Transient Ramp Experiments for the Determination of Kinetic Parameters

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1. Background

- Within the pharmaceutical industry estimates suggest that solvents make constitute 50% of process material and 70% of waste produced.[1] Increasing the use of renewable solvents is therefore a necessity to improve sustainability within chemistry led laboratories.

- Challenges arise because solvents choice heavily influences the kinetics, products and yields of a reaction meaning direct swaps are not always feasible and often require re-optimisation of reaction conditions.[2] This is a time consuming and laborious task in batch and often disregards complex solvent mixtures, which offer compromises in sustainability credentials and performance metrics.

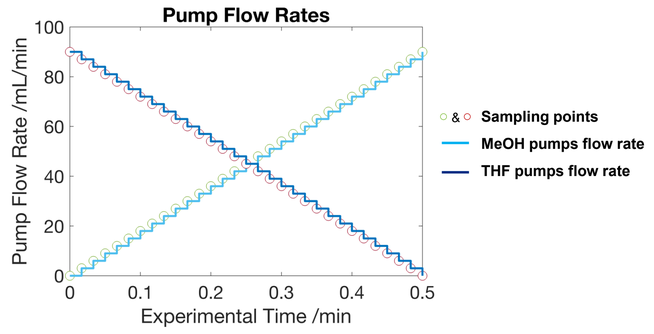


Figure 1: *Pump flowrates for solvent ramp.*

- Transient flow chemistry has demonstrated the ability to generate large quantities of data across a range of continuous and categorical variables, changing reaction conditions continuously as the experiment progresses.[3, 4] This reduces material consumption, contributing to sustainability.

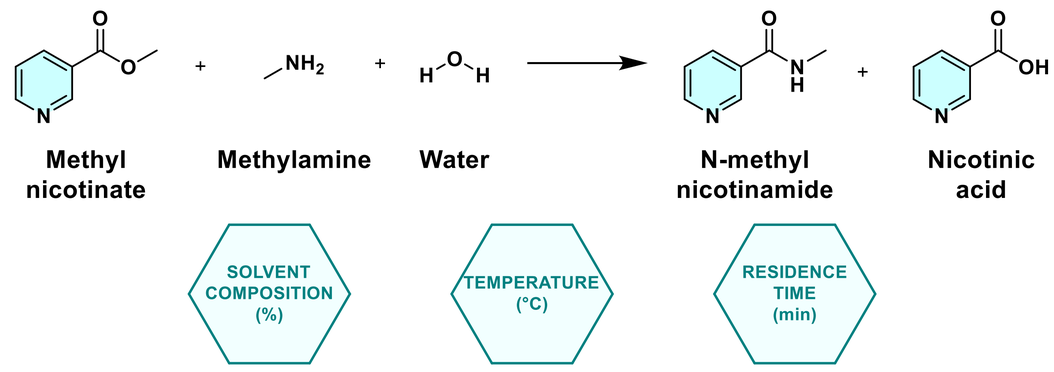


Figure 2: *Reaction scheme for the synthesis of N-methyl nicotinamide.*

- In this study, transient solvent ramps were undertaken towards the production of the pharmaceutically relevant molecule N-methyl nicotinamide,[5] with an emphasis on investigating the impact of solvent characteristics on the reaction rate constants (k) and activation energies (E_a).

2. Experimental Method

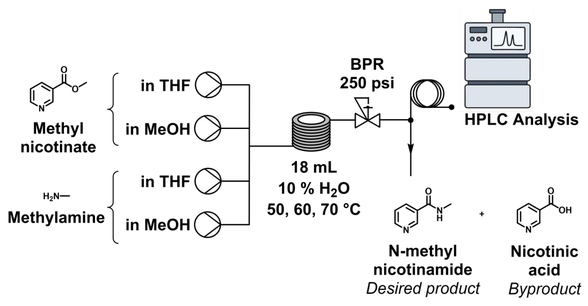


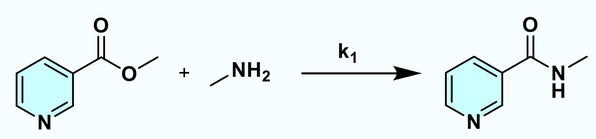
Figure 3: *Schematic diagram of the flow setup.*

Figure 4: *Flow setup for the solvent ramp experiments.*

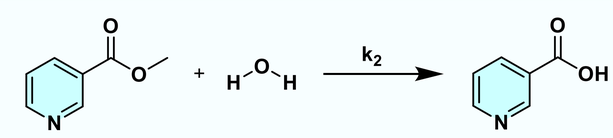
- The automated flow platform for the solvent ramp experiments utilised HPLC feed pumps, thermal reactor (18 mL) in a water bath, 250 psi back-pressure regulator (BPR), switching valve and an on-line HPLC for analysis.

- MeOH and THF solvents were ramped, changing the solvent composition in the reaction system by a defined value from 100% THF to 100% MeOH. The reaction was studied at 3 different residence times and sampled at regular intervals over 120 minutes of experimental time, allowing generation of large kinetic datasets.

