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Supporting Information

A scalable dynamic cascade flow reactor for challenging continuous heterogeneous processes

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Table of Contents

1. General remarks

Unless stated otherwise, chemicals were obtained from commercial suppliers (TCI, Acros organics, Sigma-Aldrich, Fluorochem, Apollo Scientific, Thermofisher, Carl Roth or Fluka) and used with no further purification. NMR measurements were carried out on a Bruker Avance 300 MHz spectrometer (1H: 300 MHz, 13C: 75 MHz) or a Bruker Avance III HD 400 Mhz spectrometer (1H: 400 MHz, 13C: 101 MHz). Deuterated solvents were obtained from Cambridge Isotope Laboratories or Carl Roth. Gas chromatography measurements were carried out on a Thermo Fisher GC Trace 1300 equipped with a flame ionization detector (FID).

1.1. Symbols

A_a heat transfer surface at the outside of the tube [m^2]

A_i heat transfer surface at the inside of the tube [m^2]

A_m mean heat transfer surface [m^2]

c_p specific heat capacity [J kg^{-1} K^{-1}]

d stirrer diameter [m]

D_i inner diameter [m]

k overall heat transfer coefficient [W m^{-2} K^{-1}]

$\dot{m}$ mass flow rate [kg s^{-1}]

n stirring speed [s^{-1}]

Q heat [J]

$\dot{Q}_{ex}$ exchanged heat flow [W]

$\dot{Q}_{nex}$ not exchanged heat flow [W]

s wall thickness [m]

t time [s]

ΔT temperature difference [K]

$\dot{\boldsymbol{V}}$ volume flow rate [$m^3\ s^{-1}$]

$\dot{V}_{ref}$ reference volume flow rate [$m^3\ s^{-1}$]

1.2. Dimensionless numbers

Nu Nusselt number [-]

Pr Prandtl number [-]

Re Reynolds number [-]

1.3. Greek symbols

α_i heat transfer coefficient in the tube [$W\ m^{-2}\ K^{-1}$]

α_a heat transfer coefficient in the shell [$W\ m^{-2}\ K^{-1}$]

η viscosity [Pa s]

η_W viscosity at the wall [Pa s]

λ thermal conductivity [$W\ m^{-1}\ K^{-1}$]

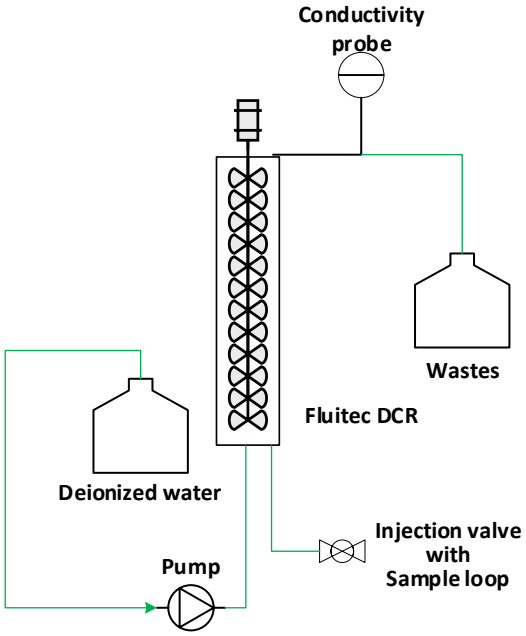
λ_W thermal conductivity of the wall [$W\ m^{-1}\ K^{-1}$]

ρ density [$kg\ m^{-3}$]

2. Residence time distribution measurements

2.1. Experimental setup

All measurements were carried out at HEIA-FR using the clear glass jacket provided by Fluitec. An HNP mzr-4605-hs microgear pump equipped with a mini Coriflow massflow controller and a Siemens automate provided by Fluitec was used to introduce water at varying flowrates. Sodium chloride tracers (0.25 M) were injected using a Rheodyne 3725i injection system with a sample loop (5 mL). An Endress-Hauser CM442 Liquiline Transmitter equipped with a Memosens CLS82E conductivity probe was used to perform online conductivity measurements at the outlet of the reactor in a custom made flowcell (Fluitec). All experiments were performed at room temperature, with temperatures of liquid at the outlet in the range of 19.5°C to 21.5°C.



2.2. Experimental procedure

Without any stirring applied, the reactor was filled with deionized water using the HNP pump and inspected for the presence of air pockets. Most air pockets could be removed by starting the stirrer at high RPM and stopping it after a few seconds of operation. Once the reactor was full of deionized water, the stirring rate was set up to match the desired parameters for the experiment and water was passed

through the reactor until the conductivity measured stabilized at a low value (1 – 2.5µS/cm). The desired flowrate for the residence time measurement was then applied. The sample loop was then filled using an excess of tracer solution and the content of the loop was injected using the Rheodyne valve to start the measurement. The experiment was considered done when the conductivity values had dropped back to the initial levels of pure deionized water. The measured curves are shown in the appendix.

This procedure was performed at various flowrates (10 – 50 mL/min) and various stirring rates 30 – 1000 rpm). MODDE 13 was used to generate a D-optimal design of experiment.

