Kinetics in Flow

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"Batch" Kinetics in Flow: Online IR Analysis and Continuous Control**

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Abstract: *Currently, kinetic data is either collected under steady-state conditions in flow or by generating time-series data in batch. Batch experiments are generally considered to be more suitable for the generation of kinetic data because of the ability to collect data from many time points in a single experiment. Now, a method that rapidly generates time-series reaction data from flow reactors by continuously manipulating the flow rate and reaction temperature has been developed. This approach makes use of inline IR analysis and an automated microreactor system, which allowed for rapid and tight control of the operating conditions. The conversion/residence time profiles at several temperatures were used to fit parameters to a kinetic model. This method requires significantly less time and a smaller amount of starting material compared to one-at-a-time flow experiments, and thus allows for the rapid generation of kinetic data.*

Current methods for generating kinetic data can be categorized as either sampling steady-state conditions in flow or generating time-series data in batch.[1] The latter method has proven particularly useful in identifying complex kinetic mechanisms.[2] Unfortunately, both of these techniques have significant limitations. Whereas continuous-flow experiments, especially in microreactors, have advantages over batch systems in terms of mixing times,[3,4] temperature control,[5,6] materials savings,[7] and the ability to perform sequential experiments without intermediate cleaning steps, batch experiments are seen as better suited to generating kinetic data because of the ability to collect data from many time points in a single experiment.[2] However, with continuous online measurement, flow experiments can generate such time-series data by a continuous variation of the flow rate in a low-dispersion reactor.[8] This analysis is possible because, under ideal conditions, a batch reactor and a plug-flow reactor have the same kinetics equation; they will have the exact same conversion as a function of conditions and time for any reaction, as time in the batch reactor corresponds to residence time in the plug-flow reactor.[1] These reactors are typically treated differently only because of deviations from ideality, such as concentration or temperature gradients from imperfect mixing.

In a recent contribution by Mozharov et al., a method that takes advantage of the ideality of microreactors to derive time-series data by flow manipulation was presented:[9] A Knoevenagel condensation in a microreactor was allowed to reach steady state at a low flow rate. Then, a step change in flow rate rapidly flushed the contents out of the reactor. As the contents exited, an inline Raman probe measured the product concentration. Although this enabled generation of a conversion curve in agreement with steady-state experiments, the exact reaction times during this flow-rate step change could not be determined because the step change was not actually instantaneous, so that graphical and empirical estimation of reaction times was required. As stated by Mozharov et al., *"The step increase in flow rate is never perfect. The system always needs some time to speed up to the higher flow rate… The exact function F(τ) during this transitional period is uncertain."*[9] This non-ideality is caused by several effects, including non-rigidity of the tubing walls and the syringe plunger, that prevent an immediate change in the pressure profile throughout the system.

With the method developed herein, a microreactor system is allowed to come to steady state at short residence time, which significantly reduces the initial waiting period before flow manipulation can begin. Uncertainty in the accurate determination of residence time is avoided through the use of a controlled ramp, rather than a step change in flow rate. This enables the rate of change in residence time to be set, which in turn allows control over the trade-off between more experimental data and experiment duration.

This new method is intended to be broadly applicable to a wide range of chemical studies for which time-series data are desired. Ideally, with inline analysis, this method could be applied to any chemical reaction that can be quenched chemically, thermally, or otherwise. However, an integrated online sensor at the end of the reaction zone would allow this method to be expanded even further. Attenuated total reflectance (ATR)-FTIR, UV/Vis, flow NMR, Raman, and fluorescence spectroscopy and other techniques could potentially be implemented.

The efficacy of this new technique was demonstrated for the Paal–Knorr reaction between 2,5-hexanedione (**1**) and ethanolamine (**2**) in dimethyl sulfoxide (DMSO; Scheme 1 and 2)[10,11] in an automated flow platform (Supporting Information, Figure S1),[12,13] which used an inline Mettler Toledo ReactIR ATR-FTIR flow cell[14] to continuously monitor the effluent from a silicon microreactor.

