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The mesoscale oscillatory baffled reactor facilitates intensified kinetics screening when the solvent is removed

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Abstract: There are numerous potential benefits of conducting chemical reactions in the absence of solvent. For instance, the risk of environmental release of the solvent is eliminated and there is the potential for intensification via increased reaction rates reducing the required reactor volume. It was previously shown that two configurations of the mesoscale oscillatory baffled reactor (heat pipe and jacketed) could address the challenge of performing exothermic reactions without a solvent, by removing or spreading out the heat released. This could lead to a new approach in green chemistry. Here, this concept was extended to reaction kinetics screening from the same exothermic imination reaction conducted without a solvent. The effects of up to three operating variables (residence time, reactant molar ratio and temperature) were screened in a single flow experiment. It was found that both reactor configurations were able to obtain the Arrhenius kinetic parameters: activation energies of 103.98 ± 3.79 kJ/mol and 98.11 ± 1.55 kJ/mol, respectively, for the two imine synthesis steps. This demonstrated that meaningful data could be obtained, even though the solventless reaction medium was changing as a function of the reaction. Other benefits of this green chemistry approach include: high reaction rates/throughputs, reduced preparation time and reduced downstream purification requirements.

Keywords: Heat pipe reactor, green chemistry, solvent-free, kinetics screening, intensification

1 Introduction

Solvents are substances/mixtures that can dissolve single or multiple solutes to produce homogeneous solutions (Reichardt, 2004). Two of the primary functions of solvents are to reduce mass transfer limitations by providing a homogeneous reaction medium, and act as heat sinks for exothermic reactions or heat distribution mediums for endothermic processes. Other uses include reaction rate/mechanism modification, product recovery (e.g. recrystallization) and spectroscopic detection/analysis (e.g. increasing the volume of micro-samples).

However, excessive solvent use can have environmental and economic consequences. For instance, the E factors (defined as kg waste/kg product) for processes involving solvents range from 1–5 for bulk chemicals (10^4 – 10^6 tons of product) to as high as 25–100 for pharmaceuticals (10 – 10^3 tons of product) (Sheldon, 2005). Additionally, solvents must be removed from the final product, usually by evaporative methods such as distillation. As well as creating additional downstream cost/complexity, the recovery of the solvent is typically only in the range of 50–80% (Sheldon, 2005). Therefore, there are increasing drivers for the adoption of ‘green solvents’ to improve sustainability by reducing waste and minimising release to the environment. The four conventional green solvent approaches are: (i) substitution (replacing hazardous/toxic compounds), (ii) bio-solvents derived from renewable sources, (iii) supercritical fluids (typically supercritical water or carbon dioxide), and (iv) ionic liquids with very low vapour pressures (Capello *et al*, 2007). However, the ideal “solvent” would be no solvent at all. Drivers for a no-solvent approach are presented in the following list. Clearly, these potential benefits are additive: intensification is achieved simultaneously through reduced equipment size, eliminated unit operations and reduced energy consumption.

- Elimination of the risk of release of environmentally active solvents
- Removal/minimisation of the requirement for downstream purification
- Intensification of the reactor volume by reducing the total reaction media volume
- Potential reaction rate enhancement through the removal of dilution effects and operation at elevated temperatures (for exothermic processes), further minimising the required reactor volume

- Reduction of the heating/cooling duties because of the smaller thermal mass of reaction media (i.e. reduced handling costs/complexity)

However, there are limitations to the adoption of a no solvent (and no catalyst) approach. Gawande *et al* (2014) reviewed the subject in detail, identifying the potential problems that may be introduced in obtaining the desired product. These include reduced yield, longer reaction times, increased energy demand to initiate reactions (e.g. high temperatures and pressures), side product formation and selectivity issues, miscibility and mixing problems, and excessive use of reagents. The alternative pathways that Gawande *et al* (2014) identified for overcoming these issues were microwaves, ultrasonics, mechanochemical mixing (such as high-speed ball milling) and ‘conventional and room temperature’ heating (i.e. heat transfer to the reaction medium via an electric heater or from a liquid-filled jacket).

Understanding of reaction kinetics is also vital to design for industrial scale synthesis, particularly when using this solventless approach. From a chemistry perspective, it must be ascertained whether the standard kinetics models are still meaningful when the properties of the reaction medium are varying (due to the bulk change in composition during the reaction). Furthermore, from an engineering perspective, there is the requirement to safely mitigate the resulting energy released from exothermic reactions, whilst maintaining uniform mixing and good plug flow.

In a previous study (McDonough *et al*, 2016), a new heat pipe oscillatory baffled reactor (HPOBR) and more conventional jacketed oscillatory baffled reactor (JOBR) were successfully used to thermally control an exothermic imination reaction conducted without the use of a solvent. The HPOBR demonstrated a 20-fold reduction in processing volume (due to solvent removal) and additional 13-fold improvement in reaction rate (because of the reduced dilution effect and higher operating temperature) compared with the conventional in-solvent method, leading potentially to 260-fold reduction in the required reactor volume, or 260-fold increase of throughput for the same reactor volume (in this case

6.9 mL). The present target application of the heat pipe and jacketed meso-reactors is exothermic processes involving at least one liquid phase.

The first aim of this investigation was to determine whether meaningful kinetic data can be observed when there is no clearly defined reaction medium. Then, the secondary aim is to demonstrate the HPOBR and JOBR as platforms for quick and logical kinetic data gathering in continuous flow mode when no solvent is present. The purpose is to intensify process screening, by reducing development times and solvent usage, and establish solventless reaction operation as an approach that could be applied at all manufacturing stages of a new chemical product (from preliminary screening through to industrial scale/bespoke production). The HPOBR and JOBR both produce high levels of plug flow, which is crucial for minimising the transition times between different steady state operating conditions, thereby accelerating the screening process. This approach has previously been used in the meso-OBR to improve development times of continuous screening compared to batch screening (Mohd Rasdi, 2014). The mixing and heat transfer rates can also be controlled using the oscillation intensity. There is also an argument that the OBR is “more ubiquitous” than the similar microreactor approach (McDonough, 2018), making the HPOBR and JOBR easily adaptable to a wide range of single and multi-phase applications. The same imination reaction as the previous study (McDonough *et al*, 2016) has again been used as a case study here.

2 Methodology

2.1 Imination Reaction

The case study used for solventless reaction screening was the imination reaction between benzaldehyde and n-butylamine to form n-benzylidene-n-butylamine and water (shown in scheme 1). This reaction exhibits a strong exothermic temperature rise, which is sufficient to exceed the boiling point of the n-butylamine (79 °C) when no solvent or thermal control is used. For reference, the estimated reaction enthalpy is -20 kJ/mol based on average bond enthalpies (Atkins and De Paulu, 2010). The isolated imine product from this reaction consists of a pale yellow oil (Parekh, 2011). The imine functional group (C=N) produces an FTIR peak around 1644 cm⁻¹, whilst the following ¹H-NMR peaks are

reported in D-chloroform solvent: δ 8.30 (1H, s), δ 7.75 (2H, m), δ 7.43 (3H, m), δ 3.64 (2H, t), δ 1.74 (2H, m), δ 1.41 (2H, s), δ 0.98 (3H, t) (Parekh, 2011). In the present study, the benzaldehyde (99% purity) and n-butylamine (99.5% purity) reagents were used as supplied from Sigma-Aldrich. No catalyst was used because the butylamine is a strong nucleophile that can readily attack the carbonyl group (Mohd Rasdi, 2014).

