RATE-BASED DESIGN OF EXPERIMENTS USING CONTINUOUS-FLOW REACTORS

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Abstract

Continuous processing is revolutionizing drug discovery and manufacture. In this paper we present rate-based design of experiments (rDoE) as a robust scale-up workflow for the development of flow processes. rDOE cycles through evolution of the system's kinetic motif and the generation of additional experimental data. The scope of the approach is demonstrated on reaction case studies in which small-scale continuous-flow reactors are employed to collect reaction profiles. The case studies demonstrate that the development of rate models for new complex organic reactions does not require significantly more development resource than optimisation of the laboratory conditions.

Keywords

Experimental design; kinetic motif; rate models, continuous processing; flow chemistry; scale-up.

Introduction

The recent uptake of continuous processing in the fine chemicals industry needs to be supported by scale up strategies that allow for changes in technology and operating conditions whilst minimising the scale up risk. Within the bulk and commodity chemical sectors scale-up, is approached by using predictive methods informed by physical properties and process rates obtained from small-scale experimentation (Stitt, 2002). In contrast, design of experiments (DoE) is a popular optimisation approach within the fine chemical industries for scale-up (Owen *et al.*, 2001). DoE requires no or little *a priori* knowledge of a reaction system. A polynomial model is developed based on the experimental observations rather than on physical relationships which exist within a system; this allows optimisation within the narrow experimental region covered, but should not be used to extrapolate (Lendrem *et al.*, 2001). Mechanistic models for the formation of complex organic molecules are perceived to be difficult to obtain, especially when transport and reaction mechanisms are not understood (Paul, 1988). Biological processes are inherently complex, with large numbers of equilibrium and rate constants, making it difficult to arrive at a full kinetic model. Thus kinetic motifs are used to represent the dynamics of biological systems in a simplified manner (Grant, 2012). In this paper we apply the concept of kinetic motifs, within the context of experimental design to build an understanding of rate processes relevant to pharmaceutical manufacture.

Results and Discussion

To efficiently evolve a kinetic motif, whilst not entailing excessive experimentation, we developed rate based design of experiments (rDoE) in which a kinetic motif evolves and is validated in a continuous cycle of learning and exploration (Hone *et al.*, 2015). rDoE has three distinct phases (Figure 1): (1) the selection of experiments and their execution in a reactor; (2) fitting a kinetic motif, including the estimation of the reaction parameters (e.g. activation energies and rate constants) and evolution of the motif if required; and (3) evaluation of confidence. With each iteration, confidence in the predictive capability grows and eventually, the model can be used to explore other processing options, equipment configurations and operational scales. The workflow for the evolution of kinetic motifs in flow through a rDoE methodology is exemplified using a Paal–Knorr reaction (Scheme 1). The reaction is known to be second order, providing a rationale for the initial motif and experimentation in which

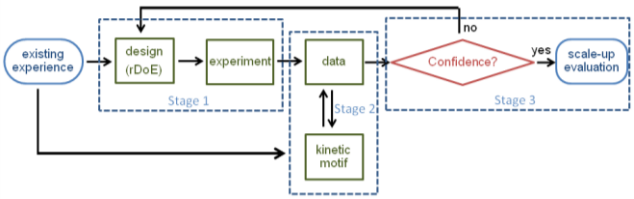


Figure 1 Workflow for the evolution and validation of kinetic motifs.

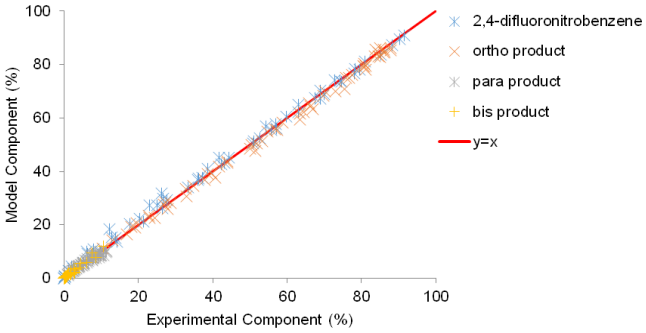
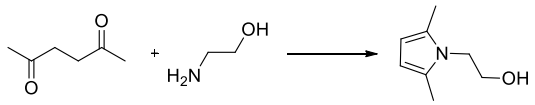


Figure 2. Predicted vs experimental fractions of the aromatic compounds of the SNAr system shows that all conditions encountered are predicted well

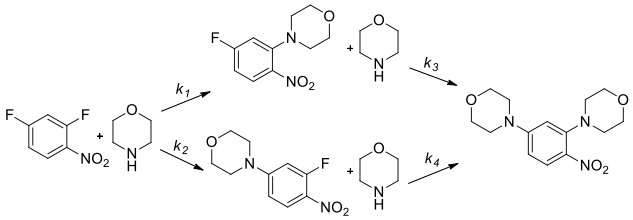
concentrations, ratios and temperature were changed to confirm this behavior.



Scheme 1. Paal–Knorr pyrrole synthesis

Subsequently we considered the influence of water concentration, not predicted by the original motif. This required the kinetic motif to evolve by including an equilibrium.

Novel process windows, such as the use of high temperatures, high concentrations and high pressures, can be accessed using continuous-flow reactors (Hessel *et al.*, 2013). To arrive at a kinetic motif which best encompasses the reaction system, the largest possible process window should be explored within a rDoE: ranging from the mildest (e.g. dilute, low temperature) to the harshest which is feasible in the equipment (e.g. concentrated, high reagent to substrate ratios, high temperature). This concept is demonstrated on a multistep aromatic nucleophilic substitution (S_NAr) reaction of 2,4-difluoronitrobenzene with morpholine to give a mixture of products (Scheme 2).



Scheme 2. Multistep S_NAr reaction.

Mild conditions allow evaluations of k_1 and k_2. Harsher processing conditions are required to generate sufficient quantities of the over-reacted di substituted species to allow evaluation of k_3 and k_4. Using the broad process envelope afforded by flow reactions gave sufficient confidence in the all rate contents of scheme 2 without the need to study intermediates in isolation. The model gave an excellent fit to all the data of each of the components, Figure 2. The kinetic motif provided extrapolates in-line with intuition based on experience. Conventional experimental designs (DoE) focus on optimising laboratory conditions. These typically result in a statistical model that can only be used for interpolation (Table 1).

Table 1. DoE vs rDoE.

Comparisons	DoE	rDoE
Needs little existing understanding	✓	✓
Process-relevant conditions	✓	✓
Prediction in different equipment	X	✓
Opportunity to extrapolate	X	✓

Conclusion

Rate based experimental design has been demonstrated to generate rate-models with reasonable accuracy but requiring similar development resources than conventional development focussed on optimisation of conditions. The kinetic motif underpinning the rate model evolve over time as the process window studied is enlarged. The use of small-scale continuous-flow reactors significantly accelerates the experimentation, and in addition allows for exploration of a wider design space than conventionally possible, thus providing additional confidence in the rate model. The kinetic motif can be used *in silico* to predict the process outcomes for new conditions, equipment or processing scale.

Acknowledgments

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