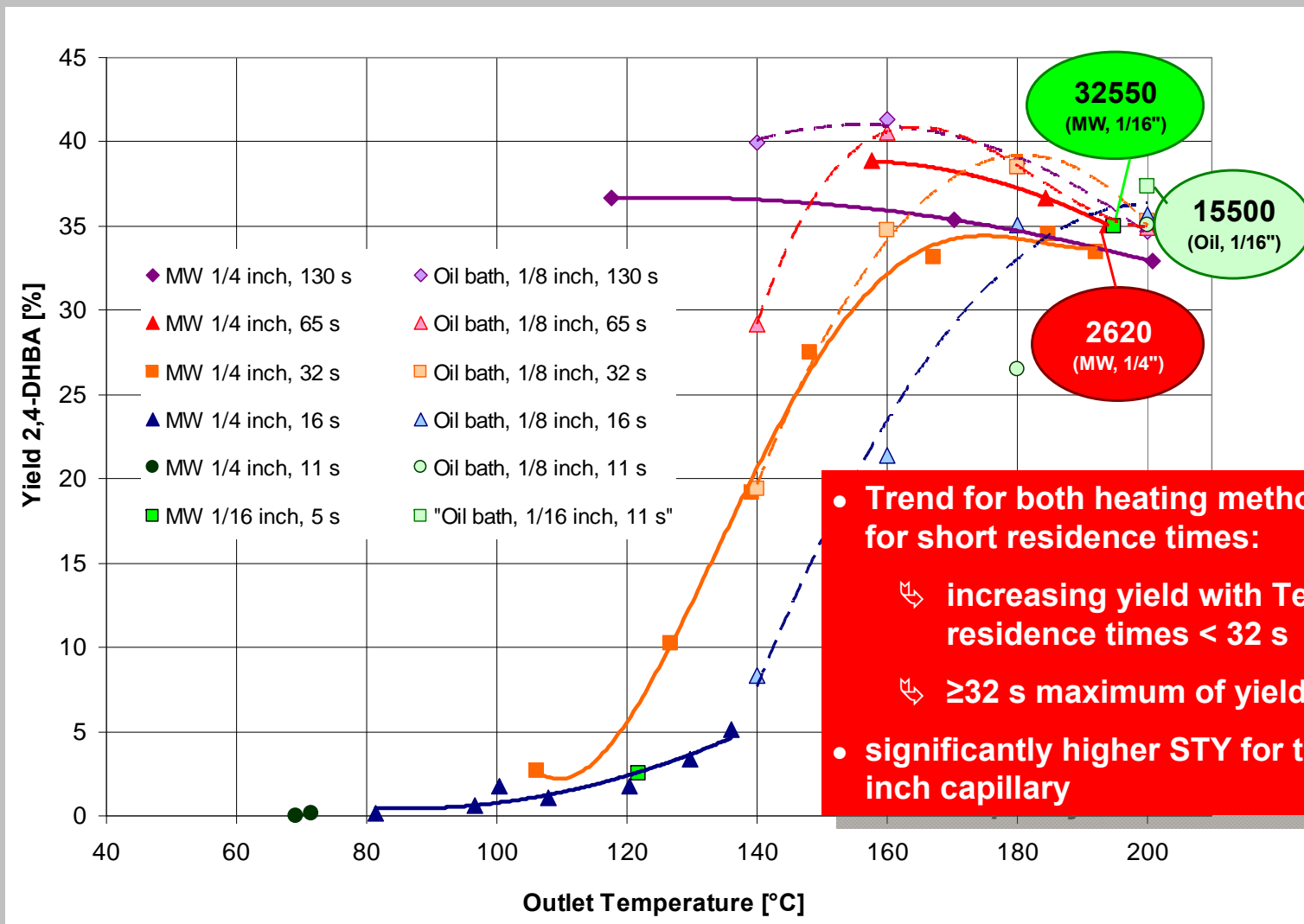


CH-IL-KS: Selectivity improvements compared with KHCO_3



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MW-A-KS: Comparison of yield vs. oil bath heating



