Development of a Modeling-Based Strategy for the Safe and Effective Scale-up of Highly Energetic Hydrogenation Reactions

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Supporting Information

ABSTRACT: A modeling-based strategy is disclosed for identifying reaction conditions for the safe and effective scale-up of highly energetic hydrogenation reactions. The model was developed within Scale-up Systems's DynoChem 2011 and takes under consideration the kinetics of the reaction, the reactor heat transfer capabilities, and the degree of mass transfer. Fourier transform infrared spectroscopy (FT-IR), heat flow, and H₂ uptake data were used to determine the reaction kinetics that were found to be most accurately described by a Langmuir—Hinshelwood type model. The scale-up model was validated within our kilo-laboratory using a 5 L reactor.

INTRODUCTION

The batchwise reduction of aromatic nitro groups to their corresponding anilines in the presence of H₂ and a suitable catalyst is a key step in the manufacture of numerous pharmaceutical intermediates. These reactions are usually highly exothermic, and their successful scale-up necessitates understanding the mixing performance of both the development-scale and proposed plant-scale reactors.¹⁻⁴ The rate of gas uptake in any gas-liquid-solid reaction, in this case a hydrogenation, is dependent on the interplay of two factors: supply-namely mass transfer, both of gas into the liquid and then from the liquid to the solid phase—and demand—the rate of gas consumption by the reaction.⁵ The driving force behind the dissolution of a gas into a liquid is the magnitude of the difference between the current gas concentration in the liquid and the maximum possible concentration of gas in that liquid at the saturation point. The saturation point is affected by the temperature, the pressure, and the solvent and is defined by Henry's Law. The gas-liquid mass-transfer coefficient, or k_1 a, is the rate constant for the dissolution of a gas into a liquid and is dependent on the surface area of the gas-liquid interface which is itself highly dependent on the degree of mixing. In the case of a hydrogenation, if the $k_{\rm L}$ a is much larger than the rate of the reaction, the concentration of H_2 in solution is maintained near the saturation concentration and the reaction is said to be kinetically controlled. However, if the $k_{\rm L}a$ is much smaller than the rate of the reaction, then the solution hydrogen concentration is close to zero, the catalyst is starved, and the reaction rate is retarded-this is described as mass-transfer control. Assuming other mass-transfer processes (namely liquid-solid mass-transfer) are not rate-limiting, then it is possible to modulate the reaction rate and consequently the rate of heat evolution by varying the $k_{I,a}$ and hence the rate of hydrogen uptake. A cautionary note is that catalyst starvation resulting from operating under mass-transfer control could potentially lead to catalyst denaturation and subsequent loss of catalytic activity. This has the potential to alter the selectivity of the reaction and result in changes to the impurity profile, meaning this approach should optimally be considered early in development to ensure that a product of acceptable quality is manufactured.^{6,7}

Recently, the heterogeneous hydrogenation of nitropyrimidine 1 was scaled-up to an 11 kg scale in a 200 L hydrogenator (Scheme 1). This reaction proved to be highly exothermic (a 20 °C exotherm was recorded within the first 20 min of the reaction in spite of maximum cooling power being applied) and the hydrogen dosing system was found to be unable to keep up with demand. As a result the operator was required to periodically adjust the agitation speed in order to control the exotherm and maintain the batch temperature within the desired range. A subsequent investigation showed that during process development the reaction had always been performed under mass-transfer control and in a system capable of very efficient heat removal, whereas in the pilot plant, due to the reduced surface area to volume ratio available for heat exchange, the heat removal capabilities were significantly lower, and the system was incapable of controlling the exotherm. As a result, a project was initiated to better understand the dependence of the reaction profile on the degree of gas-liquid mass-transfer and to develop a strategy to predict the reaction conditions required for optimum performance on scale, minimizing plant time while ensuring safety and desired product quality.