Scheme 1 – Imination reaction between benzaldehyde and n-butylamine

2.2 Reactor Configurations (HPOBR and JOBR)

The two meso-OBs (heat pipe and jacketed configurations) used for the screening experiments in the present study were the same as described previously, as shown in figure 1 (McDonough *et al*, 2016). In summary, the HPOBR used a 370 mm length stainless steel tube with 4.93 mm i.d. and 6.35 mm o.d. as the reactor. Surrounding this tube was a 350 mm length annular heat pipe operating as a two-phase closed thermosyphon, leaving the first 20 mm of the reactor tube uninsulated. This annular section was constructed from a 22.2 mm o.d. stainless steel tube with ~0.9 mm wall thickness, giving an annular thickness of 7.1 mm between the meso-OB tube and outer heat pipe wall. The JOBR similarly consisted of a 370 mm length, 5 mm i.d. and 8 mm o.d. glass tube surrounded by a 20 mm diameter and 350 mm length glass jacket. Deionised water was used as the jacket working fluid. The temperature was regulated with a 7 L refrigerated/heated bath (VWR, MX7LR-20, low profile). Both reactors included enlarged diameters (20 mm) at the outlet, which were originally designed for the incorporation of a 16 mm FTIR probe. However, the experiments in this study were conducted with a 6 mm diameter FTIR probe. It was nevertheless confirmed via salt tracer pulse experiments that this arrangement did not influence the plug flow behaviour. Both reactors had 20 mm unjacketed sections at the inlet to accommodate a custom union fitting for supplying reagents.

Figure 1 – Schematics of the HPOBR (a) and JOBR (b) | positions of the thermocouples are defined as distances from the outlet of the meso-OBR tube (McDonough et al, 2016)

2.2.1 Helical Baffles and Axial Temperature Measurement Arrangement

Helical baffles (1 mm diameter, 7.5 mm pitch) were used for the screening experiments because they produce plug flow over a wider range of oscillation intensities than other baffle designs (Phan and Harvey, 2012). Additionally, helical baffles enabled the incorporation of four thermocouples into the

reactor to measure the axial temperature profile. Measurement of the axial temperature profile simplified the kinetic modelling by removing the requirement to model heat transfer between the reaction media and working fluids of the heat pipe and jacket (explained in more detail in the results section).

Improved mixing performance using helical baffles with a central rod has previously been observed in the literature for biodiesel production (Phan *et al*, 2011). The enhancement was attributed to a suppression of flow channelling at the centre of the tube, reducing the appearance of globular and slug regimes between immiscible dual liquid phases. Further understanding of the enhancement of mixing using helical baffles with a central rod was gained through simulations validated by particle image velocimetry (McDonough, 2018). A Taylor-Couette type regime involving the appearance of dual counter-rotating vortices was observed at high oscillation intensities, where the rod further reduced convective dispersion compared to helical baffles alone. It was concluded that measurement probes, such as thermocouples, would not be detrimental to the plug flow/mixing behaviour. This was further validated using standard tracer impulse experiments and the tanks-in-series model. It was found that $N \geq 40$ was attainable for conditions corresponding to: $Re_n = 1.5-20$, $x_o = 4$ mm and $f = 2-10$ Hz (McDonough, 2018). In comparison, conventional helical baffles produce plug flow in the range of $20 < N < 40$ for similar oscillation conditions for $2.55 < Re_n < 7.2$ (Phan and Harvey, 2012).

2.3 Liquid Handling Strategy

Syringe pumps (C3000 series, TriContinent) provided both the reagent net flow rates and fluid oscillation to the meso-OBRs. The time taken for the plunger to complete one full stroke could be varied between 1.2 s and 20 min, with the spatial resolution equal to 3000 micro-steps of the plunger over a total 30 mm travel length. The net flows were supplied via 5 mL syringes while fluid oscillation was implemented with a 12.5 mL syringe. The oscillation amplitude was controlled by varying the volume dispensed by the syringe, and the frequency was controlled by adjusting the speed and acceleration settings of the lead screw. The syringe pumps were operated using text input commands using Sapphire commander software.

2.5 Solventless Reactions

2.5.1 Batch Reaction with No Thermal Control

Several batch experiments were conducted without the use of thermal control in order to assess the impact of the exotherm on the reaction. These reactions were conducted in an uninsulated round-bottom glass flask with mixing provided by a magnetic stirrer set at 500 rpm. First, 15 mL of neat benzaldehyde was added to the flask so that the tip of the FTIR probe was fully submerged. A type-K thermocouple was also placed in the liquid to measure the temperature. This data was logged via a TC-08 data logger using PicoLog software with a 1 s sampling time. Once mixing was initiated, the IR spectra began recording at a time interval of 15 s. After approximately 1 min, 15 mL of neat n-butylamine was rapidly added in order to initiate the reaction. The effect of the exotherm at 1:1 volumetric ratio was immediately apparent, with the n-butylamine partially vaporising because of the rapid temperature spike exceeding its boiling point (79 °C). Reactions were run at benzaldehyde to n-butylamine volumetric ratios of 4:1, 2:1, 1:1, 1:2 and 1:4 at a fixed volume of 30 mL.

2.5.2 Multi-Steady State and Multivariate Continuous Screening

Multi-steady state reactor operation involves maintaining a particular set of operating conditions whilst measuring the output response. Then, once a sufficiently steady-state plateau is produced, the operating conditions are changed and measurements repeated. This allows the effects of many different parameters, such as residence time, reactant molar ratio, temperature, etc., to be quickly observed in order to construct a robust model or response surface of the reaction. The goal of the screening experiments in this study was to combine the multi steady-state screening protocol previously reported for the meso-OBR (Eze *et al*, 2017; Mohd Rasdi, 2014; Phan *et al*, 2011) with design of experiments methodologies to minimise the required number of conditions.

The conditions studied in both the JOBR and HPOBR were benzaldehyde to n-butylamine volumetric ratio of 4:1–1:3 and residence times (τ) of 85–480 s. In the JOBR, the jacket temperatures were also varied in the range of 5–65°C. The molar ratio was adjusted at fixed residence time by varying the ratios of the flow rates of benzaldehyde and n-butylamine whilst keeping the total flow rate constant. The

residence time was adjusted by varying the total flow rate at fixed ratio of benzaldehyde to n-butylamine volumetric flow rate ratio. Multivariate screening was investigated for the solventless reaction screening experiments through the application of central composite experiment designs. These are discussed in more detail in Section 2.6. Prior to the experiments in the HPOBR, the desired methanol volume was placed in the annular shell using the same filling procedure as described in the previous study (McDonough *et al.*, 2016).