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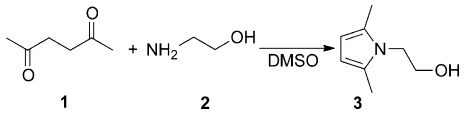
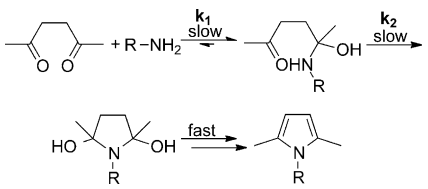


Scheme 1. The Paal–Knorr reaction.[15,16]



Scheme 2. Mechanism of the Paal–Knorr reaction.[11,17,18]

For the microreactor system used, the narrow channel widths (400 μm) allow diffusion to rapidly eliminate radial concentration gradients, which leads to minimal dispersion under the conditions tested.[1,8] Under such conditions of low dispersion, a flow reactor may be treated as a series of batch reactors (Figure 1). This treatment allows the use of well-controlled system transients to generate kinetic information much more rapidly than with traditional flow experiments;

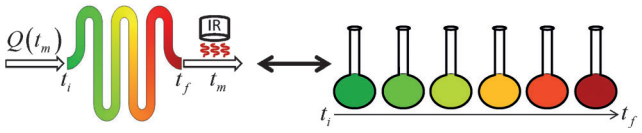


Figure 1. Treatment of a low-dispersion flow reactor as a series of well-mixed batch reactors. Color represents the extent of conversion from low (green) to high (red).

the only requirement entails that the history of each fluid element is known when it exits the reactor.

The method used to generate this time profile is to initially set the flow rate to give a short residence time, τ_0, in the system of volume V_r. After this system has reached steady-state conditions, the residence time is gradually increased at a constant rate, α, times the experiment time, t, by reducing the flow rate, Q, in a controlled manner, so that instantaneous residence time, τ_{ins}, of the system is always known.

$$\tau_{ins} = \tau_0 + \alpha t = \frac{V_r}{Q(t)} \tag{1}$$

Each "pseudo-batch" reactor passes through the reactor in a time τ, from an initial time, t_i, to the final time, t_f; both values are unique for each fluid element. The residence time that each fluid element spends in the reactor is a function of when it exits the reactor:

$$\tau = t_f - t_i = (1 - e^{-\alpha})\left(t_f + \frac{\tau_0}{\alpha}\right) \tag{2}$$

This expression can be rewritten as the linear residence time ramp,

$$\tau = \frac{S}{\alpha}\tau_0 + St_f \tag{3}$$

where S is the slope of τ versus t_f:

$$S = (1 - e^{-\alpha}) \tag{4}$$

An example of the resulting residence time profile is given in Figure S2, along with additional derivations. This method results in a predictable and accurate residence time profile. Furthermore, the reactor effluent can be measured for a longer period to reduce variability and increase data collection. This approach enables a greater sampling rate of the experimentally collected conversion data (Figure S3) with a data density that is ten times higher than that reported by Mozharov et al.,[9] which reduces the error in the estimated kinetic parameters. In combination with a more rapid analytical technique, this method could also become applicable to much faster chemical reactions. Furthermore, a lower value of S would allow the residence time to be ramped more slowly, enabling analysis at residence time intervals that are much closer together than the sampling frequency, which leads to a further increase in data density. Moreover, a lower value of S would allow the generation of time-series data that cannot be captured in batch systems because of reaction kinetics that result in complete conversion too quickly for conventional in situ analysis techniques. However, this approach would require analysis of a larger number of reactor volumes (Figure S4).

A first test of the linear-residence-time-ramp method at 130 °C with several values of S yielded residence time profiles that follow the same trend as the steady-state values, but display a slight deviation in the product concentration from the steady-state values that increased as S approached one (Figure S5). This deviation results from the small volume between the end of the reaction zone and the inline IR flow cell, owing to the thermal quench zone of the silicon reactor, the cooling block of the reactor, and the tubing that connects the reactor to the IR flow cell. This delay volume, V_d, between the reactor exit and the actual measuring point is included in the model by determining the time difference between t_f, when a fluid element exits the reaction zone, and t_m, when the concentration is actually measured.

$$V_d = \int_{t_f}^{t_m} \frac{V_r}{\tau_0 + \alpha t} dt \tag{5}$$

Solving for t_m in terms of t_f gives:

$$t_m = e^{\frac{V_d}{V_r}\alpha} t_f + \left(e^{\frac{V_d}{V_r}\alpha} - 1\right)\frac{\tau_0}{\alpha} \tag{6}$$

Substituting the relationship between t_f and τ analogously to Eq. (2) gives the residence time profile as a function of t_m:

$$\tau = Se^{-\frac{V_d}{V_r}\alpha}\left(t_m + \frac{\tau_0}{\alpha}\right) \tag{7}$$

Replotting the residence time profiles as a function of this residence time (Figure 2) reveals product concentrations for each residence time profile that are in good agreement with

