Process Optimization

DOI: 10.1002/anie.200906095

The Flow's the Thing…Or Is It? Assessing the Merits of Homogeneous Reactions in Flask and Flow**

Fernando E. Valera, Michela Quaranta, Antonio Moran, John Blacker, Alan Armstrong,* João T. Cabral,* and Donna G. Blackmond**

kinetics · microreactors · organocatalysis · reaction mechanisms

Miniaturized systems based on MEMS (microelectromechanical systems) technology designed for carrying out chemical reactions in continuous flow have received increased interest in the synthetic organic chemistry community over the past decade, following demonstration of the utility of such systems for micro total analysis (μ-TAS).[2] Microreactor technology offers many attractive features that have been widely reviewed.[3] The benefits of microreactors for mixing and heat transfer in highly exothermic reactions as a result of the significantly greater surface-to-volume ratios that these reactors exhibit have been discussed. For the synthesis of complex organic molecules of interest to the pharmaceutical industry, one of the most often cited advantages is the ability to carry out reactions under well-controlled conditions on very small scale. Impressive advances have been made towards streamlining the entire timeline of drug discovery and process development by combining multiple reaction steps in flow or reaction steps with reagent immobilization and rapid serial processing in flow to address traditional bottlenecks in workup and purification.[4,5]

In addition to these developments, general and rather sweeping claims have been made that microreactor systems accelerate organic reactions and that lower catalyst loadings and higher yields can routinely be achieved in these systems compared to those of reactions carried out in flasks. Despite these potential advantages, examples of successful implementation of microflow reaction technologies in either academic organic synthesis or industrial process research and manufacturing remain more isolated than these reports would suggest. However, the implication is that it is only a matter of time before microflow reactors will dominate laboratory studies aimed at both fundamental research and practical applications of complex organic reactions, with our current mode of operation in reaction flasks ultimately becoming a relic of the past. It seems therefore worthwhile to examine the assumptions behind this viewpoint to provide a critical analysis of "flask versus flow" as a means for effecting reactions.

It is important to emphasize that we confine the present discussion to single-phase, homogeneous reactions. Multiphase reaction systems, including droplet and interfacial flows[6,7] and systems that make use of the reactor walls to immobilize reagents or catalysts,[4,8] as well as ultrafast, molecular-diffusion-controlled reactions, are outside the scope of our comparative assessment. Even given this caveat, we are able to address many examples of transition-metal-catalyzed and organocatalytic transformations that make up a significant fraction of the reactions under investigation in academic and pharmaceutical research laboratories. By examining the fundamental principles of physical organic chemistry, thermochemistry, and transport phenomena underlying these processes, we show that in many of these cases microflow conditions should have no effect on reaction rate, product selectivity, required catalyst loading, or ultimate yield. We provide here a simple set of criteria that may be employed to assess whether a microflow setup is likely to provide benefit in a particular case.

[*] F. E. Valera, Dr. J. T. Cabral, Prof. D. G. Blackmond[+]
Department of Chemical Engineering & Chemical Technology
Imperial College, London, SW7 2AZ (UK)
Fax: (+44) 20-7594-8504
E-mail: d.blackmond@imperial.ac.uk
j.cabral@imperial.ac.uk
M. Quaranta, Dr. A. Moran, Prof. A. Armstrong
Department of Chemistry, Imperial College
London, SW7 2AZ (UK)
E-mail: a.armstrong@imperial.ac.uk
Prof. J. Blacker
School of Chemistry, University of Leeds
Leeds, LS2 9JT (UK)
E-mail: j.blacker@leeds.ac.uk
[+] Present address: Department of Chemistry
The Scripps Research Institute
La Jolla, CA 92037 (USA)

[**] Support from the EPSRC and Merck Research Laboratories is gratefully acknowledged. We thank Adam Zarth and Alexa Sabedra for and preliminary experimental work by. A.M. acknowledges a fellowship from the Fundación Ramón Areces (Spain). D.G.B. is the recipient of a Royal Society Wolfson Research Merit Award. For insight into the allusion to Shakespeare's Hamlet in the title see reference [1].

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200906095.

A Brief Primer on Reactor Design

Microfluidic reactors known as "lab-on-a-chip" systems are three-dimensional structures constructed of glass, quartz, polymers, or metals, containing microchannels in which fluids may be manipulated by electrokinetic, pressure, or flow-driven pumping. The typical ranges for channel diameter, reactor length, and total reaction volume are on the order of microns, meters, and milliliters, respectively. Figure 1 compares an example of a microfluidic chip flow reactor and a typical laboratory batch reactor consisting of a glass vial with a magnetic stirring bar.

