

# Gaining Kinetic Insights into Knorr Pyrazole Synthesis via Transient Flow Experiments

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## Highlights

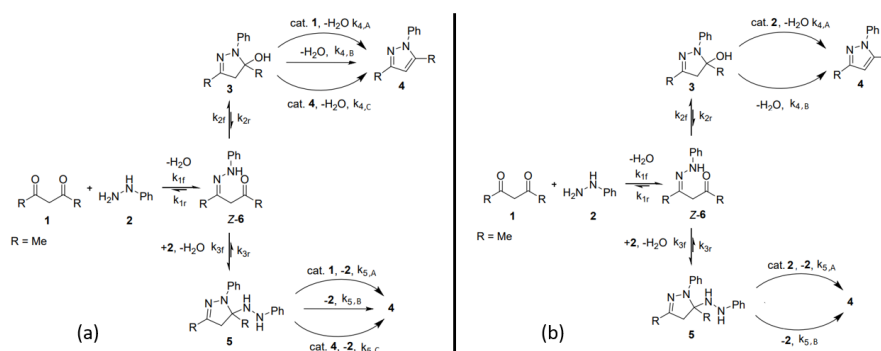
- Time-series kinetic data was generated via transient experiments.
- Kinetic model reduction techniques were used to assess plausible reaction networks.
- Model fitting and uncertainty suggest the feasibility of different reaction mechanisms.
- MbDoE was conducted for future transient experiments and model discrimination.

## 1. Introduction

The condensation of substituted diketones with phenyl hydrazine is a promising synthetic route for the production of substituted pyrazoles. Despite this, previous kinetic studies in literature have mainly been of qualitative nature<sup>[1]</sup>. As such, the development of a kinetic model capable of describing the influence of key reaction parameters (such as feed ratios, reactant substituent groups, or pH) on the product formation rate and regioselectivity remains a challenge. Moreover, a fundamental requisite in the construction of kinetic models for complex chemical systems is the availability of reliable and informative kinetic data. In the present work, high-throughput transient flow experimentation techniques were coupled with model construction and discrimination methodologies to aid in the identification of reaction networks and kinetic models capable of describing the Knorr pyrazole synthesis.

## 2. Methods

A description of the experimental setup can be found in our previous work<sup>[2]</sup>. Two competing reaction networks (Fig. 1(a) and Fig. 1(b)) were initially proposed in consideration of the gathered data and literature observations. The discrepancy between the two mechanisms concerns the final aromatisation steps; these are assumed to be product- and diketone-catalysed steps in Model 1 whereas they are hydrazine-catalysed in Model 2. The kinetic constants in the proposed mechanisms were fitted from the gathered time-series data through the formulation of a dynamic parameter estimation optimisation problem presented in Eq. 1(a)-Eq. 1(c). The objective function Eq. 1(a) is a modified least-squares expression incorporating a sparsity regularisation term which penalizes the number of non-zero reaction constants. This in turn means that model fitting and model reduction (e.g. deletion of kinetically negligible constants) were performed simultaneously.



**Figure 1.** Proposed networks for Knorr Pyrazole Synthesis. (a) Model 1 adapted from<sup>[2]</sup>; (b) Model 2.

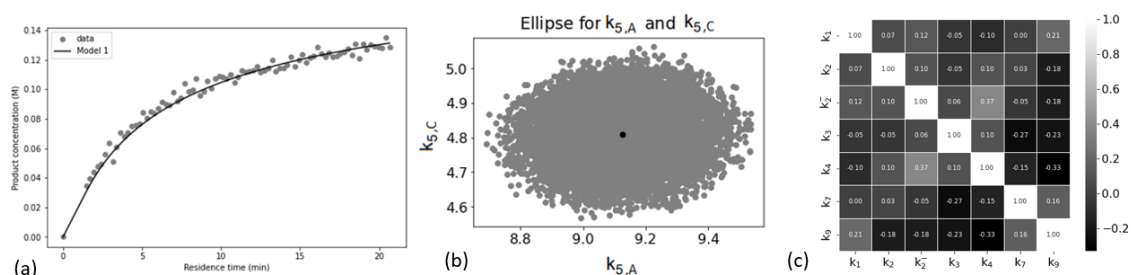
$$\min_k \sum_{i=1}^{N_p} (C_{i,E} - C_{i,S})^T \Lambda (C_{i,E} - C_{i,S}) + \omega_s \sum_{j=1}^{N_k} \frac{k_j}{k_j + \varepsilon} \quad \text{Eq. 1(a)}$$