In this paper a scale-up strategy for highly exothermic hydrogenation reactions is reported based on the creation of a suitable computational model that considers the kinetics of the reaction, the reactor heat transfer capabilities as well as the degree of gas—liquid mass-transfer. The model is able to predict both the kinetic and temperature profiles of the hydrogenation

Special Issue: Safety of Chemical Processes 14

Received: June 26, 2014





of nitropyrimidine **1** with varying temperature, pressure, substrate loading, catalyst loading, and agitation rate and has been used to predict performance upon scale-up. Fourier transform infrared spectroscopy (FT-IR), heat flow, and H_2 uptake data were used to construct a suitable kinetic model within Scale-up Systems's DynoChem 2011 which was then employed to simulate various scenarios and select appropriate process parameters.⁸ These parameters were then validated experimentally.

EXPERIMENTAL SECTION

Experimental Set-up. The hydrogenation of nitropyrimidine 1 was performed in a Mettler Toledo RC1 reactor system equipped with a 1 L glass pressure vessel rated to 90 psia, a gassing impeller (Rushton turbine with a gassing shaft), a single beavertail baffle, temperature probe, calibration heater probe, an in-line FT-IR probe and a double-valve dip-tube sampling system (see the Supporting Information for a PI&D of the experimental setup). All reactions were conducted at a constant H₂ pressure which was delivered using a Büchiglasuster BPC controller through a PKP thermal mass-flow meter calibrated for H₂. The number of moles of H₂ consumed during the reaction was calculated by integrating flow rate over time and subsequent conversion of the cumulative H₂ volume into moles using the ideal gas law.

High-pressure liquid chromatography (HPLC) calibration curves were generated for nitropyrimidine 1 and amide 5 using an Agilent 1100. Aniline was used during the reactions as an internal standard to ensure reproducible sampling and normalize peak area. Off-line HPLC analysis was conducted by removing samples (3-5 mL) through a double-valve diptube, which avoided the need to depressurize the systemmultiple blank samples were removed between samplings to prevent cross contamination. The fleeting intermediates nitroso 2 and hydroxylamine 3 (Scheme 1) were never observed in sufficient amounts, nor were standards available to allow for quantification so they were not tracked.

The FT-IR measurements were conducted using a ReactIR 45m system with a DST 9.5 mm \times 1.5 m \times 305 mm DiComp probe through the icIR software, both developed by Mettler Toledo. Differences in the spectra between 1125 and 1800 cm⁻¹ were correlated to off-line quantitative HPLC data and molar hydrogen uptake data using a partial least-squares (PLS) model. As the objective was to study the hydrogenation and not the secondary cyclization, and since the latter was found to

occur concurrently with the reduction step, for the purposes of measuring conversion both aniline 4 and amide 5 were combined into a single product species. In order to minimize the error and increase the sensitivity of the model, the second derivative of the raw data was used, and additional baseline correction and scaling were found to be necessary in order to normalize the data to accurately reflect both the initial charges of nitropyrimidine 1 and the actual conversion to aniline 4 and amide 5, as measured by HPLC. The FT-IR model was validated by leave-one-out cross-validation (LOOCV) and shown to be robust with R-squared values of 0.993 when compared against the training points and 0.979 when compared against the test points. This approach was able to extract trends from the FT-IR data that matched the reaction profile as measured by HPLC and enabled molar reaction data to be obtained without requiring off-line analysis, although samples were taken periodically to confirm the continued accuracy of the FT-IR model. Separate FT-IR models were generated for each temperature investigated to account for the temperaturedependent intensity changes of the IR spectra.

Heat-flow calorimetry was used to determine the heat flow into or out of the reaction system. The reaction temperature was controlled isothermally via the modulation of the jacket temperature. The heat flow is directly proportional to the difference of the reaction and jacket temperatures defined by the equation: $Q = UA(T_r - T_j) [Q = \text{heat flow (W)}; U =$ overall heat transfer coefficient $(W/(m^2/K))$; A = heat transfer area (m²); T_r = reaction temperature (K); T_i = jacket temperature (K)].9 The UA of the vessel was determined by applying a known amount of power via a calibration heater probe immersed in the reaction mixture and measuring the resultant change in both reaction and jacket temperatures. The reaction heat flow Qr was then calculated from the total heat flow, Q, after accounting for any other heat flows present including heat loss to the surroundings and the heat capacity of the reaction mixture.