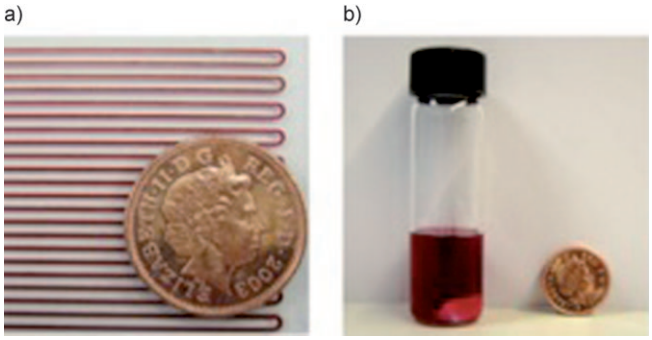


Figure 1. a) A typical microfluidic chip reactor for reaction in flow; b) a typical reaction vial with magnetic stirring bar for reaction in batch.

A microreactor typically operates under conditions that emulate "plug flow", meaning that mixing in the direction of fluid flow is minimized. As a given small volume of reactants moves along the reactor, reaction takes place within this small volume independent of the volume ahead or behind it. If mixing in the radial direction is rapid (as it typically is in single-phase microchannel reactors), each consecutive slice of reactor volume may be thought of as a separate, tiny, well-stirred reactor that accepts a feed from the small stirred reactor behind it and delivers fluid to the small stirred reactor in front of it.

Figure 2 compares this description of a microreactor with that of a flask for a reaction that exhibits first-order kinetics. The concentration of the reactant decays exponentially with time in the flask reactor. In a microfluidic device with a constant flow rate, the concentration of the reactant decays exponentially with distance along the reactor. Thus time in a flask reactor equates with distance in a flow reactor. With this comparison in mind, let's examine some of the purported advantages of microflow reactors over reaction flasks, specifically for the case of a single-phase homogeneous catalytic reaction.

Mix It Up

It is often stated that microfluidic systems offer better mixing than reactions in flasks. To understand the behavior of reactions in these systems, we need to consider both how the reactant molecules initially contact each other and how they

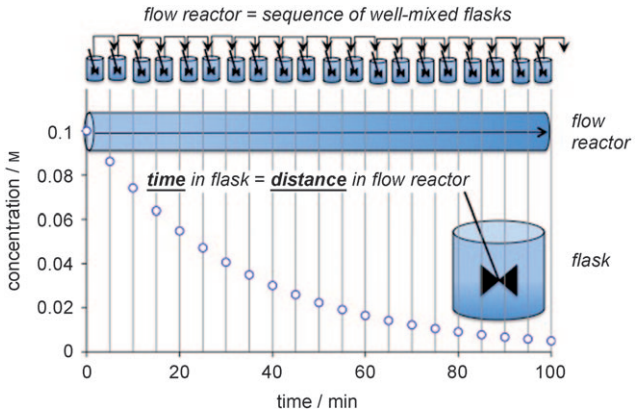


Figure 2. Reactant concentration versus time (flask reactor) or distance (flow reactor) for a simple first-order reaction under well-mixed homogeneous conditions.

mix as they flow along the reactor channel. Many microflow setups incorporate a mixing zone prior to the reactor inlet with special devices to facilitate rapid initial mixing of separate reactant streams, and novel micromixing technology is rapidly evolving.[5b,c] Then, from the point of the mixing zone onwards, flow rates in microreactors are generally controlled to provide what is known as laminar flow, in which only molecular diffusion aids the further mixing of molecules.[7,9] This is a feature that has been cited as an advantage of flow microreactors over reactions in flasks. Our task is to provide a comparative assessment of such premixed homogeneous reaction streams in laminar flow in microfluidic channels with solutions of similar concentrations in flasks. A simple calculation (see the Supporting Information) compares molecular diffusion in a microfluidic channel with that in a reaction flask, and indeed, the result is striking: whereas a molecule in the center of a typical microfluidic channel such as that shown in Figure 1a can reach the wall of that channel in a few seconds, that same molecule in the middle of a reaction vial such as that shown in Figure 1b will require the better part of a day to diffuse to the side wall! Surely this calculation confirms the great mixing advantage for the microflow reactor?

A more detailed examination reveals the fundamental flaw in this argument: the time a molecule takes to negotiate its way to the reactor wall is irrelevant for a reaction where the wall is not a participant, as it would be, for example, in the case of an immobilized reagent or catalyst. In a homogeneous solution, the driving force of molecular diffusion displaces a molecule the same distance in the same time regardless of the type of container in which it finds itself.[10] Consider as an example the reaction $\mathbf{A}+\mathbf{B}\rightarrow\mathbf{C}$, in which **A** and **B** are both fully soluble at concentrations typical of substrates in organic reactions. For reactions of small organic molecules this means that solvent molecules make up greater than 90% of the reactor contents. Any density or viscosity differences between **A**, **B**, and **C**, which in any event are likely to be small, may be neglected for the system as a whole. Even gentle stirring of a solution in a flask results in homogeneity within seconds, as may easily be demonstrated by adding a dye to a stirred

solution in a vial just as we did for the photo in Figure 1b. At any given point in time, the local concentrations of **A**, **B**, and **C** will be identical anywhere in the vial. It is these concentrations that determine how far each molecule must travel, and how long it will take, for an encounter to occur by means of molecular diffusion. This, in fact, is the relevant process for understanding reactivity in this example either in flask or flow. The time and distance to the reactor wall has no bearing on a reaction in homogeneous solution, whether in a microchannel or in a flask.