- Trend for both heating methods and for short residence times:
 - ↪ increasing yield with Temp. for residence times < 32 s
 - ↪ ≥32 s maximum of yield (<200 °C)
- significantly higher STY for the 1/16 inch capillary

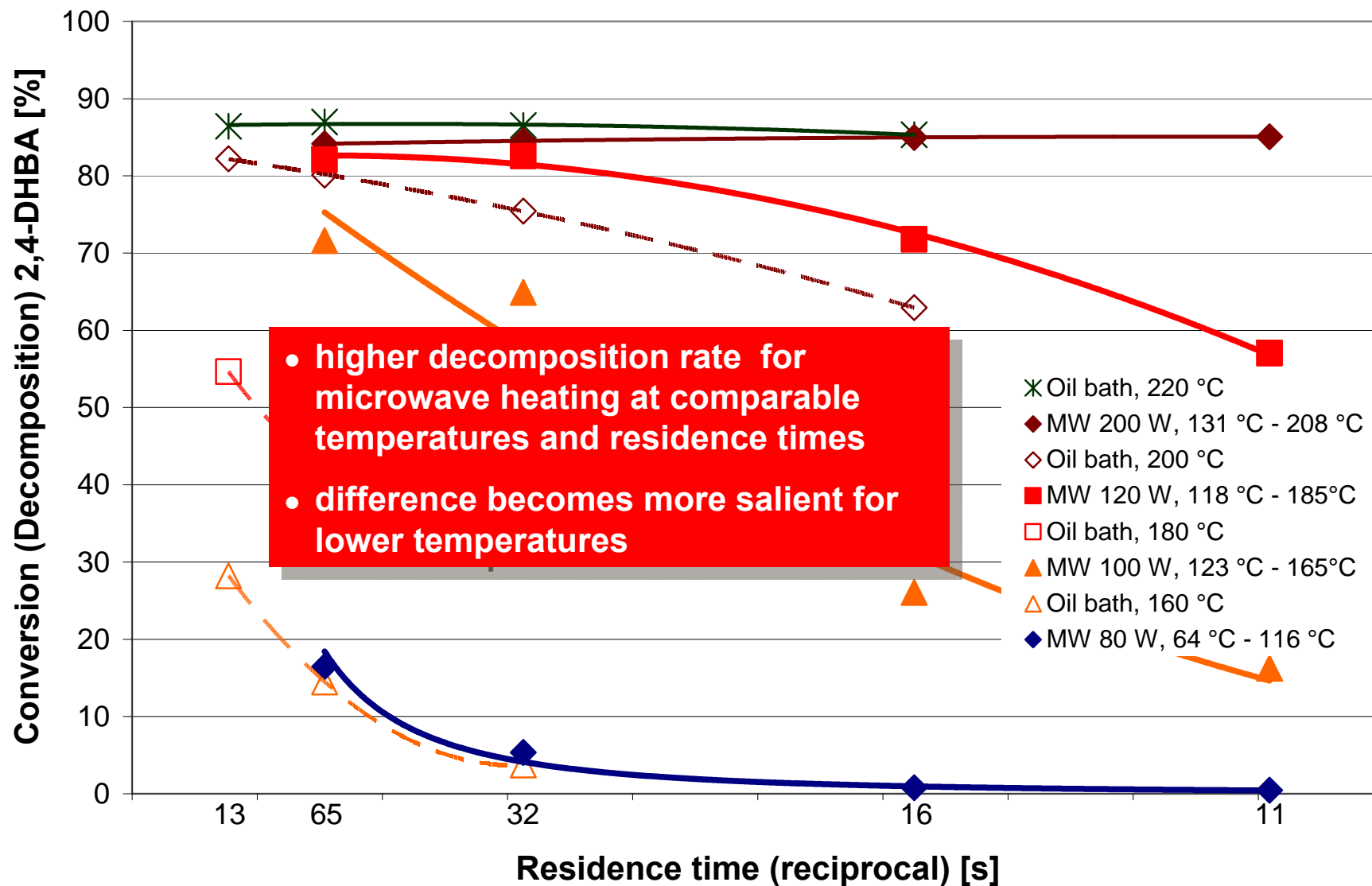
Microwave: Synthos 3000 (Anton Paar)