Determination of Mass-Transfer Coefficients. The mass-transfer coefficients were determined according to the batch absorption method.^{10–13} Each experiment was conducted in triplicate and the average $k_{\rm L}$ a value determined for each condition investigated. In order to avoid introducing error, the system leak rate was measured prior to each run and was always found to be insignificant with respect to the rate of mass-transfer induced pressure drop (typically <1 mbar/min). A statistical model was developed within JMP 9.0.0 (SAS Institute Inc.) that was then used to predict mass-transfer coefficients for

Chart 1. Data collected during the laboratory-scale evaluation of the plant conditions (agitation started at the 4 min time-point)



our laboratory reactors with varying reactor fill-volume, agitation speed, pressure, temperature, and solvent (see the Supporting Information for the experimental procedure for the determination of $k_{\rm L}a$, as well as further information on the generation of the model).

General Experimental Procedure. All reactions, unless otherwise stated, were run on a 50 g scale (nitropyrimidine 1 as the limiting reagent). The solvent, THF, was charged to a clean, dry, nitrogen flushed 1 L jacketed pressure reactor followed by all the solids (nitropyrimidine 1, ammonium metavanadate and Johnson Matthey 3% Pt/C catalyst, type B502032-3, 50% wet -not corrected for water content) and finally acetic acid. The reactor was sealed and inerted by performing three N2 pressurevacuum cycles (pressurized to 30 psia N_2) while agitating above the impeller gassing speed (in this case at 500 rpm) with all solids being visually well-suspended. The reaction mixture was then heated to the desired temperature, and a calibration was performed using the calibration heater probe in order to obtain the initial UA and heat capacity values. The reactor was inerted again by performing three N2 pressure-vacuum cycles (pressurized to 30 psia N_2) before suspending the agitation and exchanging the headspace atmosphere for H₂ by performing three pressure-vacuum cycles (pressurized to 30 psia H_2). The desired pressure of H₂ was then set, and the reaction was initiated by switching on the agitator at the desired set point. The temperature (both reaction and jacket), pressure, hydrogen flow, and FT-IR data were recorded, and samples for offline HPLC analysis were removed through the double-valve dip tube as required (the sampling lines were rinsed between samples with enough THF such that the waste solvent was visibly free of particulates). Finally, after the reaction had reached completion, the calibration was repeated using the calibration heater to obtain the final UA and heat capacity values.

RESULTS AND DISCUSSION

Evaluation of Plant Conditions. An experiment was initially conducted in the RC1 calorimeter to evaluate the plant conditions of 20 °C, 30 psia H₂, THF (5 L/kg), acetic acid (2 equiv), NH₄VO₃ (5 wt %), and 3% Pt/C catalyst (20 wt %). The agitation speed was set as high as possible (2000 rpm) in order to ensure a high mass-transfer rate. Hydrogen uptake, FT-IR, and heat flow data were all consistent with each other, showing reaction completion within 30 min and demonstrating that reaction conversion can be monitored in three different ways (Chart 1).¹⁴ Moreover, the reaction was, as expected, highly exothermic with a heat of reaction of 634 kJ/mol of reactant corresponding to a theoretical adiabatic temperature rise of 97.5 °C. Under these conditions the reaction was not isothermal, and a temperature rise of 14 °C was observed as shown in Chart 1.

Effect of Ammonium Metavanadate. Ammonium metavanadate is a common additive that was included in the original reaction conditions in order to reduce the amount of hydroxylamine 3 present during the reaction, as accumulation of such hydroxylamines is known to present a potential safety hazard.¹⁵ An additional experiment was performed using the plant conditions but omitting the ammonium metavanadate in order to determine any effect that it might have on the reaction.