$$\text{st. } \frac{d\mathbf{C}}{d\tau} = f(\mathbf{C}, \mathbf{k}); \mathbf{k}_{lb} < \mathbf{k} < \mathbf{k}_{ub} \quad \text{Eq. 1(b)}$$

where  $\mathbf{C}_{i,E}$  and  $\mathbf{C}_{i,S}$  are vectors for the experimentally measured and simulated concentrations of species, respectively.  $\mathbf{A}$  is a weighting matrix used to scale the residuals and  $\omega_s$  is the penalty weight. The number of datapoints is denoted by  $N_p$ , while  $N_k$  refers to the number of kinetic constants  $\mathbf{k}$  in a proposed reaction network. The underscripts *lb* and *ub* denote lower and upper bounds, respectively. Following parameter estimation, uncertainty analysis ensued. Parameter joint confidence intervals and correlation matrix were then computed from the covariance matrix.

### 3. Results and discussion

For both proposed networks, non-catalysed aromatisation steps were found to be kinetically negligible. The initial nucleophilic attack and ring-closure reactions were also deemed to be irreversible.



**Figure 2.** (a) Model 1 fitting results for a residence time ramp experiment with acetyl acetone reactant; (b) Joint confidence ellipsoid for two kinetic parameters in Model 1; (c) Correlation matrix for kinetic parameters in Model 1.

The reduced kinetic models exhibited good fitting performance as exemplified in Fig. 1(a), with overall mean percentage errors of 3.27% and 3.63% for Model 1 and Model 2, respectively. Furthermore, the computed parameter confidence intervals and correlation matrix suggest that most of the estimated parameters are well-identifiable and statistically uncorrelated, as shown in Fig. 1(b) and Fig. 1(c).

Despite incorporating significantly different assumptions on the final aromatisation steps, the two proposed models yielded similar fitting accuracy on the gathered time-series data. A model-based DoE methodology was therefore adopted to identify the optimal feed conditions that would enable discriminating among the two models.

The optimal feed concentrations for the discriminatory experiment were determined to be  $C_{Diketone} = 0.4$  M,  $C_{PhHy} = 0.186$  M,  $C_{Pyrazole} = 0.2$  M and  $C_{H_2O} = 0.014$  M. Over a residence time of 20.6 min, the product concentration predicted by Model 1 is 0.03 M higher than that predicted by Model 2. This can be rationalised with reference to the optimised feed conditions ( $C_{Diketone}, C_{Pyrazole} > C_{PhHy}$ ) and the key dissimilarities between the proposed mechanisms.

### 4. Conclusions

In view of the postulated reaction networks, a kinetic model construction methodology incorporating sparse regression approaches was successfully applied to analyse time-series kinetic data on the Knorr pyrazole reaction. The reduced kinetic models achieved satisfactory fitting accuracy and low parametric uncertainty, thus suggesting the advantage of high throughput data generation through transient flow experiments. Finally, a MbDoE methodology was adopted to discriminate among the proposed models, which will guide the selection of an appropriate model structure for future transient flow studies.

### References

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- [2] Schrecker, L., Dickhaut, J., Holtze, C., Staehle, P., Vranceanu, M., Hellgardt, K., & Hii, K. K. (Mimi). (2023). *React. Chem. Eng.*, 8(1), 41–46.

### Keywords

Pyrazole synthesis; Kinetic modelling; Transient flow experiments.