Confusion over the nature and relevance of different types of mixing processes is common in organic chemistry. Many chemists have experienced the frustration of trying to run a mixing-controlled reaction, and aspects of mixing-sensitive reactivity and selectivity have been studied extensively.[9] Most common examples involve regimes dominated not by molecular diffusion but by macroscopic mixing processes (for example, gas–liquid mass transfer in hydrogenations, or polymerizations where reactants and products differ significantly in viscosity). It is important to clarify that such reactions are just as problematic to run in a microfluidic channel in laminar flow as they are in a stirred flask. The question we address here, however, is the role of mixing in reaction systems where molecular diffusion is the dominant mixing process.

A chemical reaction is mixing-controlled if its half-life is on the order of, or smaller than, that of the relevant mixing process. A simple calculation reveals that when the relevant mixing process is molecular diffusion, the chemical reaction will be affected only if its half-life is less than one-billionth of a second. The present discussion focuses on homogeneous reactions that occur with half-lives on the order of minutes to hours, where well-mixed conditions may be established rapidly at the outset of the reaction. In these cases, we may conclude that molecular diffusion in a microchannel has nothing to recommend it over molecular diffusion in a flask. In fact, we rely on this conclusion intuitively whenever we monitor homogeneous reactions by NMR spectroscopy in a flask known as an NMR tube.

The Heat Is On

The discussion above tells us that in the case of reaction in homogeneous solution, laminar flow in and of itself can offer no justification for the claim that microflow conditions provide better results than those for the same reaction in a flask. But what about heat transfer? A homogeneous solution where reactants encounter each other solely by molecular diffusion may not dissipate heat rapidly, and this could become an important consideration if the reaction is highly exothermic. In a homogeneous solution, the reaction heat will evolve uniformly over the reactor volume; because the reaction itself is uniform, "hot spots" will not develop. However, the rate at which heat is removed from the reaction mixture may be different for different reactor types. Here the large surface-to-volume ratio for microflow systems may be an advantage for maintaining the reaction under controlled isothermal conditions. The argument has been made that reactions in microflow reactors may be conducted at higher temperatures than in flasks because a better thermal profile may be maintained. A recent report of a multistep flow synthesis of ibuprofen, incorporating several rapid, exothermic reactions in sequence, provides a good example of the exploitation of high surface area for heat transfer in microflow systems.[5a] Can we find a quantitative way to assess this argument for the general case?

Pharmaceutical research and development has a long history of studying the thermal profiles of reactions as a vital part of process safety, and a number of simple calculations have been established that are pertinent to the question of heat-transfer capability at both laboratory and plant scale.[11] As part of any drug development program, all chemical reactions under study will be characterized by a parameter known as the adiabatic temperature rise, ΔT_{ad} [Eq. (1)],

$$\Delta T_{ad} = \frac{\Delta H_{net}}{m_{total} C_{p,r}} \quad (1)$$

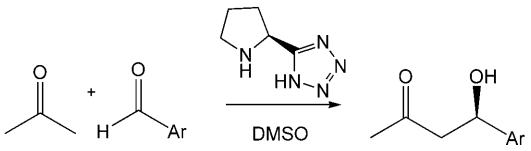
where ΔH_{net} = net heat evolved (in J); m_{total} = total moles of reactor contents; $C_{p,r}$ = average heat capacity of the reactor contents (in $J\,mol^{-1}\,K^{-1}$).

The adiabatic temperature rise characterizes a batch reactor under its worst-case scenario: if all cooling capability is lost, and all reaction heat is therefore retained within the vessel, what would be the maximum rise in temperature of the reactor contents? Knowing this value helps in assessing the possible consequences of a runaway reaction, for example predicting the onset of unwanted side reactions or the pressure buildup in the reactor if the temperature approaches the solvent's boiling point.

An Example from Organocatalysis

Even if we are not in the business of designing pressure vessels to handle worst-case process conditions, we may calculate the adiabatic temperature rise to determine the degree of excursion from isothermal conditions to be expected for a reaction carried out in a laboratory flask with poor heat transfer. This calculation can serve as a means of assessing whether a particular reaction might benefit from the heat-transfer advantages offered by microflow conditions. A recent report by Seeberger and Odedra[12] provides an example for us to consider. These authors concluded that organocatalytic aldol [Eq. (2)] and Mannich reactions could be carried out at higher temperatures and lower catalyst loadings in microflow reactors than in laboratory flask reactors because a better thermal profile can be maintained in the former.