The HPLC profile over the course of the reaction was monitored and did not show any appreciable differences compared to that of the plant conditions. Furthermore, the data shown in Chart 2 clearly showed that ammonium metavanadate did not exert a significant effect on either the rate or heat evolution of the reaction and suggested that it could be omitted from all subsequent experiments in order to simplify the reaction system and subsequent modeling activities.

Determination of Kinetic Control Conditions. In order to determine the true kinetics of the reaction, plant conditions operating under kinetic control needed to be identified. Therefore, the agitation speed was varied from 800 to 2000 Chart 2. Effect of ammonium metavanadate on the temperature and reaction profiles



rpm (corresponding to estimated $k_{\rm L}a$ values of 0.4–1.5 s⁻¹ using the model described in the Supporting Information). It was expected that the observed rate of reaction would increase as the $k_{\rm L}a$ increased until it reached a plateau at which point the reactor would be maintained near the H₂ saturation concentration. Indeed, as shown in Chart 3, above 1600 rpm

Chart 3. Effect of agitation speed on the reaction rate



there was no significant change in the reaction rate and therefore all subsequent experimentation using the RC1 1 L pressure vessel was performed at an agitation speed of 2000 rpm.

Effect of Pressure. The effect of pressure on the rate of reaction was investigated by performing two otherwise identical experiments (under the plant conditions) with a $k_{\rm L}a$ of 1.5 s⁻¹ at both 30 psia and 60 psia. The initial rate of nitropyrimidine 1 consumption was determined by measuring the gradient of the initial linear portion of the curve during the first few minutes of the reaction. The ratio of the two rates measured at the two

different pressures was found to be 1.67 which demonstrates that the reaction does not follow first order kinetics with respect to H_2 concentration. This is typical of heterogeneous hydrogenation reactors and is indicative of a more complex reaction mechanism possibly involving the adsorption of one or more of the species involved in the reaction onto the surface of the catalyst.

Effect of Liquid–Solid Mass-Transfer. In order to determine the impact of liquid–solid mass-transfer on the rate of reaction, two otherwise identical experiments (using the plant conditions) were run under conditions of gas-liquid mass-transfer control (at a $k_{\rm L}$ a of 0.4 s⁻¹), one with the typical 20 wt % catalyst loading and the other doubled to 40 wt % catalyst loading. The rates of these two reactions were identical and resulted in superimposable reaction profiles (Chart 4). It is therefore valid to assume that liquid–solid mass-transfer is not rate-limiting allowing us to neglect its contribution to the observed rate in all subsequent experiments.

Chart 4. Effect of increased catalyst loading on the reaction rate when under gas-liquid mass transfer limited conditions $(k_{\rm L}a \ 0.4 \ s^{-1})$



Development of the Kinetic Model. In order to determine the kinetics of the reduction of nitropyrimidine 1, it was important to first identify isothermal conditions under which to operate, as changes in the temperature during the course of the reaction would affect the observed kinetics. This was achieved by fixing the $k_{\rm L}a$ at 1.5 s⁻¹ and reducing the catalyst loading from the initial 20 wt % to 4 wt % resulting in a reduction of the reaction exotherm from 12.7 to 0.9 °C (Chart 5).

A kinetic model for the hydrogenation of nitropyrimidine 1 based on first-order kinetics was initially developed within Scale-up Systems's DynoChem 2011. The rate constants of the three chemical transformations (that is nitropyrimidine $1 \rightarrow$ nitroso $2 \rightarrow$ hydroxylamine $3 \rightarrow$ aniline 4 + amide 5, Scheme 1) were fitted to the available molar data obtained from a reaction performed at 20 °C, 30 psia, and 4 wt % catalyst. While good fits were obtainable for any single data set, the model was unable to be extrapolated and failed to predict the outcome of test reactions performed under varying conditions, as shown in Chart 6a. This is not surprising as it was shown earlier that the reaction does not follow first-order kinetics.