Reaction Pathway 1



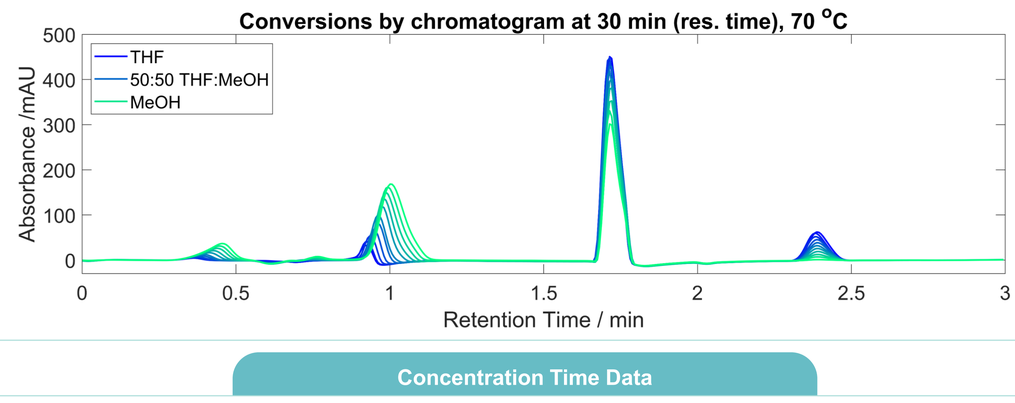
Reaction Pathway 2



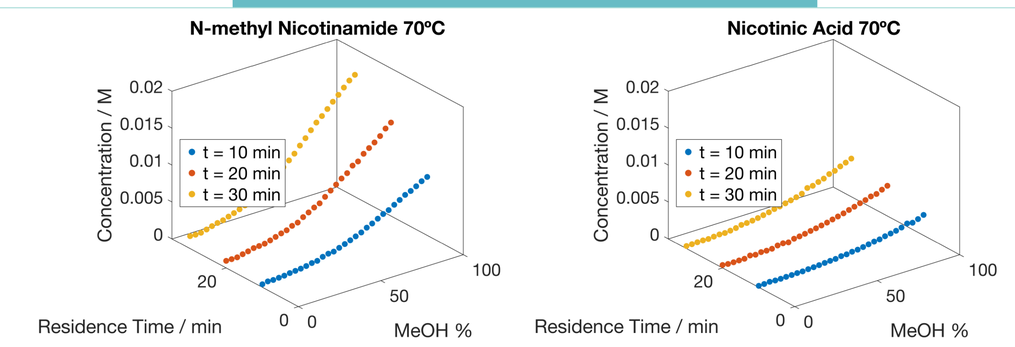
- Flow system was automated and controlled by a bespoke MATLAB interface.

3. Results and Discussion

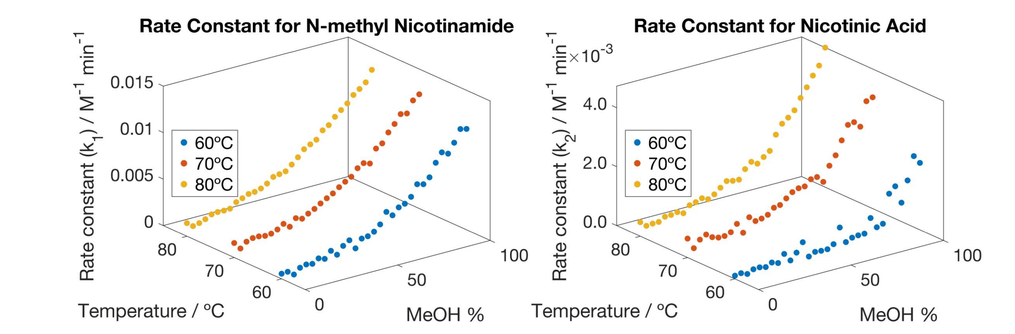
Conversions with increase in MeOH %



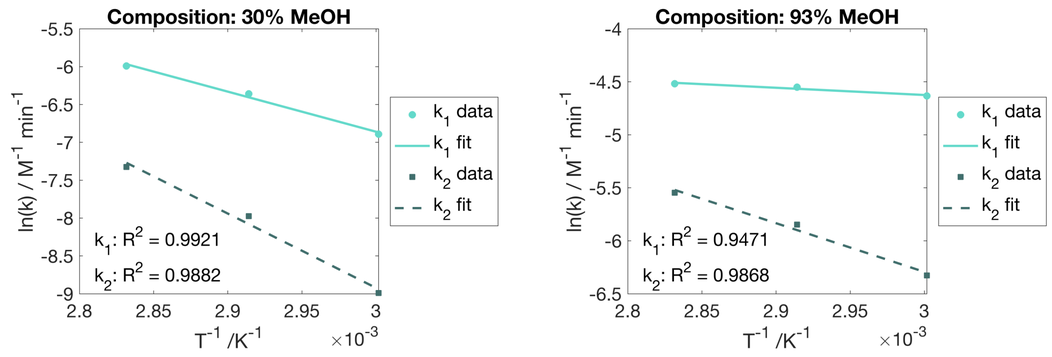
Concentration Time Data



Rate constants for k_1 and k_2



Arrhenius plots at different MeOH compositions



- Rate constants were calculated at each of the 31 solvent compositions and temperatures using an initial value problem ODE solver to fit k values by minimising difference between fitted and experimental data.

- Activation energies (E_a) were calculated using Arrhenius plots at each solvent composition and calculating the linear regression.

- The kinetic values can be used to inform process development decisions or as an input for further data analysis, focussing on the impact of solvent effect.

4. Conclusion

- Successful demonstration of transient flow experiment's ability to generate large quantities of data for kinetic studies while displaying novel approach to obtaining mixed-categorical variable kinetic parameters.

- The ramp experiment showcase a significant reduction in chemical material usage compared to steady-state or Design of Experiments (DoE) for kinetic or reaction optimisation studies.

- Future scope will include investigation of the impact of various solvent properties on the reaction kinetics.

5. References

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