The thermochemical parameters of the aldol reaction of Equation (2) are readily available. The reaction exhibits a thermodynamic heat of reaction of approximately $50\,kJ\,mol^{-1}$. A reaction mixture of 1:1 DMSO/acetone such as that used in the Seeberger study has an average heat capacity of about $139\,J\,mol^{-1}\,K^{-1}$. In that work, solutions of DMSO/acetone and 0.1M aldehyde were prepared with a total volume of 10 mL for pumping to the microreactor. With this



(2)

information we may calculate a worst-case scenario for this reaction, if this entire reservoir volume was instead placed in a reactor flask and the reaction allowed to proceed adiabatically (with no heat removal). The verdict is that the reactor temperature would rise by a maximum of 1.3 °C (see the Supporting Information). Thus at the very worst the aldol reaction of Equation (2) carried out at 60 °C will experience an increase in temperature to 61.3 °C. Of course even gently stirred flask reactors will have some modicum of heat-transfer capability, making the likely temperature excursion even lower, possibly within the limit of the flask's temperature control. This calculation makes it difficult to rationalize any significant difference between behavior in flask and flow for the reaction of Equation (2) on the basis of improved temperature profiles in the flow reactor.

Our own experience with organocatalyzed aldol reactions confirms this conclusion. We studied the reaction of Equation (2) at the lowest catalyst loading used in the Seeberger work. The reaction was carried out both at room temperature and at 60 °C, both in flasks similar to the vial shown in Figure 1 b and in microfluidic chip reactors like that shown in Figure 1 a. Reaction progress was monitored continuously in the flask by reaction calorimetry and confirmed by sampling, and was measured in the microfluidic device by sampling at different residence times. Figure 3 shows that reaction rates were identical in flask and flow. Increasing temperature resulted in an increase in yield, but that increase was the same in flask and flow. The enantiomeric excess decreased slightly with increasing temperature, as expected, but the *ee* values at each temperature were identical for reactions carried out in flask and in flow.

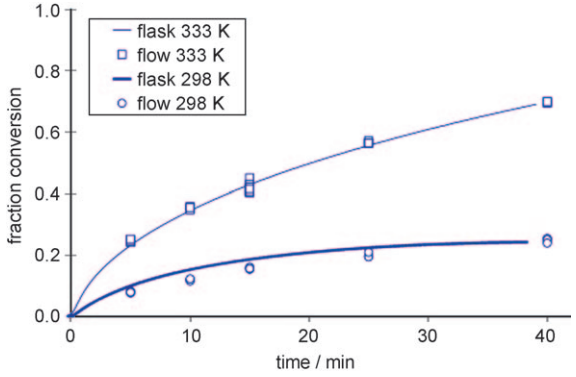


Figure 3. Comparison of fraction conversion versus time for the aldol reaction of Equation (2) (Ar = *m*-ClC_6H_5, 0.5 M; DMSO/acetone 1:1 (v/v), 5 mol% tetrazole catalyst) carried out at 25 °C and 60 °C. Reactions in 5 mL reaction vials stirred with magnetic stirring bars were monitored by reaction calorimetry and confirmed by HPLC analysis (solid lines). Reactions in a microfluidic chip reactor were monitored by HPLC analysis (open symbols). See the Suppporting Information for more details. Product *ee* at 25 °C: (69 ± 3) % *ee*; at 60 °C: (60 ± 3) % *ee*.

What led Seeberger and Odedra to the conclusion that results in flask and in flow are different for this reaction? It may simply be a case of comparing apples (results from the Seeberger lab for flow reactions at 60 °C) with oranges (results from a report by Arvidsson and Hartikka[13] for reactions in a flask at 25 °C), combined with the dangers inherent in inferring conclusions based on simple end-point analysis in the absence of time-course data. Under microflow conditions at 60 °C, it took Seeberger only 20 min to achieve the same yield at the same catalyst loading that Arvidsson reported after 40 h at room temperature. The Arvidsson study reported that a fourfold increase in catalyst concentration was required to achieve this yield at ambient temperature in a reaction time similar to Seeberger's, who cited this as evidence both that the reaction is accelerated in microflow conditions at higher temperatures, and that microflow permits the use of lower catalyst loadings. Batch results at 25 °C were compared to flow results at 60 °C. The catch is that no direct comparison of microflow reactor results at the same catalyst loadings at ambient and elevated temperatures was reported.

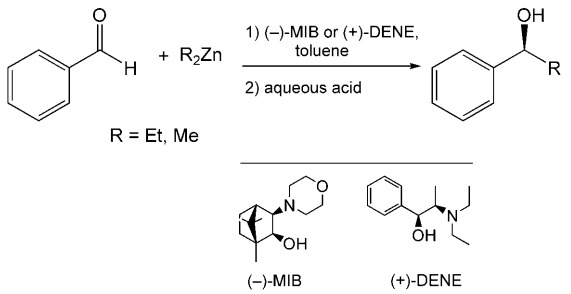
Information gained from following the time course of this reaction helps to reconcile the Arvidsson and Seeberger reports. The conversion profiles shown in Figure 3 reveal that, in both flask and flow, the reaction at ambient temperature becomes extremely sluggish over time, lagging far behind the conversion expected for first-order kinetics. This suggests that the dramatic difference in reaction time between Arvidsson's batch results at ambient temperature and Seeberger's microflow results at elevated temperatures may be attributed to catalyst deactivation at low temperatures and not to the type of reactor employed.[14] The results of Figure 3 reveal that flow conditions do not account for the difference in yield at low and high temperatures, in accordance with the prediction of the adiabatic temperature rise calculation.