2.3. Data treatment

No blank subtraction was performed on the raw data, as the initial conductivity values were negligible. Data obtained from the Endress-Hauser transmitter were treated using R (in RStudio) with a custom-made script to calculate mean residence times, variances and Bodenstein numbers. CSTR cascade equivalents could be derived either from Bodenstein numbers or by fitting the residence time distribution curves with the theoretical equation describing ideal CSTR cascades using a non-linear regression algorithm (nls in R). The following equations were adapted from literature references.[1]

Residence time function $E(t)$:

$$E(t) = \frac{Conductivity(t)}{\int_0^\infty Conductivity(t)\, dt}$$

Mean residence time τ:

$$\tau = \frac{\int_0^\infty Conductivity(t) \cdot t\, dt}{\int_0^\infty Conductivity(t)\, dt} = \int_0^\infty E(t) \cdot t\, dt$$

Dimensionless residence time θ:

$$\theta = \frac{t}{\tau}$$

Dimensionless residence time function $E(\theta)$:

$$E(\theta) = E(t) \cdot \tau$$

Variance σ^2:

$$\sigma^2 = \int_0^\infty (t-\tau)^2 \cdot E(t)\, dt$$

Bodenstein numbers Bo:

$$\frac{\sigma^2}{\tau^2} = \frac{2}{Bo} + \frac{8}{Bo^2}$$

Ideal CSTR in series $E(\theta)$:

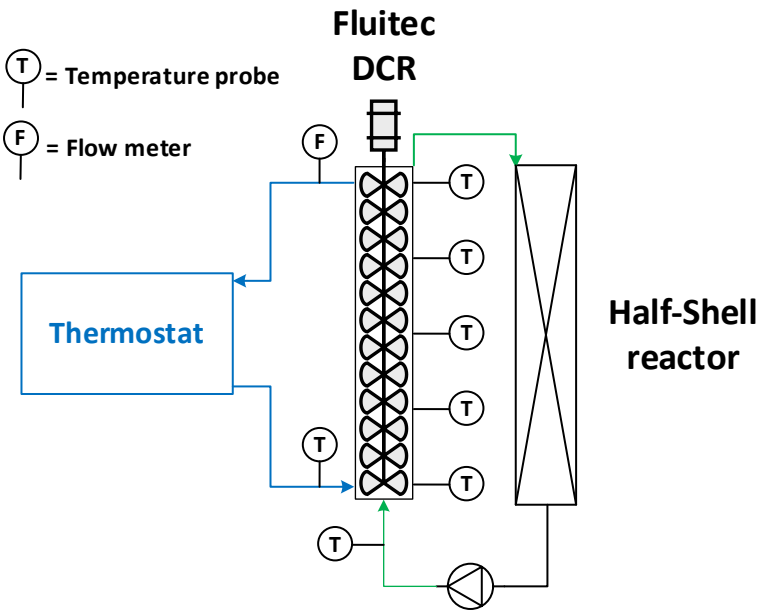
$$E(\theta) = N \frac{(N \cdot \theta)^{N-1}}{(N-1)!} \cdot e^{-N \cdot \theta}$$

Where $N = number\ of\ CSTR\ in\ series$

3. Thermal characterization

3.1. Experimental setup

The heating experiments were carried out in a DCR (Di = 36 mm, 69025, Fluitec mixing + reaction solutions AG, Switzerland) with a double jacket stainless steel housing. Isopropyl alcohol (> 99 %, C. Züger, Chemische Produkte, Aadorf, Schweiz) was dosed by a flow-controlled dosing system (DZRP-200, 63639, Fluitec) on the process side. Distilled water was used as heat transfer medium (HTM). It was supplied in co-current mode using a heating–cooling thermostat (Ministat, Peter Huber Kältemaschinenbau AG, Germany). A half-shell reactor (Di = 12.3 mm, 61751, Fluitec) was used to cool down isopropyl alcohol. The inlet temperature, the five temperature levels along the DCR and the HTM inlet temperature were measured using Pt-100 temperature probes (Class A, Pt-100, 53286, Fluitec). The HTM mass flow rate was measured by a Coriolis mass flow meter (Promass 80F15, Endress + Hauser (Schweiz) AG, Switzerland). All data were logged on an inhouse designed Siemens S7 control system. The experiments were carried out at an inlet temperature range of 25.9°C to 33.8°C and an HTM temperature range of 59.7°C to 59.9°C.



3.2. Experimental procedure

The thermostat was set to target temperature (60°C) and operated at maximum pump capacity. By the time the DCR was heated up, isopropyl alcohol (at room temperature) was fed into the DCR. The five-point temperature profile was acquired as soon as the equilibrium temperatures were reached. Isopropyl alcohol was subsequently cooled in the half-shell reactor and recirculated into the DCR.This procedure was used for various flowrates (20 – 400 mL/min) and various stirring speeds (0 – 980 rpm).