Oil bath: CC 405 (Huber)

Capillary: PEEK, 1/4 inch O.D. (1/16 inch)

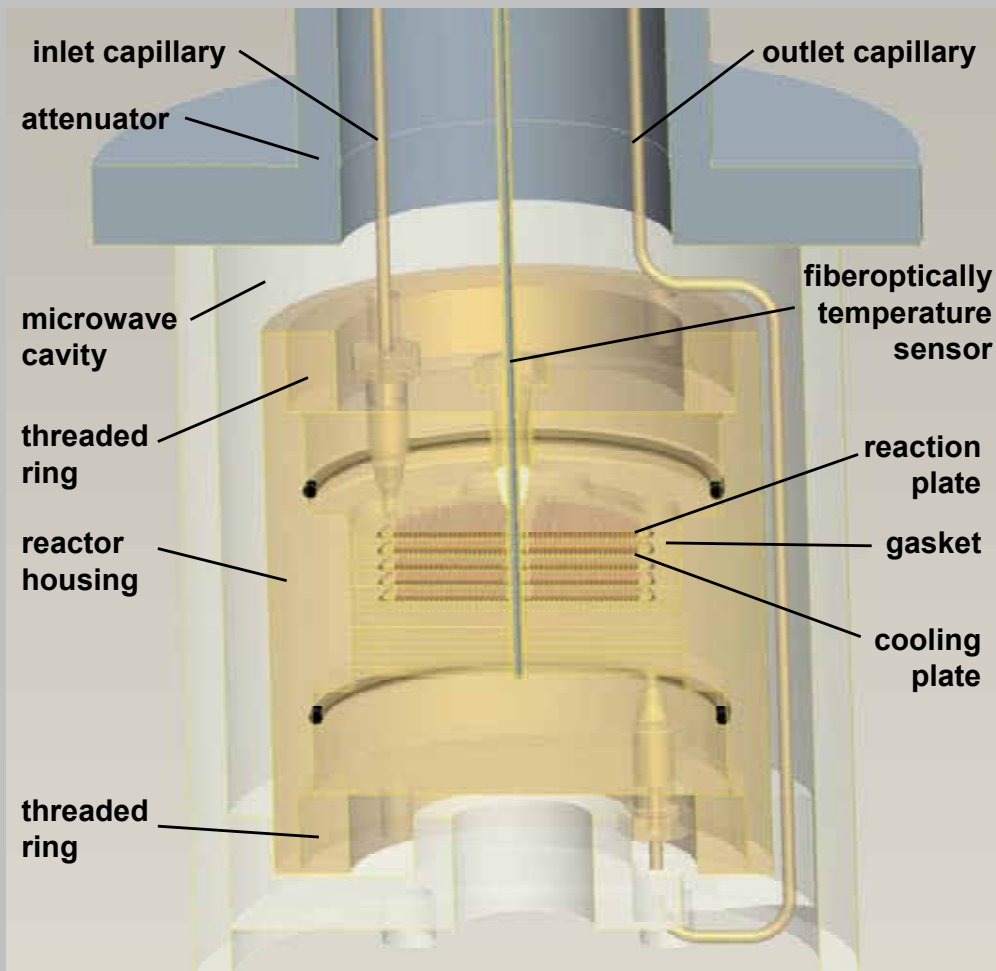
Capillary: Stainless steel, 1/8 inch O.D. (1/16 inch)