In a typical experiment, the thermocouple-baffle assembly was fitted inside the reactor, and the reactor positioned with the FTIR probe situated at the outlet. The thermocouples were connected to a TC-08 data logger with the temperatures recorded in PicoLog software. If the JOBR was used, the initial jacket temperature was set at this point. Then, the tubing/syringe pumps were primed with the neat benzaldehyde and n-butylamine before fitting the custom union to the reactor inlet. The neat benzaldehyde was also used as the oscillation pump reservoir to remove the appearance of trace impurities of solvent molecules via diffusion at the oscillation-inlet interface. To initiate an experiment, the reactor was first filled with just the neat benzaldehyde so that the FTIR tip was fully submerged. Then simultaneously, the FTIR spectra acquisition (15 s sampling time), thermocouple data logging (1 s sampling time) and fluid oscillation were initiated. After approximately 1 min, the syringe pump commands for the neat benzaldehyde and n-butylamine flow rates were activated and the multi-steady state and multivariate screening experiment conducted. Steady-state conditions were held for between 10 and 25 min.

2.6 Experiment Configurations and Overall Screening Procedure

Eight different sets of multi-steady state screening protocols were implemented in the present study. Four initial one-dimensional experiment sets investigated the effects of jacket temperature (5–65°C), molar ratio of benzaldehyde to n-butylamine (4:1–1:3) and residence time (30–480 s). In the second phase, two-dimensional screening experiments were performed, which investigated the effects of different reactant molar ratio (3:1–1:3) and residence time (85–480 s) combinations defined by central composite experiment designs. The final screening experiment was three-dimensional, and investigated

the combined effects of reactant molar ratio (3:1–1:3), residence time (200–400 s) and jacket temperature (5–20°C), with the combinations of conditions defined via a D-optimal reduction of a central composite design.

Design of Experiments (DoE) involves performing controlled experiments with systematic changes made to the operating conditions in order to identify the underlying relationships that exist between different inputs to a process. The central composite design consists of a 2-level factorial design combined with an axial star design. Here, $2^k + 2k + r$ experiments are performed ('r' being the number of centre point replicates and 'k' being the number of variables) producing a model containing the main effects, second-order effects and interactions, accounting for the tilting, curvature and "twistature" of the response surface model respectively.

Further to the central composite design, optimal experiment configurations were also considered for the solventless reactions. Optimality reduces the number of required experiments further than composite designs by employing non-orthogonal design matrices. The D-optimality criterion was used in this work. Experiment conditions in D-optimal designs are defined by maximising the determinant of the information matrix $X'X$, where X is defined by all possible available combinations of variables, the desired number of experiment points and the structure of the model. In D-optimal designs, the experiment combinations are selected to generate maximum alignment with the model structure. This makes D-optimal designs model-dependent, requiring at least some level of prior knowledge about the process in order to select the optimal experiment points.

2.7 On Line Reaction Monitoring via in situ FTIR

2.7.1 FTIR Hardware

The main tool for characterising the reactions was Fourier Transform Infrared (FTIR) spectroscopy. The spectrometer used was a Mettler Toledo ReactIR 4000 fitted with a mercury cadmium telluride band detector cooled by liquid nitrogen, and purged with dry compressed air to prevent the accumulation of water vapour in the laser path. A K6 conduit consisting of a heavy-duty 1 m length

rigid knuckled arm with 6.35 mm DiComp (diamond) probe was used for the screening experiments. This configuration allowed measurements in the regions of 4000–2200/1950–650 cm^{-1} , at a resolution of 8 cm^{-1} in the absorbance mode; spectra were referenced against an air background. The region from 2200–1950 cm^{-1} was obscured by the absorption of diamond contained in the probe. The signal-to-noise ratio was kept above the recommended minimum level of 3500. Additionally, to minimise drift bias, calibration spectra were regularly collected using the procedure outlined in 2.8. The ReactIR 4000 was controlled using iC-IR 4.2.26 software, which enabled the exporting of full time series spectra into Excel for subsequent data processing in Matlab.

2.7.2 FTIR Calibration

The benzaldehyde and n-benzylidene-n-butylamine concentrations measured by *in situ* FTIR spectroscopy were calibrated prior to each multi-steady state experiment to minimise the impact of long-range drift effects (e.g. due to IR source ageing). Calibration involved preparing small samples (typically 1–2 mL) of various mixtures of the benzaldehyde or imine product in different volumetric ratios ranging from neat benzaldehyde to neat imine. These mixtures provided the best approximation of the behaviours of the carbonyl and imine peaks in the spectral range of 1750–1635 cm^{-1} . Calibration in this range was achieved using partial least squares (PLS) regression, a tutorial for which is described by Geladi and Kowalski (1986).

The benzaldehyde was calibrated with samples taken from the bulk stock purchased from Sigma Aldrich. To calibrate the imine, it was first synthesised in the HPOBR by reacting benzaldehyde and n-butylamine in a 1:1 volumetric ratio without solvent. Approximately 200 mL of reaction product was collected and purified for 6 hours by rotary evaporation (Büchi Rotavapor R-200) at 85°C and 20 mbar. This purification process yielded ~100 mL of a dark yellow liquid, whose purity was calculated via ^1H -NMR by comparing the area of the peak at 0.96 ppm ($-\text{CH}_3$, imine) with a small amount of impurity observed at 0.875 ppm ($-\text{CH}_3$, n-butylamine), to give 98.4%. The n-butylamine was not involved in the calibration because the NH_2 peak was weak and could not be observed *in situ* when other compounds were present. It also reacted on contact with the benzaldehyde at room temperature.

Additional pre- and post-processing steps are described in the following points:

- *Pre-processing step 1.* The FTIR spectra in the wavelength range of 1750–1500 cm⁻¹ were deconvoluted using the Gaussian function in equation 1. Here y defines a peak positioned at wavenumber, c , as a function of the wavenumber, ω_n , with peak height and width equal to h and w respectively. The peaks observed in the range of 1750–1500 cm⁻¹ were benzaldehyde (C=O, 1713 cm⁻¹), imine product (C=N, 1652 cm⁻¹), water (H-O-H, 1640 cm⁻¹), aromatic (C=C, 1598 cm⁻¹), aromatic (C=C, 1550 cm⁻¹) and water (1459 cm⁻¹). For each of the spectra recorded in a single experiment, h and w were determined for each of the peaks described above using linear regression so that the combination of these modelled peaks matched the measured spectra

$$y = \frac{h}{w\sqrt{\pi/2}} \exp \left[-2 \frac{(\omega_n - c)^2}{w} \right] \quad 1$$