This behavior is indicative of the adsorption of one or more species onto the surface of the catalyst as described by the Langmuir–Hinshelwood model.^{16–18} This model accounts for

Chart 5. Effect of catalyst loading on the observed reaction exotherm (agitation started at the 3 min time point)



Chart 6. Comparison of first-order kinetic model vs Langmuir–Hinshelwood model: $k_{\rm L}a$ 1.5 s⁻¹, [nitropyrimidine 1] 0.528 M, 60 psia H₂, 20 °C



species adsorbing onto active sites present on the surface of a catalyst at a rate proportional to both the partial pressure (or concentration) of the species and the number of uncovered active sites on the catalyst. Once adsorbed onto the catalyst surface, the species react to form adsorbed products at a rate proportional to their respective concentrations on the catalyst surface. The adsorbed products finally desorb into the gas (or liquid) phase at a rate proportional to the concentration of the covered fraction of the catalyst surface. In applying the Langmuir–Hinshelwood model to this reaction system, the individual equilibrium constants for both the adsorption and desorption of each of the species present in the reaction need to be considered as well as the fundamental reaction steps, described in Scheme 1. These processes are shown in Figure 1 which also describes each phase present in



Figure 1. A graphical representation of the Langmuir-Hinshelwood type kinetic model within DynoChem 2011. The symbol "=" is used to denote a reversible reaction while ">" denotes an irreversible reaction in the forward direction. Both aniline 4 and amide 5 have been combined into a single species, product.

the system, the constituents comprising those phases along with any reactions taking place. All heat- and mass-transfer statements between the phases are also shown.

It was assumed that the rate of the adsorption processes is rapid with respect to the rate of the chemical transformations (as liquid-solid mass-transfer was previously shown not to be rate-limiting), and therefore each of the five adsorption rate constants was set to an arbitrarily high value and fixed (i.e., not fitted to experimental data, Table 1). The adsorption equilibrium constants and the rate constants of the three chemical transformations were then fitted to experimentally obtained molar data at a single temperature (20 °C). The rate constants (Table 1) obtained using this approach were able to successfully predict the outcome of a test reaction shown in Chart 6b. As mentioned previously, data were not available to describe all of the intermediate reactions, and consequently where data were not available for fitting, the modeled rate constants for those steps were not statistically significant. In this system the rate-limiting step was found to be the initial reduction of nitropyrimidine 1 to nitroso 2 (Nitrocat + H_2 cat > Nitrosocat + cat + Water) for which data were available. As only the rate-limiting step appears in the overall rate equation, the fact that the rate constants for the other steps were not significant does not have an effect on the overall prediction; in fact these rate constants could, if desired, simply be arbitrarily assigned a high value and then not fitted.

These fitted chemical rate and adsorption equilibrium constants were then fixed and, in combination with data obtained at a second temperature (40 $^{\circ}$ C), used to fit the activation energies of the three chemical transformations

 Table 1. Kinetic parameters obtained from DynoChem 2011

 using the Langmuir–Hinshelwood model

step ^a	rate constant (L/mol·s)	equilibrium constant (L/mol)	activation energy (kJ/mol)
$H_2 + cat = H_2cat$	50000 ^b	166	
Nitro + cat = Nitrocat	50000 ^b	8	
Nitroso + cat = Nitrosocat	50000 ^b	7652	
Hydroxyl + cat = Hydroxylcat	50000 ^b	4	
Product + cat = Productcat	50000 ^b	14	
Nitrocat + H_2 cat > Nitrosocat + H_2O + cat	3013		27
Nitrosocat + H ₂ cat > Hydroxylcat + cat ^c	4148		5
Hydroxylcat + H_2 cat > Productcat + H_2O + cat ^c	4901		67

"The symbol "=" is used to denote a reversible reaction, while ">" denotes an irreversible reaction in the forward direction. ^bParameter values were manually defined and not obtained through fitting to experimental data. ^cSteps are not rate-limiting therefore, kinetic parameter values are arbitrary and not statistically significant.