MW-A-KS: Comparison of product decomposition vs. oil bath heating



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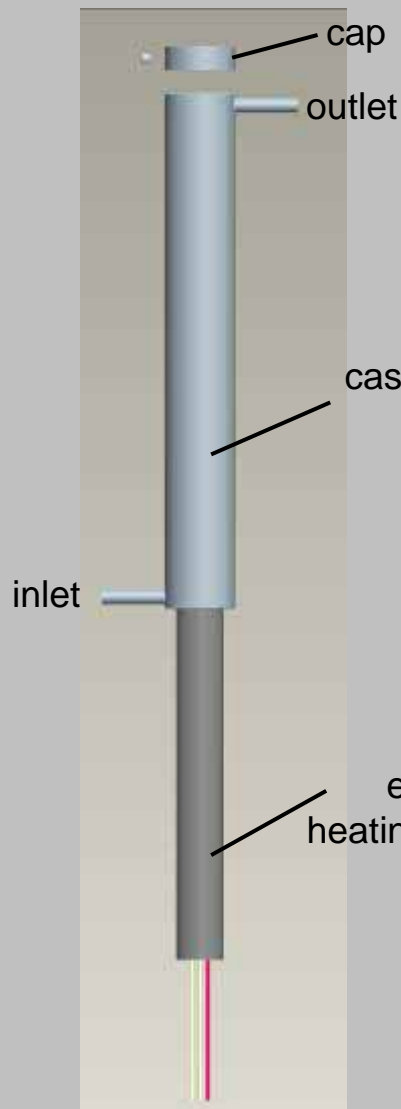
Modular microstructured reactor for microwave heating - Design



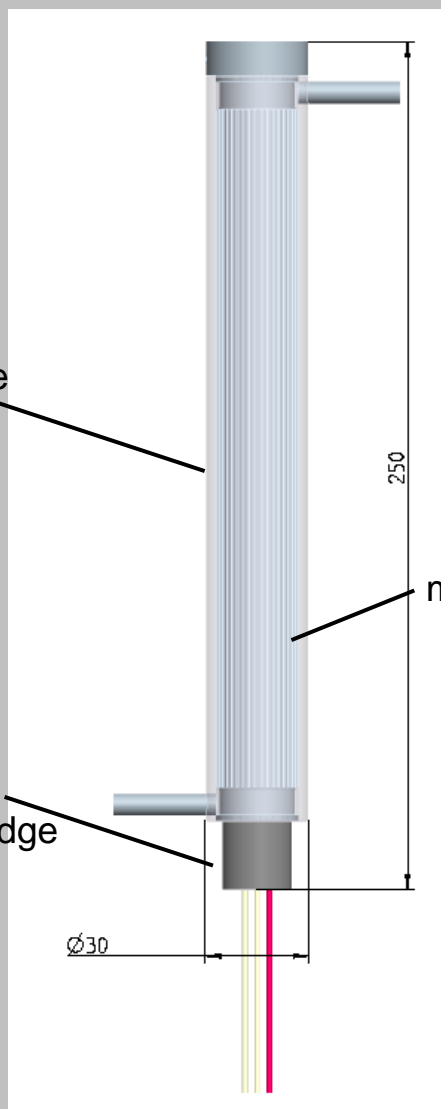
Modular microstructured reactor for microwave heating - Concept

- **Developed for continuous operation and adapted to the cavity of the CEM microwave device „Discover“**
- **Designed for pressures up to 40 bar at 150 °C**
- **Modular construction:**
 - ↪ **different numbers of reaction plates in series or parallel**
 - ↪ **enables simultaneous release of the reaction heat by a microwave transparent cooling fluid (perfluoropolyether)**
- **Integrated fibre optical temperature measurement**
- **HPLC-connectors**