- *Pre-processing step 2.* Second derivatives of the recorded spectra were calculated in order to improve the resolution of the peaks, at the cost of reduced signal-to-noise ratio, and remove baseline offsets and linear gradients induced by the appearance of water as a reaction product (Verdine and Nakanishi, 1985; Kohler *et al*, 2007). Additionally, some studies have found that the second derivative reduces the prediction error of the calibration (Bekhit *et al*, 2014), though Igne *et al* (2010) suggest its usefulness is dependent on the individual FTIR equipment. The second derivatives in this study were calculated using a 7-point normalised moving average (equation 2) proposed by Savitsky and Golay (1964).

$$\frac{d^2 A(\omega_n)}{d\omega_n^2} \approx \frac{5A_{i+3} - 3A_{i+1} - 4A_i - 3A_{i-1} + 5A_{i-3}}{42\Delta\omega_n^2} \quad 2$$

- *Post-processing.* A secondary calibration was also performed to correct the carbonyl and imine peaks subjected to attenuation by the water reaction product. Here, various amounts of water were added to small known concentrations of either benzaldehyde or the imine product and mixed vigorously using a vortex generator. Then, spectra of these samples were recorded and the peak

heights of the carbonyl and imine functional groups compared with the baseline sample (no water). The ‘true’ peak heights of the aldehyde and imine peaks were calculated by first assessing the amount of water in the recorded *in situ* spectra using the OH stretch (3600–3000 cm⁻¹) or H-O-H bend (1640 cm⁻¹). By comparing these regions with the secondary calibration data, scaling factors could be formed. These were applied to the deconvoluted peaks to increase their sizes if more water was present for a particular measurement.

3 Results and Discussions

3.1 Batch Solventless Screening

3.1.1 General Observations

Initial batch experiments were conducted for the solventless reactions to establish baseline behaviour for the continuous experiments. Figure 2 shows the benzaldehyde and imine profiles and corresponding operating temperatures measured during the synthesis of the imine in an unjacketed batch reactor at different molar ratios of the aldehyde to amine. The total reactant volume was held constant at 30 mL for each molar ratio investigated.

*Figure 2 – Solventless imine synthesis conducted in non-jacketed batch reactor (30 mL) at different molar ratios of benzaldehyde to *n*-butylamine / column 1 = 1:1 molar ratio; column 2 = excess aldehyde; column 3 = excess amine / row 1 = experimental and model benzaldehyde reactant profiles; row 2 = experimental and model imine product profiles; row 3 = experimental temperature profiles (1 s sampling rate)*

In figure 2 it can be seen that the solventless reactions were very fast, with 100% conversion reached within 100–500 s depending on the molar ratio. It was not possible to accurately determine the initial rates because of the limited sampling rate of the ReactIR 4000 system. Each molar ratio investigated produced the standard exotherm behaviour, where the majority of the energy release occurred after initial contact and mixing. This resulted in rapid temperature rises followed by a prolonged cooling

period. Based on the concentration and temperature profiles, it can be seen that the reaction rate was highest when using the 1:1 molar ratio of reactants, followed by the 2:1/1:2 then 4:1/1:4 molar ratios. This is because, as one of the reactants was used in excess, the unreacted material diluted the reaction media and acted as a heat sink for the reaction exotherm.

3.1.2 Kinetics Fitting

It was difficult to fit a kinetic model directly to the concentration data measured during these experiments because of the differing molar densities of each of the reactants and products. Here, unlike when high solvent excess was used, the bulk composition (and properties) of the solventless reaction medium changed, meaning there was no consistently defined reaction medium. Table 1 demonstrates the consequence of this effect by displaying the final concentrations of the aldehyde, amine and imine when the aldehyde and amine are reacted at different volumetric ratios assuming 100% conversion. For a 1:1 addition of benzaldehyde with the amine, 26.5 mL of the imine is produced compared with only 2.6 mL of water. Consequently, the kinetic fitting was performed in terms of moles of material instead of the concentration.

Table 1 – Final concentrations predicted by mole balance assuming 100% conversion

Aldehyde:Amine Ratio	Aldehyde Concentration (mol/L)	Amine Concentration (mol/L)	Imine Concentration (mol/L)
4:1	6.00	0	2.10
2:1	3.34	0	3.61
1:1	0	0.20	5.39
1:2	0	3.73	3.47
1:4	0	6.37	2.02

The imination reaction is described using the simple scheme shown in equation 3. Here, A, B, C, D and E refer to the aldehyde, amine, hemiaminal intermediate, imine product and water product, respectively. Additionally, k_1 and k_2 refer to the forward rate constants and k_{-1} and k_{-2} refer to the reverse reaction rate constants.

The combined mass balance and reaction kinetics equations based on this reaction scheme, written in terms of the number of moles of each component (N_i), are shown in equations 4–6. The model includes the formation of the intermediate from the aldehyde and amine reactants, and the subsequent dehydration of the intermediate to produce the imine product and water side-product. The forward reaction rate constants for both reaction steps (k_1 and k_2) were defined using the Arrhenius equation (equation 7) while the reverse rate constants were defined using the forward rate constants and equilibrium constant (K_i). The terms m , n , o , p and q refer to the reaction orders for species A, B, C, D and E, respectively.

$$\frac{1}{V} \frac{dN_A}{dt} = \frac{1}{V} \frac{dN_B}{dt} = -k_{f1} \left(\frac{N_A}{V} \right)^m \left(\frac{N_B}{V} \right)^n + \frac{k_{f1}}{K_1} \left(\frac{N_C}{V} \right)^o \quad 4$$

$$\frac{1}{V} \frac{dN_C}{dt} = k_{f1} \left(\frac{N_A}{V} \right)^m \left(\frac{N_B}{V} \right)^n - \frac{k_{f1}}{K_1} \left(\frac{N_C}{V} \right)^o - k_{f2} \left(\frac{N_C}{V} \right)^o + \frac{k_{f2}}{K_2} \left(\frac{N_D}{V} \right)^p \left(\frac{N_E}{V} \right)^q \quad 5$$

$$\frac{1}{V} \frac{dN_D}{dt} = \frac{1}{V} \frac{dN_E}{dt} = k_{f2} \left(\frac{N_C}{V} \right)^o - \frac{k_{f2}}{K_2} \left(\frac{N_D}{V} \right)^p \left(\frac{N_E}{V} \right)^q \quad 6$$

$$k_{fi} = A'_i \exp \left[\frac{-E_{ai}}{RT} \right] \quad 7$$

To fit the model to the experimental data, the measured concentrations were converted to moles using the volume of the organic phase. Additionally, to avoid the inclusion of a thermal energy balance, the measured reaction temperatures (shown in figure 2) were inserted in the kinetics model in the Arrhenius terms by interpolating their values for each step of the numerical integration. Due to the large magnitudes of the pre-exponential factors, it was not possible to fine-tune these values using Matlab's in-built solver (Levenberg-Marquardt algorithm). Instead, the pre-exponential factors were defined by trialling different combinations between 10^{18} and 10^{19} for both steps of the imination reaction. These magnitudes produced the best fit with the initial activation energies selected for regression, which were specified according to the literature (Xu *et al*, 2013).