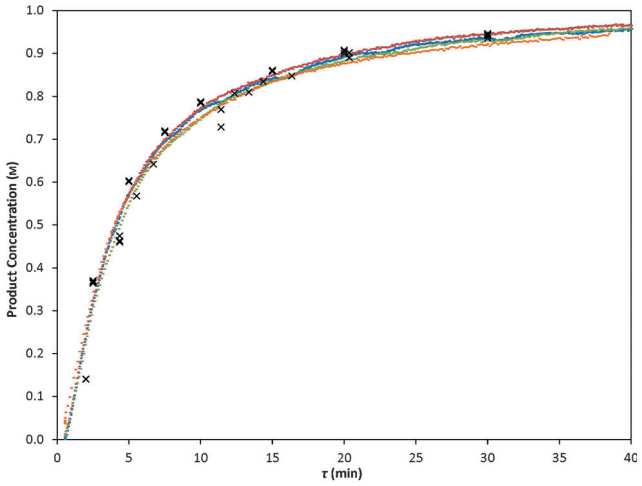


Figure 2. Residence time ramp results using corrected residence times, with $S=1/4$ (blue), $S=1/3$ (red), $S=1/2$ (green), and $S=2/3$ (orange). Steady states (×).

each other for different values of S and with the results from steady-state concentration measurements.

Next, this method was applied for the generation of conversion profiles at several temperatures. The data were then fit to a kinetic model (based on Scheme 2), in which a second-order reaction, which is first-order in each starting material, forms an intermediate that then undergoes first-order conversion, which is followed by rapid conversion into the product. The reverse reaction of the first step is assumed to be significantly slower, and thus it only has a small effect on the overall reaction rate. The automated platform was used to run reactions under multiple conditions (Figure 3a). The data generated at sample intervals of 15 seconds during the first experiment are shown in Figure 3b. These product concentration curves were then assigned to their corresponding temperatures (Figure 3c). The experiments were repeated three times, and the two kinetic parameters k_1 and k_2 (Scheme 2) were then fitted by least-squares regression in Matlab at each temperature by using every 20th data point as a test set and all other data points as the validation set. The activation energies thus obtained are 12.2 ± 0.4 kJ mol^{-1} and 20.0 ± 0.9 kJ mol^{-1} for k_1 and k_2, respectively.

This analysis demonstrates the significantly higher efficiency of this method to generate data for kinetic analysis compared with traditional steady-state techniques. The experimental data in Figure 2 could be acquired within approximately eight hours, and only 5 mL of each 2 M reactant solution was required. In contrast, had traditional steady-state reactions been performed at each temperature and at residence times of 10, 20, 30, and 40 min, allowing four residence times for steady state,[19–21] the experiment would have taken nearly two days and 13.5 mL of each reaction solution, and fewer data points would have been acquired.

For this example, the sample interval of 15 seconds that was used in our new method allowed the collection of a large number of data points for residence times between 0.5 and 40 min, and smooth conversion trends were observed. However, as mentioned previously, even with a significantly faster reaction, the use of a value of S closer to zero would enable the generation of significantly larger amounts of data than the use of typical in situ batch techniques, allowing for elucidation of the reaction profile.

