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Flow chemistry today: practical approaches for optimisation and scale-up

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ABSTRACT

A general methodology is presented as a practical approach to the design of a continuous flow process and its subsequent optimisation and up scaling. Three examples of such designs are shown. The continuous flow Swern-Moffatt oxidation shows that even for ultrafast reactions, the same methodology is still feasible, resulting in an 8.5 g/h synthesis rate. Also, the continuous flow synthesis of explosive azides shows that preparative-scale safety issues at a 1 g/h synthesis rate can be more adequately dealt with. Lastly, as an example of what process automation can accomplish, we present the novel application of an automated screening of a model reaction (the Fischer esterification) with on-line gas-chromatographic analysis. Using this set-up, we found optimal reaction conditions within a working day using minimal amounts of reagents and labour, resulting in the continuous production of the target ester at a 67 mL/h rate.

INTRODUCTION

As continuous flow chemistry is now maturing into a well-established and accepted technology (1-5) it becomes useful for researchers to define a common set of tasks to systematically design continuous flow processes and identify the optimal reaction conditions to successfully synthesise the target molecules on a preparative laboratory or industrial scale.

In this article we present the methodology we developed over the years and which is now routinely employed in our research groups on a large variety of reactions. This methodology is highlighted by a selection of three chemical reactions which were successfully converted into continuous flow processes, thereby exemplifying some major advantages over the corresponding batch processes: (i) the ability to attain sub-second reaction times, (ii) increased safety when handling potentially dangerous compounds, and (iii) automated on-line chromatographic analysis of a microreactor's effluent.

FLOW CHEMISTRY METHODOLOGY

Design of a continuous flow process

Batch processing of a chemical reaction is inherently non-linear. Whenever reactants are being introduced into a vessel, the reaction volume increases over time. Consequently, reaction conditions and mixture composition are constantly changing. As continuous flow chemistry is inherently linear, a chemical reaction needs to be looked upon with a different mindset – stock solutions are introduced into a microreactor at the desired molar ratio and react over the course of the microreactor volume. Thus, in a continuous system every molecule is treated equally, whereas in batch this changes over the course of the process.

One of the main advantages of the linearity of a continuous process is that the reaction parameters are less interdependent than in a batch process. Therefore it is easier to measure the effect of the reaction parameters on reaction behaviour. Linear processes are also much more easily scaled up, since they are effectively always in steady-state. The inherent transient nature of a batch process requires constant time-dependent control mechanisms, while continuous flow chemistry merely requires control mechanisms operating over space.

The industry's challenge now lies in exploiting these benefits such that tightly controlled and reproducible continuous flow processes are realised. We show that such a robust process can be obtained by (i) roughly screening parameter ranges for optimal reaction conditions (e.g. highest yield, lowest reactant costs), (ii) subsequent multivariate optimisation, and (iii) final validation on preparative laboratory scale.

Multivariate optimisation

To provide more insight in a continuous flow process, a multivariate optimisation experiment can be conducted, often in conjunction with a (non-)optimal design. After analysis has extracted all relevant information from the optimisation samples, they can be conveniently fit to a model. From the model, optimal reaction parameters can be selected, depending on the process requirements. It can also be used to obtain information about the kinetics of the reaction and the robustness of the process (6-8).

### Validating on preparative laboratory scale

Once optimal conditions have been identified, the process can be scaled up to a larger reactor to validate the robustness of the optimum, and to perform an actual production run on multigram scale.

CALCULATIONS

Parameter approach

It has been shown empirically that when conducting continuous flow experiments, it is often most convenient to approach an experiment by its reaction parameters. These parameters can be divided into *input parameters* (reaction time, reaction temperature, molar ratio), *intrinsic parameters* (microreactor volume, stoichiometric ratios, concentrations of the used solutions) and *output parameters* (flow rates, microreactor temperature).

47

In this approach, one chooses the input parameters and uses the intrinsic parameters to calculate the output parameters. The relations between the parameters are visualised in Figure 1.

Figure 1. Flow chemistry parameters. Input parameters in blue, intrinsic parameters in green, output parameters in black.
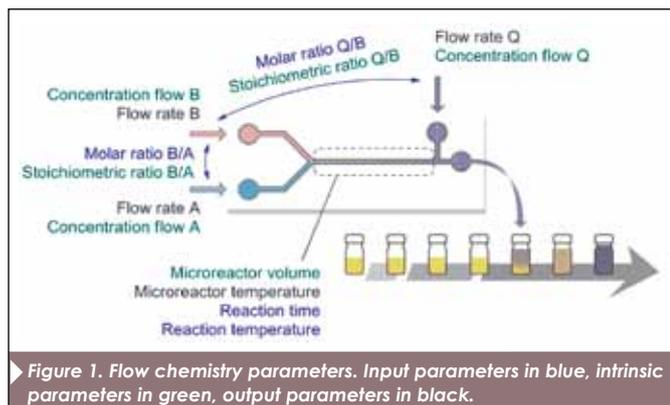
The molar ratio is defined by both flow rates, solution concentrations and the respective stoichiometric ratio between the reactants. The reaction time (or *residence time*) is defined by the microreactor volume, divided by the sum of flow rates through the reaction channel. Note that for more degrees of freedom (less dependency between reactant ratio, reactant concentration and reaction time) an additional solvent flow should be introduced.