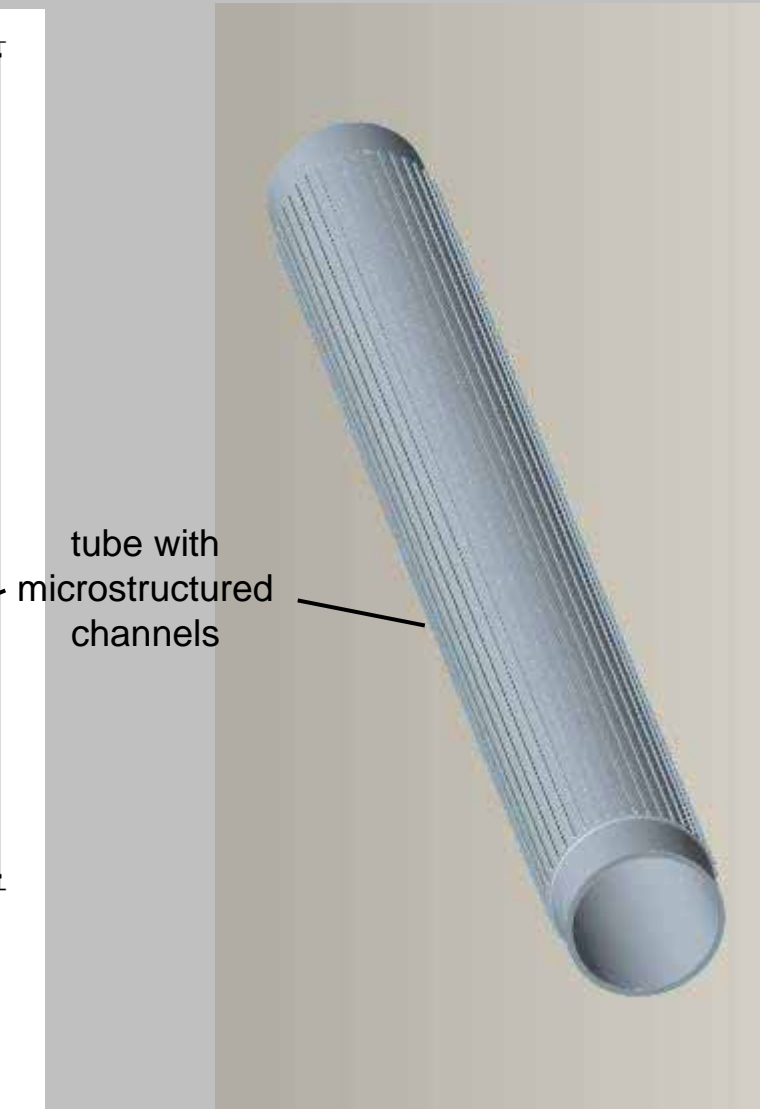
Electrical heated microstructured reactor for liquids - Design