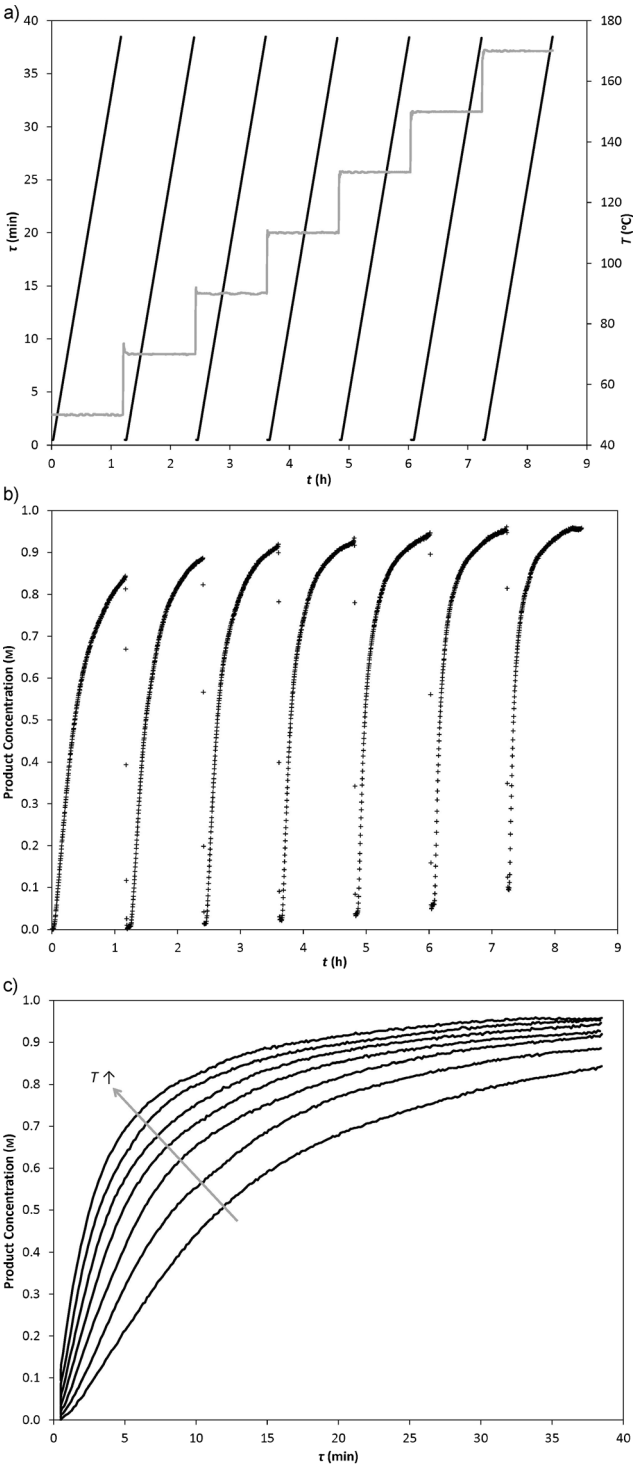


Figure 3. a) Residence time ramps (——) and temperature steps (——) used in the experiments. b) Product concentration determined by inline IR analysis at sample intervals of 15 seconds. c) Product concentration as a function of residence time at different temperatures; from top to bottom: 170, 150, 130, 110, 90, 70, and 50 °C.

We have developed a method that rapidly generates time-series reaction data from flow reactors, analogous to classical batch reaction data and in agreement with traditional steady-state flow analysis. The approach was implemented with an automated microreactor system, allowing for rapid and tight control of operating conditions. The resulting conversion/residence time profiles at several temperatures were used to fit parameters in a kinetic model, in agreement with experiments. This approach could be used to generate time-series data in flow for a wide range of chemical reactions. Furthermore, this method could be extended to other parameters, such as performing concentration ramps.

Experimental Section

The microfluidic system that was used in this work is depicted in the Supporting Information, Figure S1, which includes a schematic representation of the silicon microreactor. Two Harvard stainless steel syringes were loaded separately with solutions of 2,5-hexanedione (**1**) and ethanolamine (**2**) in dimethyl sulfoxide (DMSO; 2 M), which resulted in a solution with 1 M concentrations upon mixing in the reactor. One syringe was placed on each of two Harvard syringe pumps (PHD 2000) to control the residence time. The flow rates were updated every second through linked RS-232 communications to a Dell (Optiplex 960) computer. These syringe pumps were connected to a silicon microreactor[22] with a 120 μL reaction zone and a cooled inlet/outlet zone, the temperature of which was maintained at 22 °C with a recirculating VWR chiller (model 1171MD). The cooled section allowed the reactant streams to mix fully before the reaction occurred and thermally quenched the reaction. The temperature of the reaction zone was controlled with an Omega (CN9311) controller and an Omega (CSH-102135/120 V) heating cartridge. The controller was connected to the computer with an RS-232 cable to read the measured reactor temperature and program the temperature set point. Furthermore, because of the high heat transfer coefficient of silicon, the temperature of the reaction zone could be quickly changed between set points and the fluid stream rapidly reached the desired temperature in both the reaction and quench zones. A Mettler Toledo ReactIR iC 10 that was outfitted with a DiComp ATR flow cell (10 μL) was used for continuous inline monitoring, averaging 30 spectrum scans, which were saved to an Excel file once every 15 s. Labview software (version 8.5.1) on the computer communicated with the syringe pumps and temperature controller and read the IR Excel export files to determine the reaction conversion based upon calibrations to peak heights. Matlab scripts (version 2010b) within Labview controlled the reaction temperature set points and syringe-pump flow rates.

For the data in Figure 3, once the temperature had equilibrated at a set point, and the residence time had equilibrated at τ_0, the residence time ramp ran for 70 min. The temperature set point was then changed to the next set of conditions, and the process was repeated. The duration was set at 70 min by adding 10 min to the time that would be necessary for t_f to reach 40 min, allowing the residence time ramp to cover nearly the full range of reaction conversions, with additional time for the reactor effluent to reach the IR flow cell.

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