Table 2 summarises the kinetic parameters determined from the solventless batch experiments using equations 4–7, while figure 2 compares the resulting model with the experimental data (plotted using the averaged data). The experimental data at a molar ratio of 4:1 (excess aldehyde) was excluded from the fitting process in order to validate the screened parameters.

Table 2 – Summary of kinetics parameters obtained from the solventless batch screening experiments

Kinetics Parameter	1:1	1:2	1:4	2:1	Average
m (aldehyde order)	0.988	0.970	1.001	1.023	0.998 ± 0.027
n (amine order)	0.990	0.974	1.002	1.029	0.999 ± 0.023
o (intermediate order)	2.009	1.900	1.999	2.044	1.988 ± 0.062
p (imine order)	0.994	1.022	0.998	0.989	1.001 ± 0.015
q (water order)	0.994	1.022	0.997	0.988	1.000 ± 0.015
A_1' (L/mol.s)	2×10^{18}	2×10^{18}	2×10^{18}	2×10^{18}	2×10^{18}
$E_{a,1}$ (J/mol.K)	120.00	119.91	119.00	121.03	119.99 ± 0.83
K_1	158	158	150	147	153.3 ± 5.6
A_2' (L/mol.s)	9×10^{18}	9×10^{18}	9×10^{18}	9×10^{18}	9×10^{18}
$E_{a,2}$ (J/mol.K)	100.00	99.99	99.00	99.5	99.62 ± 0.48
K_2	3000	3002	2987	3027	3004.0 ± 16.7

It can be confirmed in figure 2 that there is reasonable agreement between the model and experiment data at the training (1:1, 1:2, 1:4 and 2:1 molar ratios) and validation (4:1 molar ratio) conditions. For reference, the four training conditions had R^2 values for the imine of 0.85, 0.67, 0.97 and 0.87 respectively whilst the validation set had an R^2 of 0.45 for the imine.

Based on the magnitudes of the equilibrium constants, it can be seen that both steps of the overall reaction are essentially irreversible. The higher irreversibility of the second reaction was a consequence of the immiscibility between the water product and organic reaction phase. The phase separation of water produced an equivalent extractive-reaction that moved the equilibrium towards the products. All reactions were also second order overall. Based on these results, the reaction orders can be removed from the model fitting process for the multi-steady state data to improve the number of degrees of freedom for regression. The activation energies of the first and second reactions were found to be 119.99 ± 0.83 kJ/mol and 99.62 ± 0.48 kJ/mol respectively. These are lower than the predicted activation energies reported in the literature for the similar reaction between benzaldehyde and iso-butylamine in

a solvent: 154.4 kJ/mol and 116.7 kJ/mol (Xu *et al*, 2013). The lower energy barriers obtained in this work could be a result of reduced steric hindrance of n-butylamine compared with t-butylamine and improved stabilisation of the hemiaminal intermediate/transition species (e.g. through the higher polarity of the solventless reaction media). Nevertheless, it can be concluded from these batch experiments that meaningful reaction kinetics parameters can be determined from the solventless experiments.

3.2 Continuous Solventless Screening

3.2.1 One-Dimensional Multi-Steady State Screening

The effects of jacket temperature, reactant molar ratio and residence time on the solventless imination reaction were initially studied in flow using one-dimensional screening experiments using either the JOBR or HPOBR configurations. Figure 3 shows the resulting concentration profiles of the aldehyde reactant and imine product and corresponding operating temperatures produced. The results of all three experiments demonstrate that clear step changes were observable between different steady state operating conditions. The induction times were all achieved within 1–1.5 residence times, similar to previous studies (Eze *et al*, 2017), indicating a high degree of plug flow and therefore precise control of the residence time. This could, for instance, enable a third reagent to be added at a targeted stage of a reaction. Note that the sawtooth behaviour of the concentrations was a consequence of slow priming of the syringe pumps to avoid cavitation; observation of this effect further confirms the good plug flow behaviour.

In figure 3a, the jacket temperature of the JOBR was adjusted manually from 5°C to 65°C in increments of 10°C whilst keeping the flow rate and molar ratios fixed. Improved isothermal behaviour was observed at higher jacket temperatures, and near 100% aldehyde conversion was produced for temperatures greater than 45°C.

In figure 3b, the molar ratio of aldehyde to amine was adjusted from 4:1 to 1:3, then from 1:3 to 2:1 with a fixed residence time of 120 s and jacket temperature of 20°C in the JOBR. The consistency of

the aldehyde and imine concentrations for decreasing and increasing aldehyde ratios shows there are no hysteresis effects. The highest imine concentration occurred at a 1:1 reactant ratio (as described in table 1), producing a corresponding yield of $95.1 \pm 0.04\%$. An excess of either the aldehyde or amine diluted the imine, producing a smaller concentration and lower operating temperature. Dilution in excess amine was found to be more prominent than excess aldehyde, possibly due to water's miscibility with the amine; a single phase was observed when using excess amine, whilst a biphasic mixture was observed for excess aldehyde.

In figure 3c, the residence time was linearly ramped up from 30–480 s in 8 consecutive steps in the HPOBR. The aldehyde reached approximately 100% conversion for residence times over 60 s, whereas the imine concentration continually increased as residence time was increased. This suggests there was an accumulation of the intermediate at low residence times. Hemiaminal intermediates are usually thermodynamically unstable (Iwasawa *et al*, 2007), but they have been observed when using similar neat ammonia solutions (Chudek *et al*, 1985). Lower standard deviation of the imine yield was also observed at higher residence times. This correlates with improved isothermal behaviour. For example, the yield increased from $75 \pm 1.81\%$ at 30 s residence time with an axial temperature spread of $\sim 30^\circ\text{C}$ to $99.5 \pm 0.39\%$ at 480 s residence time with a temperature spread of $\sim 5^\circ\text{C}$.

In the HPOBR, there was also a strong competing temperature effect produced when changing the residence time because there was no active thermal control (compared to the JOBR). It was not possible in the present configuration to adjust the working fluid volume during the experiments to optimise the heat spreading effect to achieve isothermal behaviour at different operating conditions. Additional energy input to the HPOBR to force isothermal behaviour was briefly considered, however it was difficult to overcome the complex coupling dynamics between the reaction, heat pipe and PID temperature controller. One solution might be to use a variable conductance heat pipe (VCHP) that actively controls the heat removal rate by adjusting the amount of non-condensable gas in the vapour space to control the condenser length.