exploded view



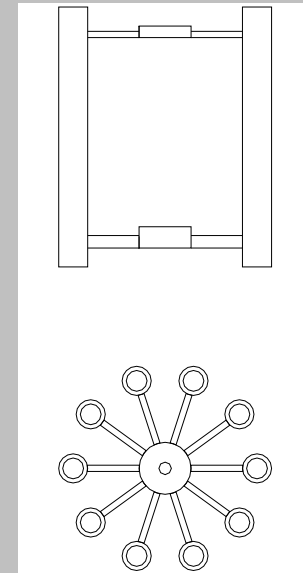
general view



part with microstructured channels

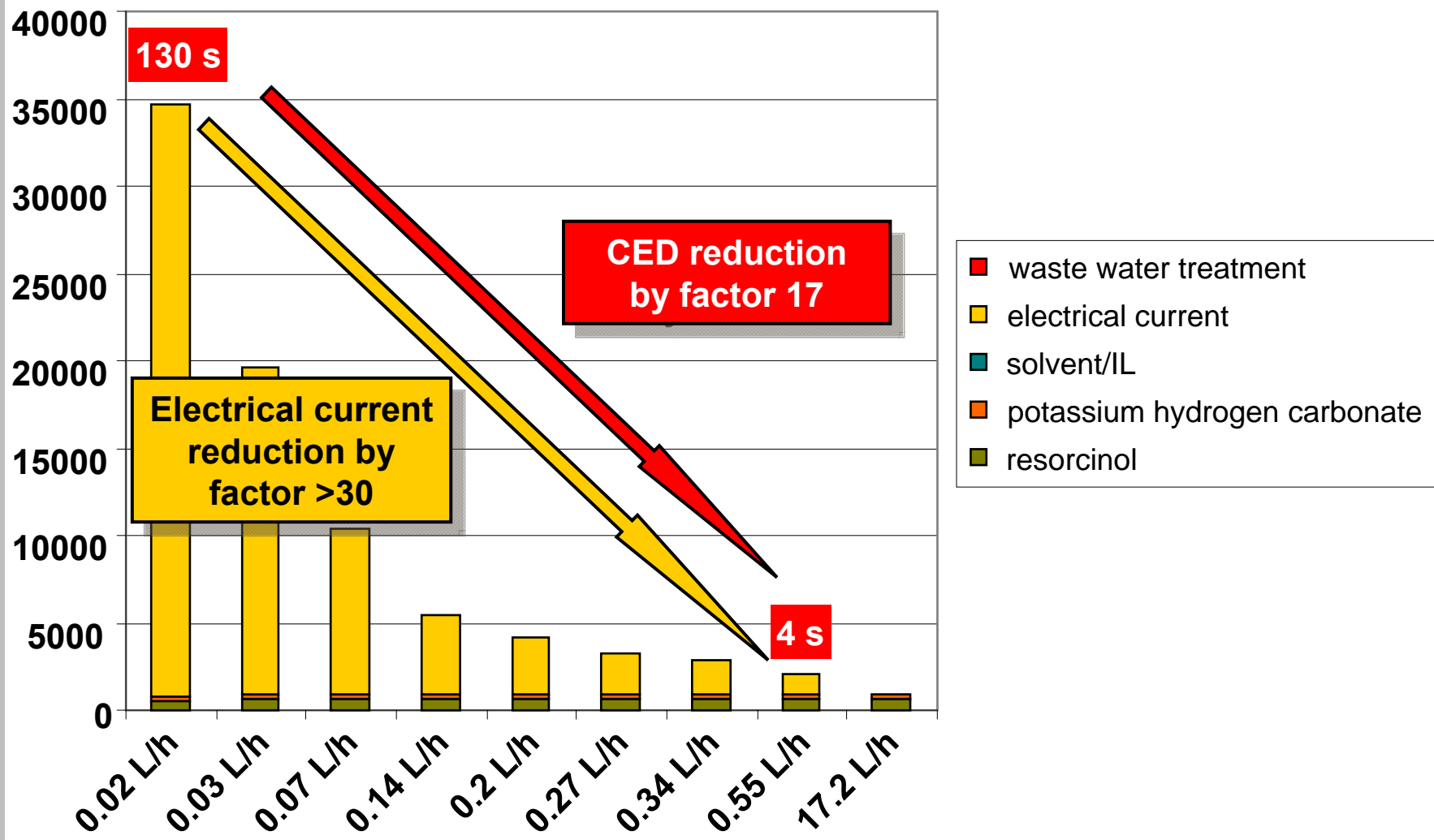
Electrically heated microstructured reactor for liquids - Concept

- **Comparable cross-sectional area with the 1/16 inch capillary**
 - ↳ **use of advantages for small dimensions:**
 - higher yields
 - better selectivity
- **40 fold higher productivity due to (internal) equalling-up**
- **Energy savings compared to oil bath heating by reason of**
 - ↳ **thermally controlled power consumption**
 - ↳ **direct electrical heating**
- **Promising results of pre-tests with an existing gas heater**
- **Scale-up to pilot-scale by external numbering-up using a starlike distributor and collector**