3.3. Calculations

Overall heat transfer coefficients (*k*) were found by fitting the temperature profile using the following heat flow balance and the segment-wise calculation of the exchanged heat flow $\dot{Q}_{ex}$ and not exchanged heat flow $\dot{Q}_{nex}$, as described in earlier work.[2]

Heat flow balance:

$$\mathbf{0} = \frac{\boldsymbol{dQ}}{\boldsymbol{dt}} = \boldsymbol{\dot{Q}_{ex}} - \boldsymbol{\dot{Q}_{nex}}$$

Exchanged heat flow $\dot{Q}_{ex}$:

$$\boldsymbol{\dot{Q}_{ex}} = \sum_{j=1}^{n} \boldsymbol{k_j} \cdot \boldsymbol{A_{a,j}} \cdot \Delta \boldsymbol{T_j}$$

Not exchanged heat flow $\dot{Q}_{nex}$:

$$\boldsymbol{\dot{Q}_{nex}} = \sum_{j=1}^{n} \boldsymbol{\dot{m}} \cdot \boldsymbol{c_p} \cdot \Delta \boldsymbol{T_j}$$

For each *k* value a certain *Nu* number for the process side was found by calculations using heat exchanger characteristics and the ring-slit-correlation of the double jacket. The *Nu* correlation (Eq. 2 in the main paper) was found by best fit of the calculated *Nu* numbers to the experimental *Nu* numbers:

$$\boldsymbol{Nu} = \mathbf{0.0176} \cdot \left(\frac{\dot{\boldsymbol{V}}}{\dot{\boldsymbol{V}}_{\boldsymbol{ref}}}\right)^{\mathbf{0.5546}} \cdot \boldsymbol{Re}^{\frac{2}{3}} \cdot \boldsymbol{Pr}^{\frac{1}{3}} \cdot \left(\frac{\boldsymbol{\eta_W}}{\boldsymbol{\eta}}\right)^{\mathbf{-0.14}}$$

where $\dot{\boldsymbol{V}}_{\boldsymbol{ref}}$ = 1 mL/min and *Re* and *Pr* were calculated according to the following equations:

Reynolds number *Re*:

$$\boldsymbol{Re} = \frac{\boldsymbol{n} \cdot \boldsymbol{d}^2 \cdot \boldsymbol{\rho}}{\boldsymbol{\eta}}$$

Prandtl number *Pr*:

$$\boldsymbol{Pr} = \frac{\boldsymbol{c}_\mathbf{p} \cdot \boldsymbol{\eta}}{\boldsymbol{\lambda}}$$

Based on the calculated *Nu* numbers, the *k* values were predicted using the following equations:

Heat transfer coefficient in the tube $\boldsymbol{\alpha}_\mathbf{i}$:

$$\boldsymbol{\alpha}_\mathbf{i} = \boldsymbol{Nu} \cdot \frac{\boldsymbol{\lambda}_\mathbf{i}}{\boldsymbol{D}_\mathbf{i}}$$

Overall heat transfer coefficient *k*:

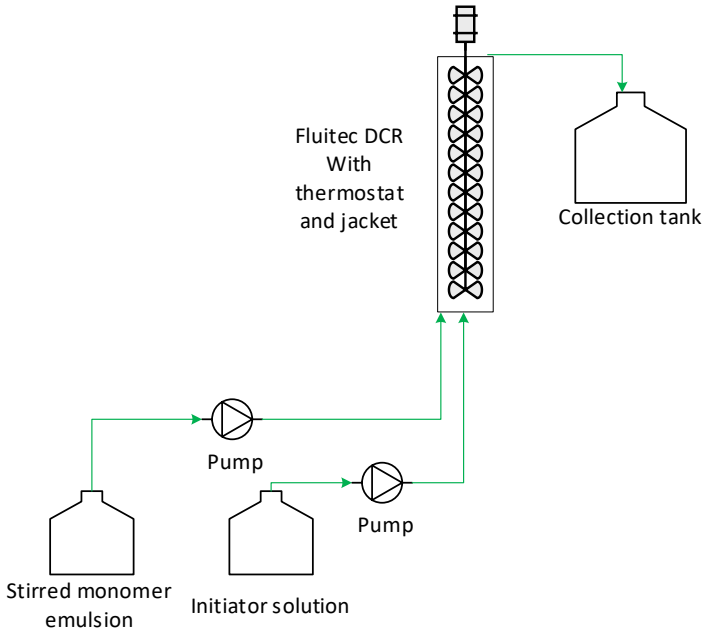
$$\boldsymbol{k} = \frac{\mathbf{1}}{\frac{\mathbf{1}}{\boldsymbol{\alpha}_\mathbf{a}} + \frac{\boldsymbol{s} \cdot \boldsymbol{A}_\mathbf{a}}{\boldsymbol{\lambda}_W \cdot \boldsymbol{A}_\mathbf{m}} + \frac{\boldsymbol{A}_\mathbf{a}}{\boldsymbol{\alpha}_\mathbf{i} \cdot \boldsymbol{A}_\mathbf{i}}}$$

4. Application tests

Unless stated otherwise, Vapourtec SF-10 pumps were used to introduced liquids and suspensions in the DCR with PFA tubing of 1/8" outer diameter.

4.1. Emulsion polymerization

Experimental setup:



Preparation of reagents (to be scaled accordingly to the duration of the experiment):

Reagent bottle A: Butyl acrylate (300 g, 2.341 mol), sodium dodecylbenzenesulfonate (6.0 g, 2 wt% monomer weight, 88% assay) and deionized water (650 mL) were emulsified using an IKA Ultraturrax T25 at 10000 rpm for 5 minutes. Once emulsified, the emulsion was kept under strong stirring for the rest of the experiment using a magnetic stir plate.

Reagent bottle B: Potassium persulfate (6 g, 0.031 mol, 2 wt % monomer weight) was dissolved in deionized water (500 mL).