Flow markers approach
When looking at the above approach, it becomes clear that the *actual* flow rates (as opposed to the *set* flow rates) largely determine the outcome of a continuous flow experiment. Deviations in flow rates translate to deviations in molar ratio and reaction time, which could lead to erroneous observed results. An approach to circumvent this issue is to add flow markers or internal standards to each solution, which is discussed in detail by Nieuwland et al. (9).

PRACTICAL APPLICATIONS

In the sequel, we briefly present showcases for the complete workflow of designing a continuous flow process, subsequent optimisation and finally validation on larger scale.
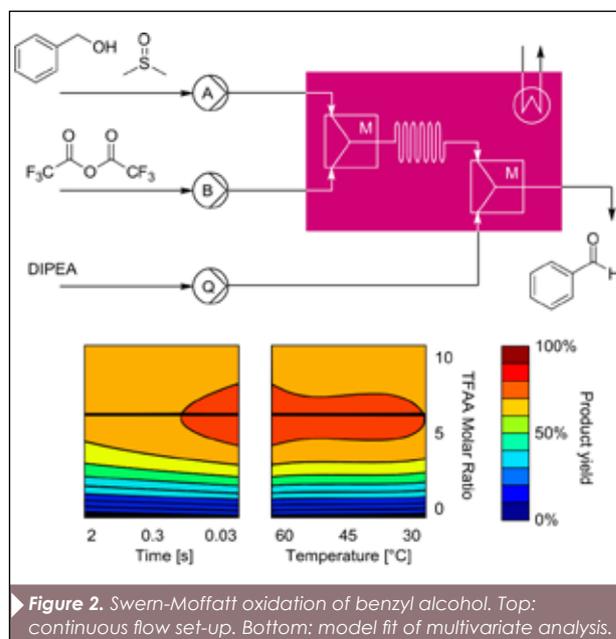
Swern-Moffatt oxidation
One of the advantages of continuous flow chemistry is the possibility of performing ultrafast reactions at elevated temperatures, thereby avoiding the need for slowing down the reaction by excessive cooling (10-12).
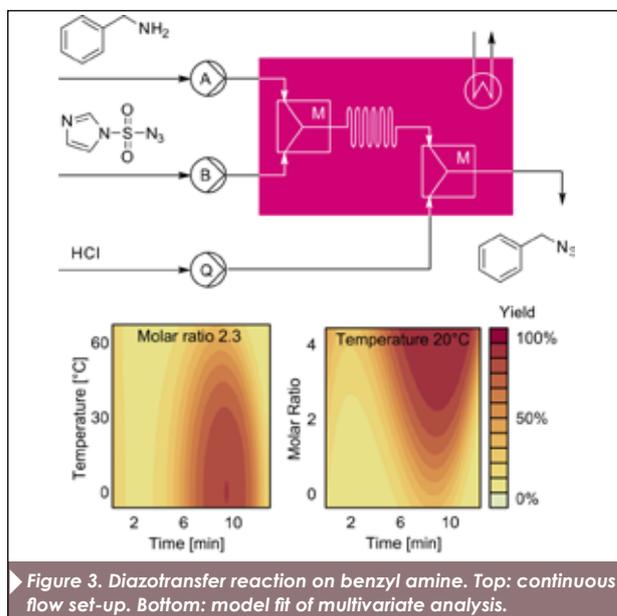This so-called *flash chemistry* is exemplified in the continuous Swern-Moffatt oxidation of primary alcohols (Figure 2), using a sub-microliter microreactor and millisecond reaction times in the *Future*Chemistry *Flow*Start B-200. With the *Future*Chemistry *Flow*Screen C-300 automated optimisation set-up, optimal reaction conditions were found at a reaction time of 32 ms and a temperature of 70°C, which is 150°C above the regular batch reaction temperature (13). A subsequent scale-out of the optimal conditions to a larger reactor in the Uniqsis UQ-1020 *Flow*Syn equipped with a *Future*Chemistry Q1030 microreactor module (4600 times the size of the optimisation microreactor) yielded the target molecule in an 8.5 g/h rate at 89 percent isolated yield (14). This application shows that even for very fast reactions, one-to-one scale-out to a bigger system is still feasible, provided that the reaction has a rather robust optimum.