Although these results demonstrate that the aldol reaction of Equation (2) may be carried out just as effectively in typical laboratory flasks as in a microflow apparatus, a further important question to address is that of heat-transfer considerations upon scale-up. We may turn again to the experience of pharmaceutical process development, where a common rule-of-thumb states that the heat-transfer rate that plant reactors may safely handle has an upper limit of roughly 50 $W L^{-1}$. If we estimate a rate constant of 0.001 s^{-1} for the reaction of Equation (2), the maximum reaction heat flow under the conditions described above is calculated to be approximately 5 $W L^{-1}$, an order of magnitude below the operating limit, and comfortably within safely scalable operating conditions.

Thus both our calculations and our experimental data, for both laboratory flask and plant scale, fail to support the suggestion that microflow reactors can dramatically shorten the reaction time and allow use of reduced catalyst loadings for the reaction of Equation (2). The thermal profile for the aldol reaction is not difficult to maintain at elevated temperatures in standard reaction flasks or in standard plant-scale equipment. Improved heat transfer is not justified as a rationale for employing flow conditions in this case and cannot account for improved performance.

An Example from Organometallic Chemistry

While these results show that the aldol reaction of Equation (2) does not present a significant challenge for mixing or heat transfer in laboratory flasks or plant-scale reactors, more significant thermal profiles can be exhibited by other organic transformations of higher exothermicity. One such reaction we have investigated is shown in Scheme 1, the



Scheme 1. Asymmetric alkylation of aldehydes by the aminoalcohol catalyst MIB.

asymmetric alkylation of benzaldehyde with dialkylzinc reagents catalyzed by amino alcohols. This reaction is mechanistically complex, exhibiting significant nonlinear effects in catalyst *ee*. Noyori and co-workers have studied this reaction extensively[15] and have demonstrated that the catalyst forms inactive homochiral and heterochiral dimers that exist as reservoirs in equilibrium with active monomer catalysts. Blackmond[16] has noted that in such a case, the strong positive nonlinear effect in product *ee* will be accompanied by a strong suppression in reaction rate.

Organometallic alkylation reactions are typically highly exothermic, and the thermodynamic heat of reaction for the case of Scheme 1 is measured to be about 190 kJ mol^{-1}, roughly a factor of four greater than that of the aldol reaction of Equation (2). The well-studied reaction of Scheme 1 provides an opportunity to compare the flask and flow behavior of a thermally more challenging and mechanistically more complex homogeneous catalytic reaction.

The reaction of Scheme 1 was carried out at room temperature under identical conditions in a stirred reaction flask and in a microfluidic reactor. In both cases the reaction medium is homogeneous, with all species remaining dissolved in solution over the course of the reaction. Under the conditions of these reactions, the adiabatic temperature rise is calculated to be roughly 20 °C, confirming that this reaction presents a significantly greater challenge than the aldol reaction of Equation (2) for effective heat transfer in a flask.

Figure 4 shows the reaction rate and product *ee* for the reaction of Scheme 1 carried out using diethylzinc and (−)-MIB catalysts of varying *ee* values. The reactions in flow and flask exhibit similar behavior. Both modes of operation reveal the strong nonlinear effect in product *ee* as a function of catalyst *ee* that is characteristic of this reaction, and both confirm the predicted rate suppression as catalyst *ee* is lowered. These results suggest that even for this more highly

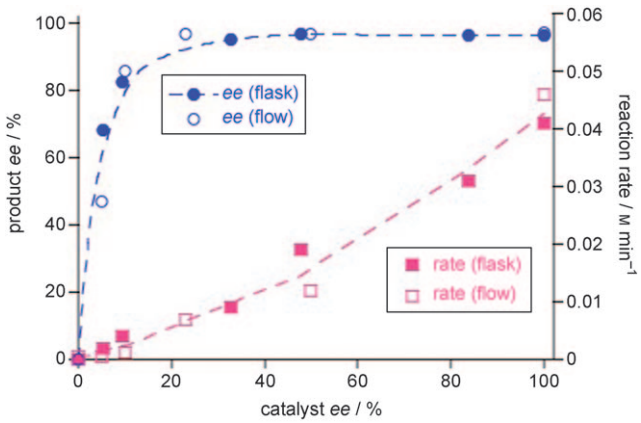


Figure 4. Reaction rate (squares) and product *ee* (circles) as a function of catalyst *ee* for the asymmetric alkylation of benzaldehyde with Et_2Zn catalyzed by 8.5 mol% MIB (Scheme 1) carried out in a reaction vial (filled symbols) and in a microfluidic reactor (open symbols).

exothermic reaction, the simple stirred glass vial is able to remove heat as efficiently as the microflow reactor.[17]