Flow reaction:

In an empty DCR at 1000 rpm with a jacket temperature set to 70°C, reagent bottle A was pumped at a flowrate of 4 mL/min and reagent bottle B at a flowrate of 2 mL/min. The presence of polymer can be

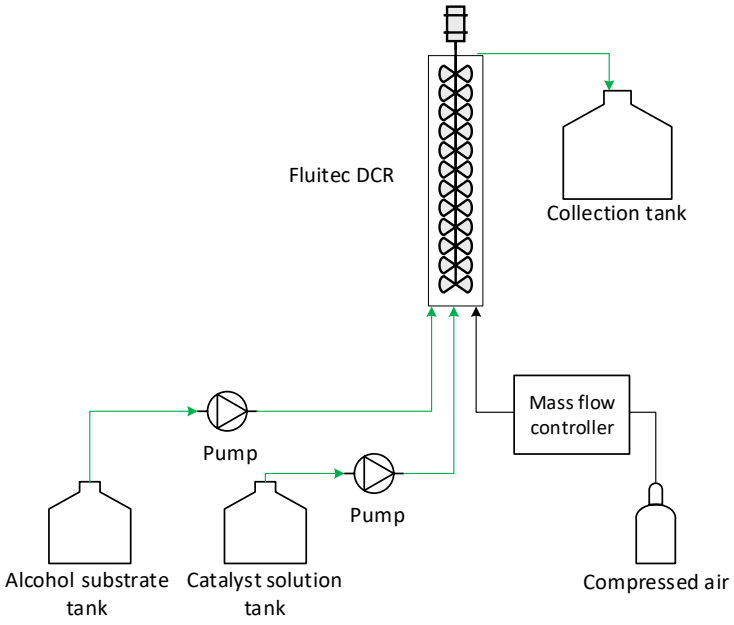
proven by precipitation of an aliquot with brine, resulting in coagulation of polybutyl acrylate. Once all the reagents were introduced, both lines of the peristaltic pumps were transferred to a bottle containing 800 mL of 4 g/L of SDBS in deionized water and the introduction was continued with the total flowrate unchanged. After introduction of the SDBS solution, the reactor was emptied using a 3-way ball valve at the bottom of the reactor and the reactor was rinsed with 4 g/L SDBS solution (20 mL/min), followed by deionized water. The reactor was then cooled down to 25°C, emptied through the 3-way valve and the stirring shaft was inspected visually for fouling.

4.2. Stahl-Hoover oxidation

General remarks:

TPGS-750M, a waxy solid, was dissolved in distilled water to the desired concentration. A Bronkhorst mass flow controller was used to regulate the air flow in the reactor. The solutions listed below are to be scaled according to the duration of the experiment

Experimental setup



Catalyst solution:

To a solution of TPGS-750M (1000 mL, 2 wt% in H_2O) were added TEMPO (7.71 g, 49 mmol, 0.1 equiv), (2,2-bipyridine 7.66 g, 49 mmol, 0.1 equiv) and N-methylimidazole (3.7 mL, 74 mmol, 0.15

equiv). The solution was then stirred for 10 minutes (magnetic stirring). Copper (I) bromide (7.03g, 49 mmol, 0.1 equiv) was added just prior to starting the flow experiment.

Benzyl alcohol solution:

Benzyl alcohol (53.00 g, 490 mmol, 1.0 equiv) was dissolved in acetonitrile (195 mL).

Flow reaction.

From an empty DCR, compressed air (100 mL/min) was introduced in the DCR and the stirring was set to 900 rpm. The catalyst solution was then introduced using a flowrate of 3.8 mL/min, while the benzyl alcohol solution was introduced at a flowrate of 0.8 mL/min. Conversions were determined by NMR from aliquots that were extracted immediately using 0.1 M HCl and ethyl acetate. Commercial samples of benzaldehyde and benzyl alcohol were used as reference material for peak assignments.

4.3. Continuous Grignard reagent formation

General remarks:

2-MeTHF was dried over molecular sieves overnight (except for experiments with undried solvents). Magnesium powder (20-230 mesh) was purchased from Sigma-Aldrich (catalogue number 254126). Magnesium slurries (max 2 wt% in 2-MeTHF) were activated using commercial 1 mol% DIBAL-H (20 wt% in toluene) or 4-methoxyphenylmagnesium bromide (0.5 M in THF). They were introduced in the reactor using one Vapourtec SF-10 pump from a bottle kept under a nitrogen atmosphere and under strong stirring (magnetic stirring). Those suspensions were then always introduced at a set flowrate of 10 mL/min. 4-bromoanisole solutions concentrations and flowrates were adjusted for each experiment to obtain the desired concentration in the reactor. Prior to any reaction, the DCR was flushed with nitrogen for 10 minutes. The collecting 15 L reactor (BüchiGlasUster miniPilot) was filled with approximately 4.5 L of ammonium chloride solution in water (0.5 M) at a jacket temperature of 15°C under a flow of nitrogen. PT100 probes connected to a PicoLog PT-104 data logger were used to perform temperature measurements.

Flow reaction (no batch activation):

The DCR jacket temperature was set to 50°C and the two Vapourtec pumps were used to fill the whole system with 2-MeTHF. Stirring in the DCR was then applied at 617 rpm for the rest of the experiment. The desired amount of magnesium was pre-loaded using one pump at a flowrate of 10 mL/min, assuming a fully homogeneous suspension. Once the desired amount of magnesium was introduced, the halide pump was started at the desired flowrate (magnesium pump still running). Aliquots of the reaction were collected from a 3-way valve placed before the 15 L quench tank and directly quenched with 0.5 M ammonium chloride. Conversions were measured by GC (using decane as internal standard) or NMR, comparing the ratio of 4-bromoanisole to anisole.