Organic azide synthesis
Another advantage of continuous flow chemistry is the microreactor's low hold-up volume, offering increased safety when working with potentially explosive compounds at elevated temperatures.

Figure 2. Swern-Moffatt oxidation of benzyl alcohol. Top: continuous flow set-up. Bottom: model fit of multivariate analysis.

Delville et al. showed that it is possible to transform an amine to the corresponding azide in good yield in the *Future*Chemistry *Flow*Start B-200 (Figure 3), using a shelf-stable diazotransfer reagent (15). Multivariate optimisation in the *Future*Chemistry *Flow*Screen C-300 showed declining yields at temperatures above 30°C and reaction time longer than 10 min, probably due to reagent or product decomposition. However, optimal conditions were found which could be scaled up 200-fold to preparative scale in the Uniqsis UQ-1020 FlowSyn equipped with a FutureChemistry Q1030 microreactor module, delivering the target azide at around 1 g/h.

Figure 3. Diazotransfer reaction on benzyl amine. Top: continuous flow set-up. Bottom: model fit of multivariate analysis.

FISCHER ESTERIFICATION USING IN-LINE GC ANALYSIS

One of the most striking advances in microfluidic process intensification is the direct coupling of reaction and analysis apparatus. Most commonly used for this purpose are linear spectroscopy methods (UV-vis, IR, Raman, NMR), which have the added advantage of being able to monitor a fluidic stream in-line (16, 17). On-line chromatographic analysis (HPLC, UPLC, GC) has also been used, which has the added ability to analyse complex reaction mixtures (18-20). Using these methods, it is now possible to directly analyse a microreactor's effluent without the need of

manual sample-taking, decreasing both effort and the possibility of inducing errors. In addition, the inherent compatibility of both a reaction and the analysis being in continuous flow, the need of using expensive and error-prone autosamplers is eliminated.

The Fischer esterification was used as a model reaction in an automated optimisation, using an on-line GC method. A conventional GC system was coupled to a *Future*Chemistry *Flow*Screen C-300 microreactor system with a sample loop valve, which was automatically controlled by uploading a set of experimental data points to the system's hardware. This set-up provided a fast way to obtain in-depth knowledge about a continuous flow process through multivariate optimisation, without the need for sample-taking and subsequent work-up steps. The set-up shown in Figure 4 was used to rapidly screen the Fischer esterification using gas chromatography. After stabilisation of the microreactor system, the sample loop valve switched to *inject* mode with a subsequent burst of injection solvent to initiate a new measurement. The remaining time, the valve was in *load* mode, during which the sample loop was continuously filled with the microreactor outflow.

Multivariate optimisation

In the optimisation of the Fischer esterification, three parameters (reaction time, temperature and molar excess ratio) were varied using a D-optimal selection of 40 data points (21). The used ranges are given in Table 1.

Parameter	Range
Reaction time (min)	1.0 to 10
Temperature (°C)	30 to 90
Molar ratio (alcohol/acid)	0.5 to 2.0

▶ *Table 1. Parameter ranges for the optimisation of the Fischer esterification.*

After analysis, the experimental data were processed using the *Flow*Fit software package to obtain a reaction model fit with an average (but well-distributed) residual error of around 5 percent between actual and predicted ester yield. The resulting model showed that ester yield improved with either one of the three parameters increasing. Chromatographic yields above 95 percent were observed at a temperature of 90°C, reaction time of 7.0 min and alcohol molar ratio of 1.8.

Scale-out to preparative scale

The above optimal parameters were scaled out 200-fold using the Uniqsis *Flow*Syn with a 20 mL stainless steel coil reactor heated at 90°C. The experiment was run for 22.5 min, yielding around 25 mL isoamyl acetate (GC pure) after work-up. This corresponds to a 73 percent isolated yield at a 67 mL/h synthesis rate. The relatively low isolated yield is attributed to sub-optimal distillation equipment and close boiling points of the product and the alcohol.

CONCLUSION

We have established a readily usable method for designing, optimising and validating continuous flow processes.

These methods are becoming widely established thereby clearly demonstrating that flow chemistry is transforming from an academic novelty to a widely applicable technology.

The examples of flow chemistry processes clearly show the benefits: ultrashort reaction times can readily be employed due to excellent heat and mass transfers, operating conditions and safety are improved due to inherent confinement of the reagents and reactive intermediates.

Furthermore, analysis coupling and process automation pave the way to obtain fast knowledge about a chemical reaction. In that way, and using the inherent benefits of flow chemistry, the complete trajectory of designing chemical processes, up to performing them at industrial scale can be streamlined and drastically shortened.

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49

▶ *Figure 4. Flowchart illustrating automated optimisation. GC injection pathway in blue.*