Scaling up dialkylzinc alkylations can present a challenge. The reaction using enantiopure catalyst (Figure 4) requires the reactor to remove approximately 100 W L^{-1} at its maximum, which would not be acceptable on large scale. Therefore we may consider whether operation in a microflow reactor makes sense for this reaction at larger scale. It turns out that such a reaction has been safely and successfully scaled up in a commercial process by Avecia. Interestingly, the process they developed involved neither batch nor flow methods but an optimized plant-scale protocol termed "semi-batch" operation, which many lab chemists will recognize intuitively as a means of controlling exothermic reactions. A solution of dimethylzinc in toluene was fed slowly over time to a 20 L capacity batch reactor containing a toluene solution of benzaldehyde and 5 mol% (+)-DENE catalyst at 60 °C under nitrogen. This operation prevents accumulation of the flammable alkylzinc compound in the reactor and provides a means to control the reaction by metering the potential heat evolution from the reactor over time. Importantly, compared to laboratory studies this protocol had negligible effect on the product *ee*. The process was designed to handle small amounts of methane byproduct formed during the reaction as well as the more significant quantities released during the acidic quench carried out in the same pot. Gases generated during a reaction are more difficult to deal with in a microflow reactor, as they can result in pressure changes, phase splitting and blockage. We may calculate further that if we wish to achieve the same productivity in the same time with a microflow system as with Avecia's semibatch process, we would need to set up an array of roughly 8000 microflow reactors of typical diameters (see the Supporting Information).

Semibatch operation draws on the best of both flow and batch processes, offering a straightforward means of meeting the process safety challenges presented by the thermal profile and flammability considerations, while preserving reaction efficiency and product selectivity. Roberge et al.[18] have pointed out that many reactions amenable to semibatch

operation on account of fast kinetics or high exothermicity might be carried out efficiently using microreactor technology, but they cite the flexibility and versatility of semibatch equipment as the main advantages. Significant gains in yield are required to justify the additional capital expenditure associated with flow technology. In the Avecia example, the semibatch protocol was economically and environmentally more feasible than constructing and operating a microflow reactor array, because no modifications to the standard plant batch reactor were required, and no material losses inherent in the start-up of flow operation were incurred.

A further point is also worth noting: the aim of many microreactor studies is to demonstrate that reaction time may be decreased compared to reaction times in batch reactions. The Avecia scaleup provides an example where optimizing the reaction time would not improve the overall process efficiency. In common with many reactions, the process bottleneck in this case was the workup and isolation of the product, time which must be spent whether the reaction is carried out in batch, semibatch, or flow. This is where the integrated approach advocated in the work of the Ley group,[4] employing microflow sequentially in a variety of unit operations, has much to offer.

Mass and Heat Revisited

We've shown that for many typical single-phase, homogeneous catalytic reactions, neither mixing nor heat-transfer considerations make a general and compelling argument for the use of microflow over batch reactions. In these cases, the choice of reactor generally will depend on the specific goals of the investigation. One advantage of flow operation arises when only very small quantities of reagents are available, as in the early stages of drug development. Microflow operation has also been employed to advantage for rapid screening of catalysts, substrates, and reaction types.[19] High throughput resulting from "scale-out", the setting up of multiple flow reactors in parallel, has also been suggested as an advantage, although, as demonstrated in the example above, this may not be practical in every case and may be more advantageous for the continuous long-term operation more often associated with the production of bulk chemicals rather than pharmaceuticals. These points must be weighed against the added cost of construction and technical complexity of such systems.[20] In current pharmaceutical development, continuous processing has a role in accurately controlling reaction termination and for cases where material buildup and inventory can be important for safety reasons, but these applications are primarily in flow systems larger and less technically complex than micro scale.[21]

Basic Kinetics: The Choice Is Yours

For any new reaction process under development, investigations to ascertain the kinetic characteristics of the reaction—rate constants and concentration dependences—are vital for reaction optimization and successful scale-up regardless of the reactor type to be employed. These parameters are intrinsic to the reaction and thus are scale-transparent and independent of reactor type. We may pose the question: can this basic kinetic information be obtained more efficiently in a microflow reactor than in a flask?

It has been recognized that a key to understanding a reaction's kinetic parameters is observation of its time course.[22] The ability to monitor reaction progress virtually continuously in a flask reactor by a variety of methods (commonly including immersible spectroscopic probes and reaction calorimetry) has become commonplace over the past several decades, while in situ detection remains a key challenge for microflow reactor systems. In the absence of special construction or implementation of special analytical devices,[19] microflow systems rely on discrete sample collection at the reactor outlet followed by analysis, typically by HPLC or an ex situ spectroscopic technique.

Our results (Figure 3) for the aldol reaction of Equation (2) may be called upon to highlight the differences between flask and flow for obtaining intrinsic kinetic information. Reaction progress for the flow system was measured by taking samples at residence times corresponding to different conversions, obtained by a series of changes in the reactant stream flow rates. Changing the flow rate initially produces unsteady-state flow, and the rule-of-thumb is that steady-state operation requires flushing with 1.5 reactor volumes of fluid. If our use of the microflow system is motivated by a desire to save precious material, there may be cause for chagrin upon learning that the five different (conversion, time) data pairs shown in Figure 3 for a given microreactor experiment require more than ten times the total volume of a single reaction. In addition, collecting these samples requires a minimum of 200 min—five times greater than the total reaction time in the flask!