Note: For the conversion calculation, it is assumed that 4-bromoanisole is cleanly converted to 4-methoxyphenylmagnesium bromide during the process, and that anisole is obtained cleanly after the acidic aqueous quench. While other side products (homocoupling) may be produced, it was determined from NMR spectra that only negligible amounts of side products were obtained under those conditions. Reactions labelled as “full conversions” indicate that no 4-bromoanisole could be detected by GC or NMR.

Flow reaction (batch activation):

The DCR jacket temperature was set to 50°C and the two Vapourtec pumps were used to fill the whole system with 2-MeTHF. Stirring in the DCR was then applied at 617 rpm for the rest of the experiment. The desired amount of magnesium was pre-loaded using one pump at a flowrate of 10 mL/min, assuming a fully homogeneous suspension. Once the desired amount of magnesium was introduced, 0.1 equivalent of halide was introduced in the reactor using the 2nd pump. It was then left to react until no more heat was released (monitoring through the temperature probe at the outlet of the jacket). Both pumps were then started at the required flowrate. Aliquots of the reaction were collected from a 3-way valve placed before the 15 L quench tank and directly quenched with 0.5 M ammonium chloride.

Conversions were measured by GC (using decane as internal standard) or NMR, comparing the ratio of 4-bromoanisole to anisole.

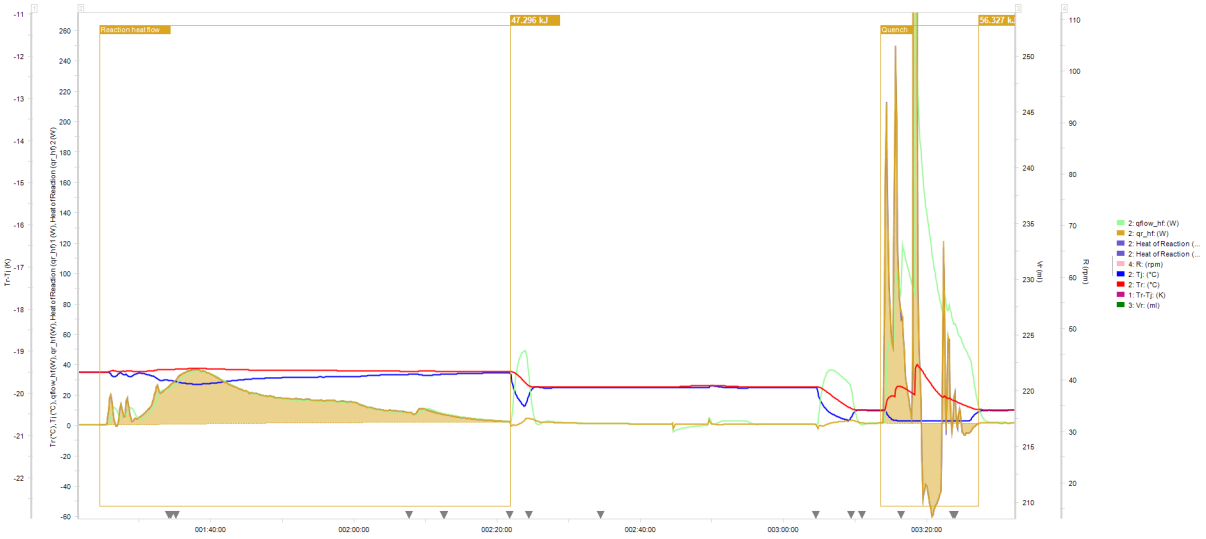
Thermal safety:

Differential scanning calorimetry (DSC) measurements were carried out using a Mettler Toledo TGA/DSC 1 Star system and a sealed gold crucible. 4-methoxyphenylmagnesium bromide (0.5 M in THF) was purchased from Thermofisher (Acros).

Reaction enthalpy measurements were carried out using an RC1mx from Mettler Toledo in batch from magnesium turnings and 4-bromoanisole in 2-MeTHF.