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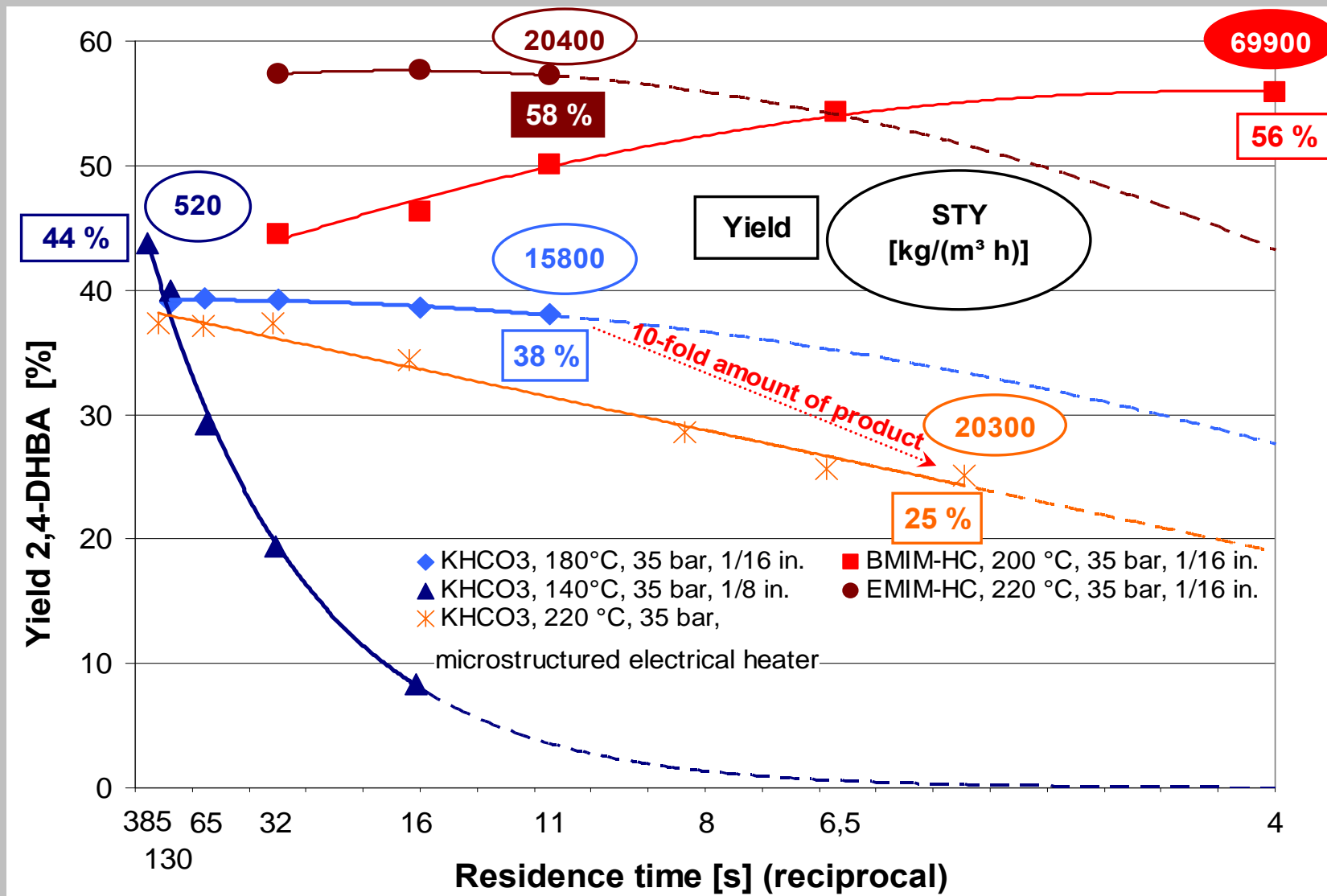
Cumulative Energy Demand (CED) – Influence of residence time



S. Huebschmann, D. Kralisch, V. Hessel, U. Krtschil, V. Kompter, Chem. Eng. Technol. 2009, 32, No. 11, 1757–1765

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Progress achieved - Overview



U. Krtschil, V. Hessel, D. Reinhard, A. Stark, Chem. Eng. Technol. 2009, 32, No. 11, 1774–1789

Summary

- Reaction profits from process intensification enabled by Novel Process Windows and micro reaction engineering:
 - **Advantages at higher temperatures** and the thereby enabled short residence times:
 - ↪ **massive increase in space-time yields** whereas yields are only moderately decreased
 - ↪ **lowering** or almost avoidance **of by-product formation**
 - ↪ predominance of **advantages for small dimensions**
 - **Best yields and space-time yields** if reactive ionic liquids are used
 - No increase in yield if additional near-critical CO₂ was applied
- Improvement for microwave heated capillary reactors compared to oil bath heating with respect to doubling of space-time yield
- Dedicated **microstructured reactor for microwave heating** and enabling simultaneous release of the reaction heat by liquid cooling developed and manufactured
- **Electrically heated microstructured reactor** for liquids **developed**, suited for lab and pilot scale by numbering-up

Outlook

- **Experimental testing of the microstructured reactor in the microwave and comparison to results gained with the capillary reactor**
- **Manufacture of the electrically heated microstructured reactor**
- **Its application in comparative experiments**
- **Erection of a pilot plant and testing of a industrial interesting reaction at industrial site**

Acknowledgement



Directorate Micro and Milli Process Engineering



Thank you for your attention!