Figure 3 – One-dimensional screening of the solventless imination reaction conducted in the JOBR and HPOBR / (a) effect of jacket temperature in the JOBR with $\tau = 145$ s and $Re_o = 307$ ($x_o = 2$ mm, $f = 5$ Hz) / (b) effect of molar ratio of benzaldehyde to n-butylamine in the JOBR with $\tau = 120$ s, $Re_o = 307$ ($x_o = 2$ mm, $f = 5$ Hz) and jacket temperature = 20°C / (c) effect of residence time in the HPOBR with $x_o = 2$ mm and continuously reducing oscillation frequency ($f = 7$ –4 Hz) and Fill Ratio = 19 / row 1 = concentration profiles, row 2 = temperature profiles (legend refers to the temperatures at four points along the inner meso-OBP tube; see figure 1)

3.2.2 Two-Dimensional Multi-Steady State Screening

Based on the observations of the one-dimensional screening experiments, multi-dimensional screening of the solventless imination reaction was deemed achievable. The effects of residence time and reactant molar ratio on the solventless imination reaction were subsequently studied simultaneously in both the JOBR and HPOBR configurations. Here, 13 different operating conditions combinations, defined according to 2D central composite experiment designs, were tested in a single continuous flow experiment. The resulting concentration profiles and operating temperatures are shown in figure 4.

In both reactors it took 1–1.5 residence times to reach steady state. The only exception was the first HPOBR condition, which required ~40 minutes to attain thermal steady state. This is attributable to the low power input of the reaction at this residence time (~4 W based on an enthalpy of -19 kJ/mol). As with the one-dimensional screening experiments, no hysteresis effects were present; the centre point of the design was replicable five times in both reactors. There was also no obvious evidence for interaction effects between the reactant molar ratio and residence time. Here, higher residence times produced higher imine concentrations for both excess aldehyde and excess amine ratios. In the JOBR and HPOBR, the steady state plateaus were held for 20 min and 40 min respectively. It is clear these could be substantially shortened, offering a significant time saving than demonstrated in this study.

The HPOBR was more isothermal across the reactor length than the JOBR, but at a higher operating temperature. This is because the HPOBR functions predominantly as an energy spreader, while the JOBR instead removes heat at all points from the reactor at a rate proportional to the temperature difference between the reaction and jacket fluid (McDonough *et al*, 2016). The higher operating temperatures in the HPOBR resulted in higher aldehyde conversions. For example, at a 1:1 ratio of aldehyde to amine and residence time of 150 s, the HPOBR and JOBR produced aldehyde conversions of $93.5 \pm 0.42\%$ and $54.3 \pm 0.13\%$ respectively.

Figure 4 – Two-dimensional screening of the solventless imination reaction conducted in the JOBR and HPOBR | central composite experiment design exploring the effects of residence time ($\tau = 85$ –480 s) and molar ratio of benzaldehyde to *n*-butylamine ($MR = 3:1$ – $1:3$) at 13 different combinations with $Re_o = 307$ ($x_o = 2$ mm, $f = 5$ Hz) | (a) JOBR (jacket temperature = 20°C) and (b) HPOBR (Fill Ratio = 19) | row 1 = concentration profiles, row 2 = temperature profiles (legend refers to the temperatures at four points along the inner meso-OBR tube; see figure 1)

3.2.3 Three-Dimensional Multi-Steady State Screening

An advantage of the JOBR in this particular study was that thermal effects of the solventless reaction could be independently explored in flow by adjusting the jacket temperature. In the HPOBR, it was not possible to adjust the working fluid volume within a single experiment, meaning the operating temperatures were only defined according to the selection of residence time and feed ratio of the reactants. This feature of the JOBR was consequently exploited in a three-dimensional experiment design, which studied the effects of reactant molar ratio, jacket temperature and residence time in a single continuous flow experiment using the multi steady state approach. To improve the efficiency of

this screening experiment further, a D-optimal strategy was also implemented. Here, it was assumed all three variables were linearly correlated with the kinetics parameters and that the molar ratio and temperature had second order effects. These assumptions were based on the structure of the kinetics model used for the batch screening tests (described in section 3.1.2). Here, changing the residence time only affects the reaction conversion, whilst changing the molar ratio and temperature may introduce non-linear changes in the reaction rates. The resulting design space consisted of 8 experiment conditions defined by the axial star points of a face centred central composite design. The results of this experiment are summarised in figure 5.

As in the previous JOBR experiments, non-isothermal behaviour was produced, where the inlet temperature was consistently higher than the downstream and outlet temperatures. This occurred because the reaction exotherm was strongest near the reactor inlet and there was no heat spreading mechanism as in the HPOBR. At the highest jacket temperature (20°C), with an average reaction temperature of 25°C, the respective aldehyde conversion and imine yield were $93.7 \pm 0.05 \%$ and $73.8 \pm 0.45 \%$. In addition, at the largest residence time, the conversion and yield were $87.5 \pm 3.11 \%$ and $78.5 \pm 4.7 \%$ respectively. Two sets of conditions were also replicated to establish repeatability. It can be seen that both replicates of the 12.5°C/3:1/300 s (plateaus 2 and 6 in figure 5) and 12.5°C/1:1/200 s (plateaus 3 and 7 in figure 5) combinations produced the same concentrations, showing again that there are no hysteresis effects.

Figure 5 – Three-dimensional screening of the solventless imination reaction conducted in the JOBR / D-optimal central composite experiment design exploring the effects of residence time ($\tau = 200\text{--}400$ s), molar ratio of benzaldehyde to n-butylamine ($MR = 3:1\text{--}1:3$) and jacket temperature ($T_j = 5\text{--}20^\circ\text{C}$) at 8 different combinations with $Re_o = 307$ ($x_o = 2$ mm, $f = 5$ Hz) | (a) concentration profiles, (b) temperature profiles (legend refers to the temperatures at three points along the inner meso-OBRTube; see figure 1)

This D-optimal strategy further improves the efficiency of the screening experiments in addition to the multi-dimensional dynamic screening modes of previous studies (Mohd Rasdi, 2014; Eze *et al*, 2017). In the present study, the number of experiments of a central composite design was reduced from 20 to 8 on the assumption of the behaviour of the reaction kinetics model towards the three variables considered (residence time, molar ratio and temperature). This represents a 60% reduction in both reagent consumption as well as screening time. The advantage of the meso-OBRTube here compared to a batch system is these experiments can be conducted in a “one-shot” approach, whilst providing better heat transfer and control over the mixing.