Contrast this with the data density available from our flask reaction using an in situ probe, where we collected roughly 700 separate (conversion, time) data pairs over the course of the 40 minute reaction. Of course, one might envisage ways to emulate this in a microfluidic system by setting up multiple analysis points along a reactor channel, and indeed such methods are under development, but they are clearly technicially far more complex than than the simple immersion of a probe in a flask. It would be difficult to argue that there is any straightforward way at present to obtain hundreds of analytical measurements of reaction progress in a microflow reactor with the ease that we currently can obtain the same information in a flask. In the aldol reaction example, we can make the argument that the information provided by continuous monitoring of this reaction was the key to solving the conundrum presented by Seeberger's comparison of flask and flow methods, which relied on single-point analysis.

Intense research in the area of detection for microflow systems is ongoing,[19] and future developments promise to be exciting. However, at present, the simple reaction flask coupled with in situ monitoring remains the most concise and information-rich means of characterizing the intrinsic kinetic behavior of a typical one-phase, homogeneous catalytic reaction. This remains true whether the process ultimately will be run in batch or in flow at large scale. Indeed,

the measurements required for both process safety analysis and to determine the basic kinetics of pharmaceutical reactions are carried out in batch,[18b] even if the reaction will eventually be run in flow. The intrinsic kinetic information rapidly and efficiently gleaned from in situ monitoring of a flask reactor is valid for the design of flow operation, if that turns out to be a practical solution. The example above leaves us with a clear choice: flow (obtaining a mere five data pairs requires ten reactor volumes of fluid and 200 min), or flask (700 data pairs require only one reactor volume of fluid and 40 min). Given these numbers, why would you choose to go with the flow?

Summary

The decision of whether to run a reaction in a flask or in a microflow reactor must be made on a case-by-case basis. In this Essay, we have offered discussion points to weigh that decision specifically for the case of one-phase, homogeneous catalytic reactions. We have addressed mixing considerations as well as the role of heat transfer, introducing simple calculations that help to assess these issues both at the laboratory and at the plant scale. We argue the case for a simple flask coupled with a probe for monitoring reaction progress as the most efficient and information-rich means of obtaining a comprehensive kinetic analysis that may then be used to help choose the optimal reactor type.

A "road map" is given in Figure 5 to summarize these points. The future for the combination of microflow reactors and organic synthetic chemistry is indeed bright, and many novel and creative applications for these reactor systems will find their place in academic and industrial laboratories. This Essay advocates placing highest priority on considering a holistic picture including careful study of the process thermochemistry and relevant transport phenomena as well as the reaction chemistry and production requirements in order to make the decision wisely.

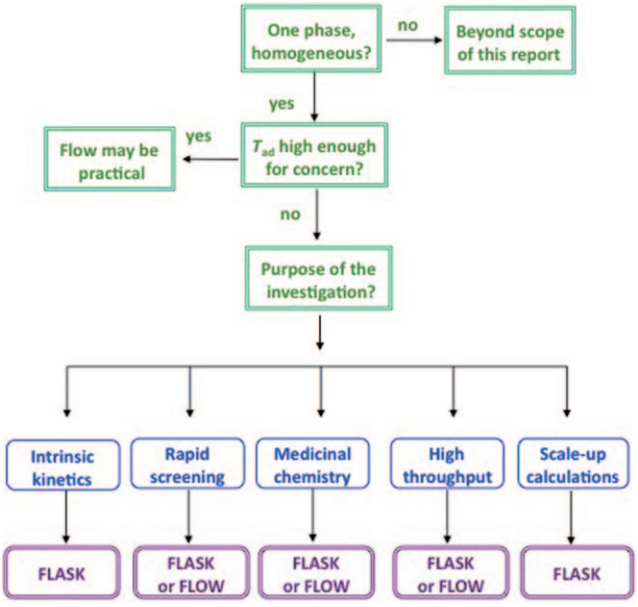


Figure 5. Road map for assessing the feasibility of carrying out a reaction in flask versus in a microflow reactor.

Received: October 29, 2009
Published online: February 24, 2010

[1] The title of this Essay is a rephrasing from Shakespeare: "The plays's the thing…" (Hamlet, Act II, Scene II), which signifies the importance of the "play within a play" in Hamlet's quest for incontrovertible evidence of his uncle's guilt in the murder of his father. Here we assess the evidence for the case that microflow reactors provide more efficient results than flasks for homogeneous catalytic reactions.

[2] A. Manz, N. Graber, H. M. Widmer, *Sens. Actuators B* **1990**, *1*, 244.

[3] a) K. Geyer, T. Gustafsson, P. H. Seeberger, *Synlett* **2009**, *15*, 2382; b) M. Brivio, W. Verboom, D. N. Reinhoudt, *Lab Chip* **2006**, *6*, 329; c) P. Watts, S. J. Haswell, *Chem. Soc. Rev.* **2005**, *34*, 235.