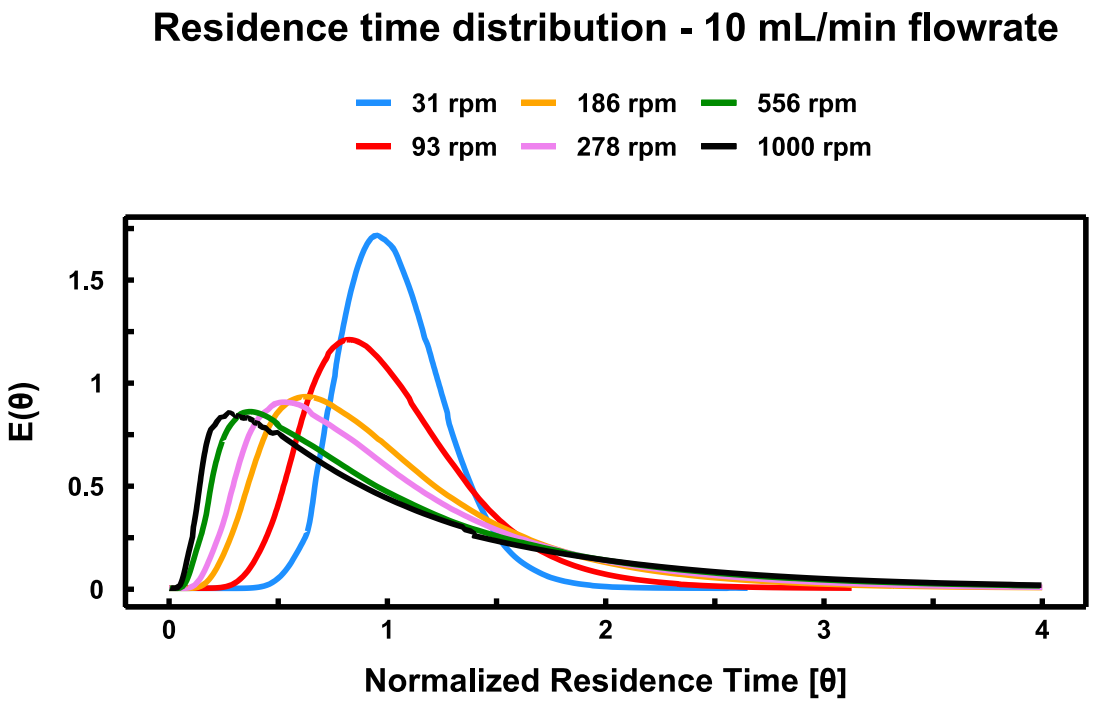
- Reaction enthalpy of the Grignard formation: -295 kJ/mol (1557 J/g)
- Reaction enthalpy of the aqueous quench: -352 kJ/mol (1882 J/g)

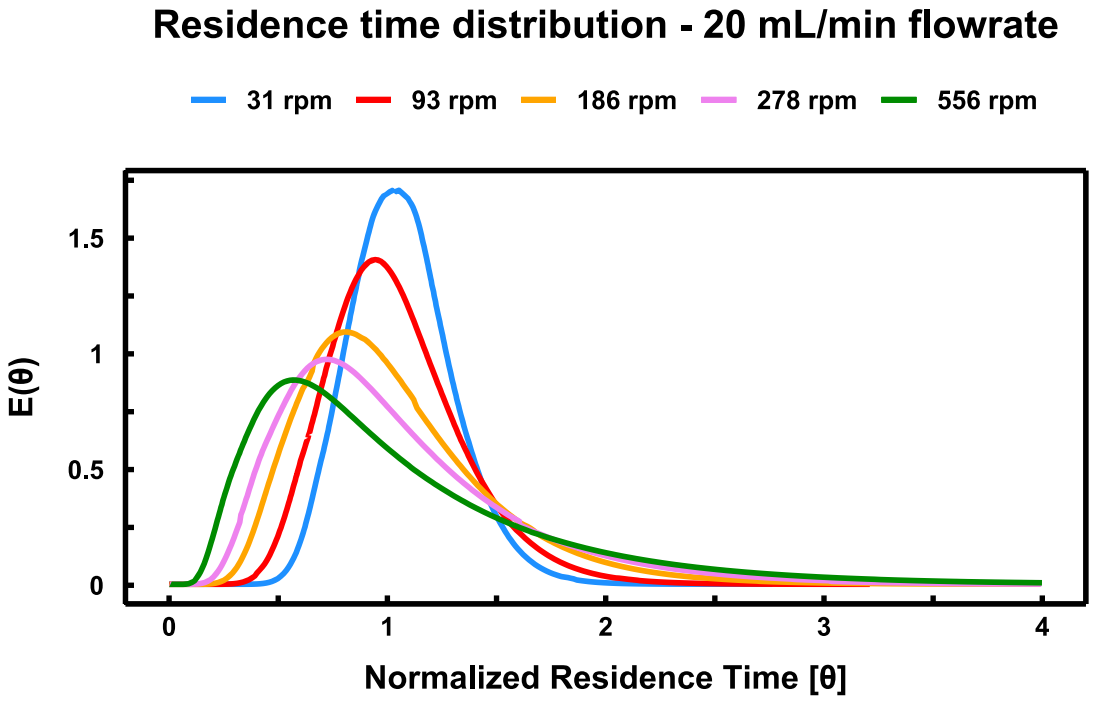
RC1 data (0.16 mol scale)