3.2.4 Kinetics Fitting

For the continuous screening experiments, the unsteady state axial dispersion model was used to describe the molar flows of the reactants and products as a function of time and position (residence time) within the reactor. Here, the diffusion term was excluded to simplify the regression. This was

justified by the minimal induction times observed between different steady states in the multi-steady state screening experiments. The reaction itself was modelled using the same kinetic model structure implemented in the batch experiments, but with the reaction orders fixed at second order overall. To avoid the problems encountered by the different molar densities of the reaction components in these solventless experiments, the model was expressed in terms of the molar flow rates (F_i) by using the volumetric flow rate, ' v_T '. The resulting partial differential equations (equations 8–12) were solved using explicit finite differencing, an example of which is shown in equation 13. The subscript 'k' refers to the current residence time (i.e. position within the reactor) while the superscript 'j' refers to the time point.

$$\frac{\partial F_A}{\partial t} = -\frac{\partial F_A}{\partial \tau} - \frac{[k_{f1}F_A F_B - (k_{f1}/K_1)F_C^2]}{v_T} \quad 8$$

$$\frac{\partial F_B}{\partial t} = -\frac{\partial F_B}{\partial \tau} - \frac{[k_{f1}F_A F_B - (k_{f1}/K_1)F_C^2]}{v_T} \quad 9$$

$$\frac{\partial F_C}{\partial t} = -\frac{\partial F_C}{\partial \tau} + \frac{[k_{f1}F_A F_B - (k_{f1}/K_1)F_C^2 - k_{f2}F_C^2 + (k_{f2}/K_2)F_D F_E]}{v_T} \quad 10$$

$$\frac{\partial F_D}{\partial t} = -\frac{\partial F_D}{\partial \tau} + \frac{[k_{f2}F_C^2 - (k_{f2}/K_2)F_D F_E]}{v_T} \quad 11$$

$$\frac{\partial F_E}{\partial t} = -\frac{\partial F_E}{\partial \tau} + \frac{[k_{f2}F_C^2 - (k_{f2}/K_2)F_D F_E]}{v_T} \quad 12$$

$$F_{A_k}^{j+1} = F_{A_k}^j - \frac{\Delta t}{\Delta \tau} (F_{A_k}^j - F_{A_{k-1}}^j) - \frac{\Delta t}{v_{T_k}^j} [k_{f1_k}^j F_{A_k}^j F_{B_k}^j - (k_{f1_k}^j / K_{1_k}^j) (F_{C_k}^j)^2] \quad 13$$

A thermal energy balance was difficult to formulate for this reaction because it required a reliable heat transfer coefficient between the reaction media and tube wall (for both glass and stainless steel), accurate measurement of the jacket temperature difference (JOBR), and an unsteady state model of the two-phase vapour-liquid flows in the annular thermosyphon (HPOBR). Consequently, as with the solventless batch experiments, the measured reaction temperatures were used in the Arrhenius terms in the model to avoid the requirement for a thermal energy balance. The reaction temperatures were

measured at four points in the reactor: thermocouple tips were placed at 30 mm, 130 mm, 230 mm and 330 mm from the reactor outlet (see figure 1 for reference). These were subsequently interpolated across the full reactor length by fitting 3-term models to the four data points. In the JOBR, a Gaussian model was capable of describing the observed higher inlet temperatures, while a simpler second order polynomial model could be used for the HPOBR. Figure 6 shows examples of these interpolated temperature profiles obtained from the 2D screening of molar ratio and residence time in the JOBR and HPOBR. The rate constants at each spatial and temporal node were computed for each iteration of the fitting process using these interpolated temperatures as well as the current guess of the kinetics parameters (pre-exponential factors, activation energies and equilibrium constants).

Figure 6 – Interpolated temperature profiles obtained in the 2D screening of reactant molar ratio and residence time in the (a) JOBR and (b) HPOBR

Table 3 summarises the resulting kinetics parameters determined from the solventless multi-steady state screening experiments using equations 8–12 and the interpolated reaction temperature method. As with the batch data, the pre-exponential factors were pre-screened by trialling different values between 10^{18} and 10^{19} .

It was not possible with the temperature screening only configuration (table 3a) to identify six kinetic parameters that gave a satisfactory fit to the model with the experimental data. This configuration involved ramping the jacket temperature from 5 to 65°C in 10°C increments. Here, the model flow rates were insensitive to operating temperatures less than ~45°C. This screening configuration was the only ‘true’ uni-dimensional protocol, because when changing the molar ratio or residence time (in configurations ‘b’, ‘c’ and ‘d’), the operating temperature also changed in response to the changing the overall energy input to the reactors. Thus, it can be concluded that one-dimensional temperature screening is less robust than multi-dimensional screening in which the temperature is also changed.

Table 3 – Summary of kinetics parameters obtained from the solventless multi-steady state screening experiments

Kinetics Parameter	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)
A_1 (L/mol.s)	-	2×10^{18}	2×10^{18}	2×10^{18}	2×10^{18}	2×10^{18}	2×10^{18}	2×10^{18}
$E_{a,1}$ (kJ/mol)	-	100.39	102.09	105.80	103.74	109.45	107.41	99.00
K_1	-	150	150	150	150	150	150	150
A_2 (L/mol.s)	-	7×10^{18}	7×10^{18}	7×10^{18}	7×10^{18}	7×10^{18}	7×10^{18}	7×10^{18}
$E_{a,2}$ (kJ/mol)	-	98.05	97.94	98.36	99.90	99.41	98.10	95.04
K_2	-	2999	3000	2999	3000	3000	2960	2999

(a) 1D Screening: Jacket Temperature ($T_j = 5\text{--}65^\circ\text{C}$) (JOBR)

(b) 1D Screening: Molar Ratio ($MR = 4:1\text{--}1:3$, $T_j = 5^\circ\text{C}$) (JOBR)

(c) 1D Screening: Molar Ratio ($MR = 4:1\text{--}1:3$, $T_j = 20^\circ\text{C}$) (JOBR)

(d) 1D Screening: Residence Time ($\tau = 30\text{--}480$ s) (HPOBR)

(e) 2D Screening: Molar Ratio & Residence Time ($MR = 3:1\text{--}1:3$, $\tau = 99\text{--}480$ s, $T_j = 20^\circ\text{C}$) (JOBR)

(f) 2D Screening: Molar Ratio & Residence Time ($MR = 3:1\text{--}1:3$, $\tau = 99\text{--}480$ s, $T_j = 40^\circ\text{C}$) (JOBR)

(g) 2D Screening: Molar Ratio & Residence Time ($MR = 3:1\text{--}1:3$, $\tau = 99\text{--}480$ s) (HPOBR)

(h) 3D Screening: Molar Ratio, Residence Time & Jacket Temperature ($MR = 3:1\text{--}1:3$, $\tau = 200\text{--}400$ s, $T_j = 5\text{--}20^\circ\text{C}$) (JOBR)

Various examples comparing the modelled molar flow rates with the experimental values are shown in subsequent figures. Figure 7 shows the molar flow rates obtained from the one-dimensional screening of residence time using the HPOBR, figure 8 compares the molar flows obtained in the HPOBR using the 2D central composite experiment designs, and figure 9 shows the results of the three-dimensional D-optimal experiment design run in the JOBR. Generally, adequate matches were observed between the numerical and experimental data in both reactor configurations in each screening configuration. In figure 9, the slight overshoot of the modelled imine molar flow at plateaus 3 and 7 could be a

consequence of slightly under-compensating for attenuation of the imine concentrations measured by *in situ* FTIR in the presence of water.