[4] a) I. R. Baxendale, S. V. Ley, A. C. Mansfield, C. D. Smith, *Angew. Chem.* **2009**, *121*, 4077; *Angew. Chem. Int. Ed.* **2009**, *48*, 4017; b) I. R. Baxendale, J. J. Hayward, S. Lanners, S. V. Ley, C. D. Smith in *Microreactors in Organic Synthesis and Catalysis* (Ed.: T. Wirth), Wiley-VCH, Weinheim, **2008**, chap. 4.2, pp. 84–122; c) I. R. Baxendale, J. J. Hayward, S. V. Ley, *Comb. Chem. High Throughput Screening* **2007**, *10*, 802.

[5] a) A. R. Bogdan, S. L. Poe, D. C. Kubis, S. J. Broadwater, D. T. McQuade, *Angew. Chem.* **2009**, *121*, 8699–7802; *Angew. Chem. Int. Ed.* **2009**, *48*, 8547–8550; b) T. Kawaguchi, H. Miyata, K. Ataka, K. Mae, J. Yoshida, *Angew. Chem.* **2005**, *117*, 2465; *Angew. Chem. Int. Ed.* **2005**, *44*, 2413; c) S. Suga, A. Nagaki, J.-I. Yoshida, *Chem. Commun.* **2003**, 354.

[6] a) Z. T. Cygan, J. T. Cabral, K. L. Beers E. J. Amis, *Langmuir* **2005**, *21*, 3629; b) T. Wu, Y. Mei, J. T. Cabral, C. Xu, K. L. Beers, *J. Am. Chem. Soc.* **2004**, *126*, 9880.

[7] T. M. Squires, S. R. Quake, *Rev. Mod. Phys.* **2005**, *77*, 977.

[8] J. Kobayashi, Y. Mori, K. Okamoto, R. Akiyama, M. Ueno, T. Kitamori, S. Kobayashi, *Science* **2004**, *304*, 1305.

[9] J. R. Bourne, O. M. Kut, J. Lenzner, *Ind. Eng. Chem. Res.* **1992**, *31*, 949–958.

[10] Noncontinuum molecular effects can be safely ignored in such liquid microreactors as Knudsen number $Kn \ll 1$ ($=\lambda/L$, the ratio of the molecular mean free path λ and the macroscopic lengthscale L).

[11] *Process Chemistry in the Pharmaceutical Industry* (Ed.: K. G. Gadamasetti), Marcel Dekker, New York, **1999**.

[12] A. Odedra, P. H. Seeberger, *Angew. Chem.* **2009**, *121*, 2737; *Angew. Chem. Int. Ed.* **2009**, *48*, 2699.

[13] A. Hartikka, P. I. Arvidsson, *Eur. J. Org. Chem.* **2005**, 4287.

[14] The strikingly nonlinear kinetics in catalyst concentration reported in reference [12]—a fourfold increase in catalyst loading reducing the reaction time from 40 h to 10 min—would seem to implicate catalyst deactivation even based on this simple end-point analysis.

[15] M. Kitamura, S. Suga, S. H. Oka, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 9800.

[16] D. G. Blackmond, *Acc. Chem. Res.* **2000**, *33*, 402.

[17] The Omnical reaction calorimeter in which these batch reactions were carried out does not employ special reactors, special heat-transfer equipment, or special stirring, but simply a well-controlled isothermal environment. The reactor itself is exactly the vial shown in Figure 1 b, an off-the-shelf, disposable 16 mL glass GC/HPLC vial fitted with a plastic-coated magnetic stirring bar. Thus our protocols for carrying out reactions in flasks match those found in any standard organic chemistry laboratory.

[18] a) D. M. Roberge, L. Ducry, N. Bieler, P. Cretton, B. Zimmermann, *Chem. Eng. Technol.* **2005**, *28*, 318; b) D. M. Roberge, *Org. Process Res. Dev.* **2004**, *8*, 1049.
[19] a) C. T. Martha, N. Elders, J. G. Krabbe, J. Kool, W. M. A. Niessen, R. V. A. Orru, H. Irth, *Anal. Chem.* **2008**, *80*, 7121; b) S. A. Leung, R. F. Winkle, R. C. Wootton, A. J. de Mello, *Analyst* **2005**, *130*, 46.
[20] A recent report by Wirth and Brandt highlights the technical challenges that arise even when flow conditions are warranted on account of hazardous chemicals: J. C. Brandt, T. Wirth, *Beilstein J. Org. Chem.* **2007**, *5*, No.30.
[21] Personal communication, S. P. Mathew, Chemical Research and Development, Reaction Engineering, Pfizer Global R&D.
[22] a) J. S. Mathew, M. Klussmann, H. Iwamura, F. Valera, A. Futran, E. A. C. Emanuelsson, D. G. Blackmond, *J. Org. Chem.* **2006**, *71*, 4711; b) D. G. Blackmond, *Angew. Chem.* **2005**, *117*, 4374; *Angew. Chem. Int. Ed.* **2005**, *44*, 4302.