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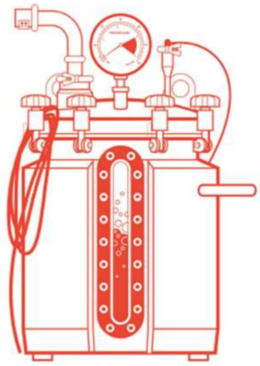

Modeling-Based Approach Towards Quality by Design for a Telescoped Process.

This Zahnd

Bachelor thesis, Chemical Process Technology

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Abstract

A synthesis step, consisting of two sub-steps A and B was investigated by applying a model based approach. Deepening the process understanding was achieved through performed experiments, which also led to the generation of valuable knowledge for future improvements. A kinetic model consisting of 12 reactions and 15 components was successfully established. The model predicts the effects of changes in process parameters on quality. On this basis recommendations for process optimizations have been formulated.

Introduction

The applied approach is aimed towards continuous improvement by persisted reevaluation of process understanding based on new knowledge available.

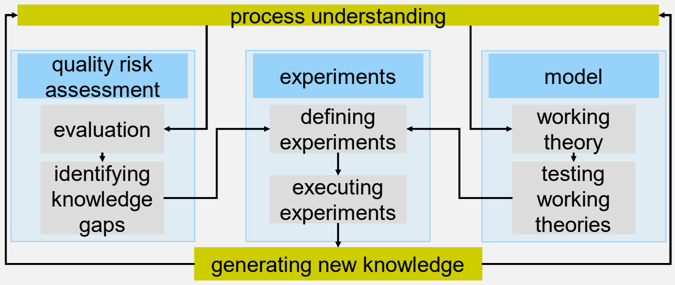

Figure 1: quality by design approach - general strategy for a kinetic model.

The investigated synthesis is a *N*-demethylation over two steps:

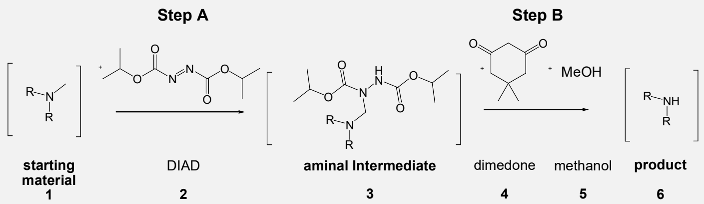

Figure 2: synthesis scheme for the investigated synthesis steps.

Concentrations of starting material and product were obtained through HPLC-measurements. The kinetic model was established based on experiments with varying process parameters. Some model parameters were also obtained based on the evaluation of dynamic DSC experiments.

Figure 3: experimental setup. 1: reactor; 2: dosing pump; 3: stirrer; 4: automated sampler; 5: scale for dosing pump

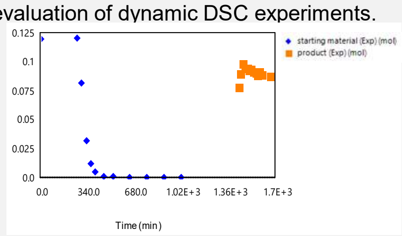

Figure 4: example of experimental HPLC data acquired.

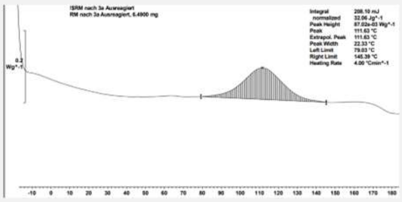

Figure 5: example of a DSC-measurement used to model decomposition reaction.

Results

These kinetic parameters were used to establish a kinetic model. It is able to predict the process in the normal operating ranges (NORs) of the quality relevant process parameters with an adequate accuracy.

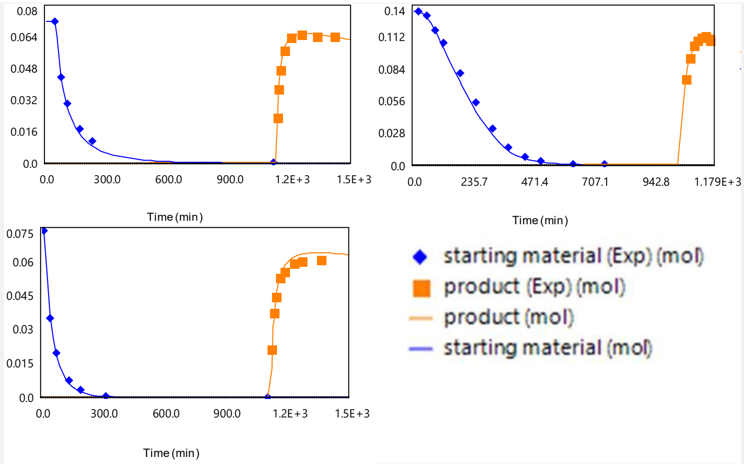

*Figure 6: comparison of selected experimental data (points) with model prediction (solid lines) of starting material **1** in blue and product **2** in orange.*

Contour plots were created using Dynochem® through multiple simulations. These simulations were done with varying process parameters to examine their effects on a process response. Based on these, new NORs are defined that are predicted to meet the quality standard.

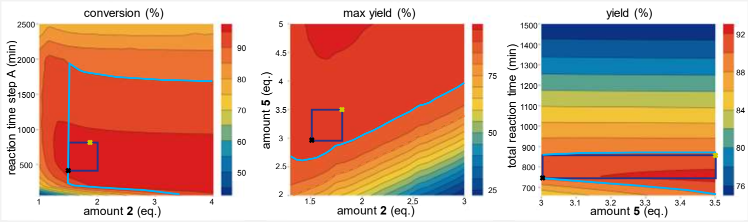

Figure 7: selected contour plots. Light blue line is the quality limit based yield, and the dark blue box are the NORs. Black and Yellow x represent the conditions used in verification experiments performed.

Verification experiments of the model were then performed applying new optimized process parameters.

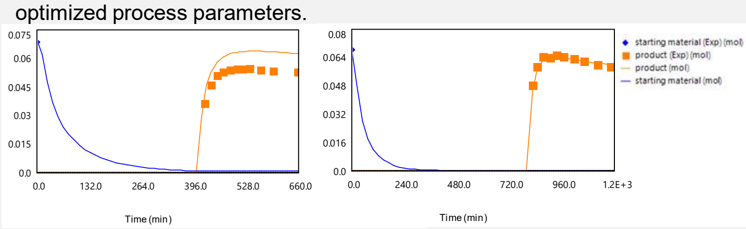

Figure 8: comparison of predicted product amount/time curves and measured data for verification experiment 1 (black cross in Figure 7) on the left and verification experiment 2 (yellow cross in Figure 7) on the right. Orange is product, blue is starting material, solid lines are model predictions, squares are measured data points. Green solid line is 90% yield.

The second verification experiment matches model predictions, with a yield of 96%. The discrepancy observed in the first verification experiment shows the limits of the model and will be a valuable starting point for future improvements to the process understanding.

Conclusions

A kinetic model for the investigated process steps was successfully established with fitted kinetic parameters that are able to predict process responses. The observed discrepancy between the model prediction and the first verification experiment is only present in experiments at low DIAD **2** concentrations was already shown to arise from a DIAD **2** decomposition that can be investigated in the future. Thanks to the increased process understanding resulting from this work, improvements to the process have already been made. Further optimizations based on the newly generated knowledge are expected to not only be direct improvements of the process, but also enhancements made to control strategies. The developed workflow can also be applied to other processes, enhancing upcoming and preexisting R&D efforts.