Figure 7 – Comparison of model and experimental multi-steady state reaction profiles for the solventless imination reaction conducted in the HPOBR / one-dimensional screening of residence time ($\tau = 30\text{--}480\text{ s}$) / with $x_o = 2\text{ mm}$ and continuously reducing oscillation frequency ($f = 7\text{--}4\text{ Hz}$) /

$$R^2_{\text{aldehyde}} = 0.83, R^2_{\text{imine}} = 0.92$$

Figure 8 – Comparison of model and experimental multi-steady state reaction profiles for the solventless imination reaction conducted in the HPOBR / two-dimensional screening of reactant molar ratio ($MR = 3:1\text{--}1:3$) and residence time ($\tau = 85\text{--}480\text{ s}$) using 2D central composite experiment design / with $Re_o = 307$ ($x_o = 2\text{ mm}$, $f = 5\text{ Hz}$) / $R^2_{\text{aldehyde}} = 0.63$, $R^2_{\text{imine}} = 0.73$

Figure 9 – Comparison of model and experimental multi-steady state reaction profiles for the solventless imination reaction conducted in the JOBR / three-dimensional screening of reactant molar ratio ($MR = 3:1-1:3$), residence time ($\tau = 200-400$ s) and jacket temperature ($T_j = 5-20^\circ\text{C}$) using *D*-optimal experiment design / with $Re_o = 307$ ($x_o = 2$ mm, $f = 5$ Hz) / $R^2_{aldehyde} = 0.71$, $R^2_{imine} = 0.37$

The average first and second reaction activation energies ($E_{a,1}$ & $E_{a,2}$) determined from the solventless continuous screening experiments were 103.98 ± 3.79 kJ/mol and 98.11 ± 1.55 kJ/mol respectively. It was found that $E_{a,1}$ determined in flow was 13.35% lower than the batch result, while $E_{a,2}$ was comparable for both the batch and continuous experiments. However, the pre-exponential factor for the second reaction was 7×10^{18} L/mol.s in flow compared to 9×10^{18} in batch. This means at 50°C , the forward rates for both reaction steps in flow were 387 times and 1.36 times larger than the in-batch results respectively. The large disparity of the first step is likely to be a result of the poor thermal control in the batch reactor. At first contact of the reagents, the temperature quickly exceeded the boiling point of the butylamine reactant resulting in partial vaporisation followed by condensation of the amine. This quenching effect was not reproducible with the kinetics model used. To suppress this unwanted vaporisation in batch, it is recommended to perform this solventless reaction in a sealed vessel under elevated pressure, or in a vessel with significant heat transfer area and cooling capacity. This was not attempted in the present study because the main focus was on the in-flow screening experiments using the two meso-OBR configurations.

The equilibrium constants again imply that both reactions were substantially shifted towards the product side of the equilibrium (toward the intermediate for the first reaction step, and towards the imine and water for the second reactions step). The larger constant for the second reaction was a result of the phase separation of the water product, which produced an extractive reaction effect. This means the equilibrium constants reported in this study are a function of both the mixing condition and reaction. These “observed” equilibrium constants were nevertheless comparable for both the continuous and batch experiments.

4 Conclusions

In this study, the Arrhenius kinetics parameters of a solventless imine synthesis reaction were successfully and rapidly determined using continuous flow experiments in OBRs with two forms of jacket: a conventional flow through jacket (in the “JOBR”) and an annular heat pipe (the “HPOBR”). In the absence of solvent, both the heat pipe and jacketed reactor configurations have demonstrated the ability to mitigate the exothermic temperature rise and show that meaningful kinetic data can be derived via such screening. Beyond the advantages reported in previous screening using meso-OBRs, up to a 70% theoretical reduction of material/time usage was realised through the application of design of experiments by studying the effects of three variables in flow (residence time, reactant molar ratio and temperature).

The slight deviation from isothermal behaviour in the HPOBR, and significant deviation in the JOBR were unexpectedly found to be useful for determination of thermally dependent kinetics parameters. Although the changing temperature was an uncontrolled variable, the change in temperature in combination with other changes (such as residence time or molar ratio) created more robust fitting. This was because this methodology allowed the spatial and temporal ‘history’ of the reaction to be captured in addition to the temporal ‘history’ recorded at the outlet using *in situ* FTIR. Here, thermal effects could still be distinguished from experiments that did not use temperature as a direct screening variable.

In contrast to the batch reactor, both the JOBR and HPOBR were able to mitigate the reaction temperature below the boiling point of the amine reactant, through heat removal and heat spreading respectively. The HPOBR also retained the advantage of being entirely passive, meaning fully automated screening protocols could be easily implemented. The main advantage of the JOBR in the context of screening was the ability to separately adjust the operating temperature using the jacket, without needing to change the molar ratio and residence time (though this required manual adjustment of the jacket temperature). Both reactors should be easily adaptable to other exothermic reactions, as both allow adjustment of the “cooling capacity” using the heat pipe/jacket working fluid. For highly exothermic reactions, the heat pipe could also be coupled with a heat sink to allow both heat spreading and heat removal.

Other advantages demonstrated in this study are: reduced preparation time (no need to dilute the reactants in a solvent); higher reaction rates and higher throughputs; more robust monitoring of the reaction via *in situ* FTIR in the presence of water; no downstream solvent removal; design of experiments ensured a consistent design space was explored (so that the kinetics model was not weighted towards a certain combination of conditions); and reduced material/time requirements compared to full response surface mapping.

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Nomenclature

A_i	Arrhenius pre-exponential factor for reaction i ($i = 1, 2$) (L.s.mol^{-1})
$A(\omega_n)$	Absorbance at wavelength ω_n
$E_{a,i}$	Activation energy for reaction i ($i = 1, 2$) (J.mol^{-1})
c	Centre point of Gaussian FTIR peak (cm^{-1})
f	Oscillation frequency (Hz)

F_i	Molar flow rate of component i (mol/s)
h	FTIR peak height
k_{fi}	Forward reaction rate constant for reaction i (i = 1, 2) (L.s.mol ⁻¹)
K_i	Equilibrium rate constant for reaction i (i = 1, 2)
m	Reaction order
n	Reaction order
N	Number of equivalent tanks-in-series
N_i	Number of moles of component i (mol)
o	Reaction order
p	Reaction order
q	Reaction order
R	Universal gas constant (8.314 J.mol ⁻¹ .K ⁻¹)
t	Time (s)
T	Temperature (K)
T_j	Jacket temperature (K)
V	Volume (m ³)
V_{hp}	Volume of the annular heat pipe (m ³)
V_m	Volume of methanol working fluid in the heat pipe (m ³)
v_T	Volumetric flow rate (m ³ /s)
w	FTIR peak width (cm ⁻¹)
x_o	Oscillation amplitude (m)

Greek Letters

Δt	Time step size for finite difference method (s)
$\Delta \tau$	Step size of residence time for finite difference method (s)
μ	Fluid viscosity (Pa.s)
ρ	Fluid density (kg.m ⁻³)
τ	Residence time (s)

ω_n Wavenumber (cm^{-1})

Dimensionless Groups

FR Heat pipe fill ratio ($=V_m/V_{hp}$)

Re_n Net flow Reynolds number ($=\rho v D/\mu$)

Re_o Oscillation Reynolds number ($=2\pi f x_o \rho D/\mu$)

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