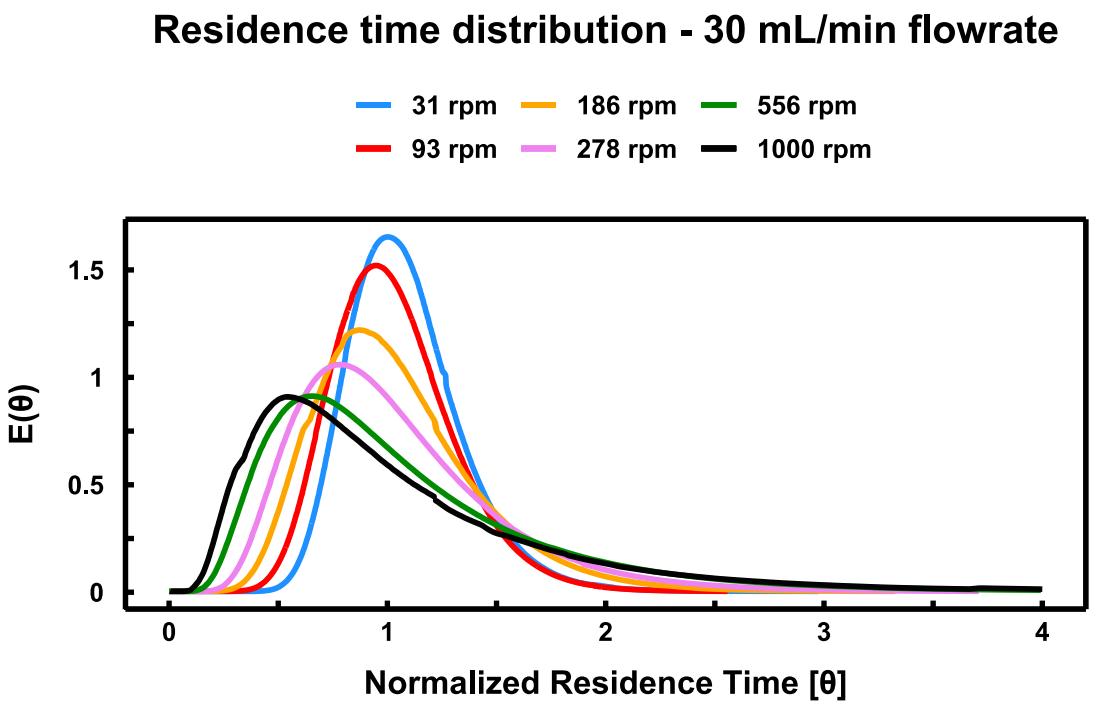


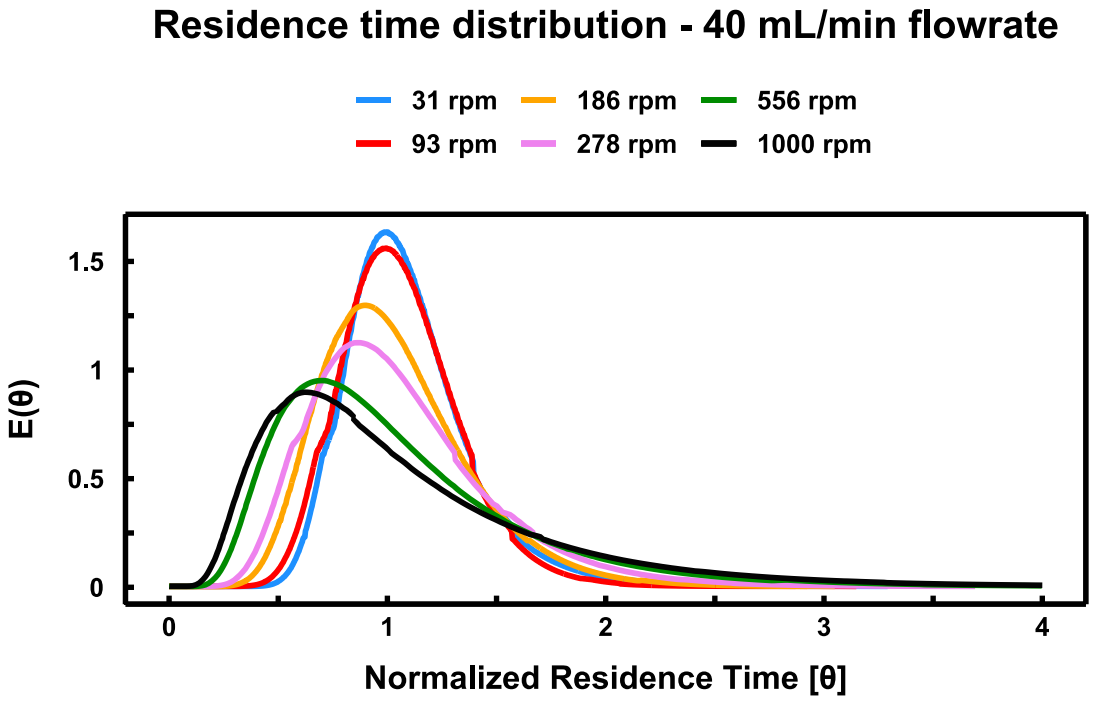
5. Appendix

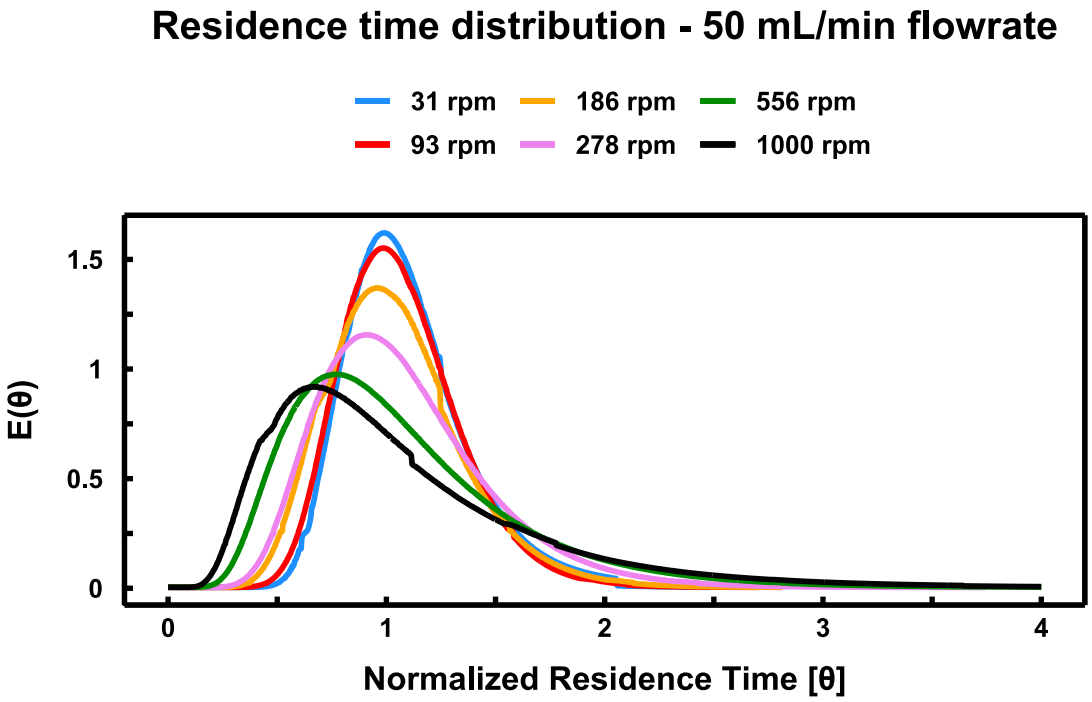
Residence time distribution curves:

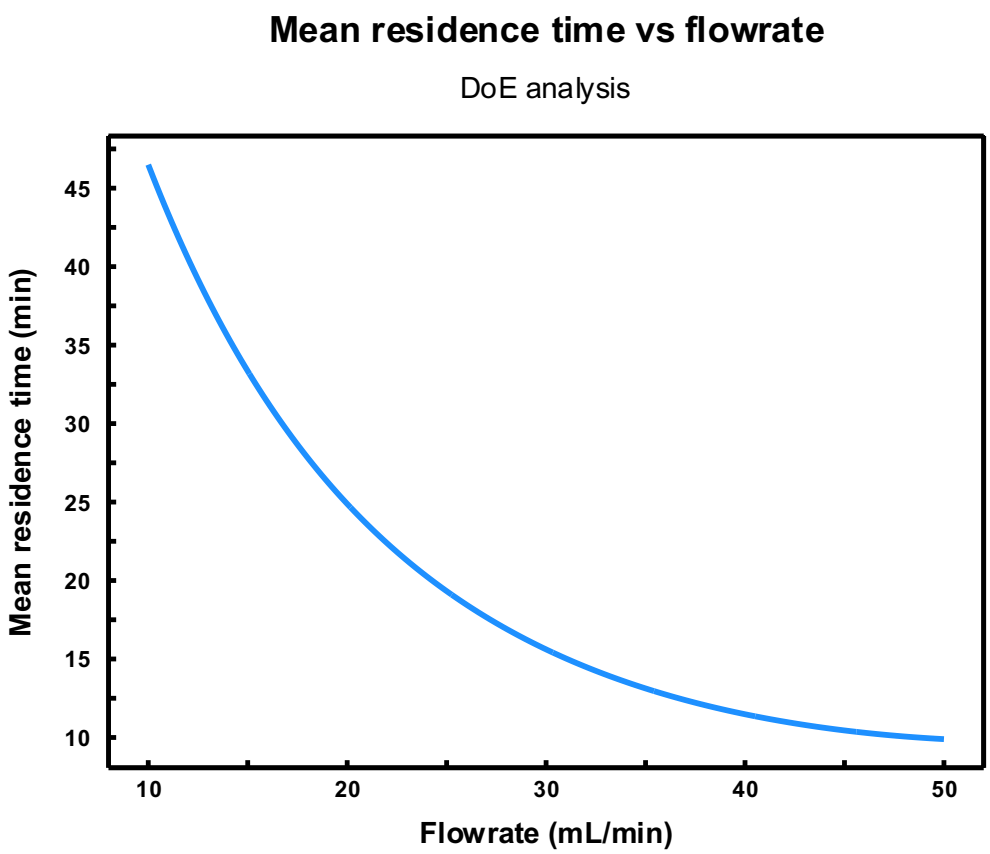





Residence time distribution - 30 mL/min flowrate
31 rpm
186 rpm
556 rpm
93 rpm
278 rpm
1000 rpm
E(θ)
1.5
1
0.5
0
0
1
2
3
4
Normalized Residence Time [θ]


Residence time distribution - 40 mL/min flowrate
31 rpm
186 rpm
556 rpm
93 rpm
278 rpm
1000 rpm
E(θ)
1.5
1
0.5
0
0
1
2
3
4
Normalized Residence Time [θ]


Residence time distribution - 50 mL/min flowrate
31 rpm
186 rpm
556 rpm
93 rpm
278 rpm
1000 rpm
E(θ)
1.5
1
0.5
0
0
1
2
3
4
Normalized Residence Time [θ]


Mean residence time vs flowrate
DoE analysis
Mean residence time (min)
45
40
35
30
25
20
15
10
10
20
30
40
50
Flowrate (mL/min)

6. References

[1] O. Levenspiel, 'Chemical Reaction Engineering, 3rd Ed.', Wiley VCH, **1998**.

[2] M. Moser, A. G. Georg, F. L. Steinemann, D. P. Rütti, D. M. Meier, *J. Flow Chem.* **2021**, *11*, 691, DOI: 10.1007/s41981-021-00204-y.