(Table 1). These activation energies were then successfully used to predict reaction outcomes at other temperatures (e.g., $30 \ ^{\circ}C$) demonstrating the ability to accurately model the temperature dependency of the system.

In order to model the heat flow of the reaction, once all of the kinetic parameters had been fitted, the heats of reaction (ΔH) of the three chemical transformations were fitted to experimentally obtained heat flow data. This attempt yielded no advantage, in terms of statistical significance, over simply using standard literature values for the heats of these transformations. As such it was decided to use the literature values moving forward.

Development of the Physical Model. The kinetic model was then expanded to include the physical aspects of the system, including the equipment used, namely the hydrogen dosing system and the heat exchanger. In addition, the relationship between agitation rate and the mass-transfer coefficient $k_{L}a$ was defined. Using $k_{L}a$ values obtained from the developed statistical model, a simple regression of agitation speed vs mass-transfer was plotted, and the slope and intercept of this straight line were included in the model enabling the selection of the appropriate $k_{\rm L}$ a for any defined agitation speed within the regressed range. The maximum rate of hydrogen dosing was obtained from the equipment specifications sheet. A simple regression defining the relationship between the heat transfer coefficient (UA) and the agitation speed was created from experimentally obtained data and used to define the reactor's varying heat removal capability with changing agitation speeds. The response of the heat exchanger was defined by proportional and integral (PI) gain constants. Initial attempts to fit the PI constants to experimental data failed. Therefore, they were obtained by manually varying them until the resultant model was visually able to describe the reaction temperature profile of a test reaction performed within the equipment. In order to model jacket temperature the heat exchanger would need to be fully characterized, for example the relationship between the master and slave controller, the flow characteristics of the heat transfer fluid, and the type and response time of individual valves within the system would all need to be defined. As the goal of the project was to model the reaction temperature and predict the maximum exotherm, such characterization was not performed.

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However, the loss to the surroundings was accounted for by creating a "surroundings phase" within the model. This "surroundings phase" was assigned a mass several orders of magnitude larger than that of the reaction system and was given the initial temperature of 22 °C (i.e., ambient temperature). Heat transfer statements were defined between each of the reaction phases (headspace and bulk liquid) and the "surroundings phase". The UA values defining the extent of this heat transfer were then fitted to supplied reaction temperature data. This approach was found to be very effective and permitted the generation of modeled reaction temperature data that provided a good fit to experimentally obtained test data across the investigated temperature range of 20–40 °C.

Validation of the Physical Model. The physical model was then applied to the original plant conditions (described in the first section) and used to predict the maximum reaction temperature under different mass-transfer conditions in a laboratory scale 5 L Hastelloy C-22 pressure reactor. Not surprisingly these predictions (shown in Chart 7) show that the

Chart 7. Effect of k_{La} on maximum reaction temperature in a 5 L pressure reactor, experimental results (points) vs predicted (line)



maximum reaction temperature increases with increasing $k_{\rm L}a$ (or agitation speed) and that it should be possible to control the maximum reaction temperature to within a defined limit, simply by selecting the appropriate agitation speed. A number of reactions were performed on a 320 g scale with respect to nitropyrimidine **1**, to test the validity of these predictions. The results obtained from one of these experiments (700 rpm, $k_{\rm L}a$ 0.5) are shown in Chart 8 and demonstrate good agreement to the predicted temperature profiles, while the maximum exotherm measured during each experiment is plotted against the predicted curve in Chart 7.

CONCLUSIONS

It has been demonstrated that the highly exothermic hydrogenation of a substituted nitropyrimidine can be successfully modeled by performing a small number of reactions and taking advantage of in-line process analytical tools (FT-IR and H_2 gas uptake) to collect detailed reaction profile data without necessitating the tedious analysis of off-line samples. Utilizing Scale-up Systems's DynoChem 2011, it has been possible to use this data to create both a comprehensive kinetic model and a simplified physical model capable of predicting reaction temperature profiles as well as the maximum expected exotherm, as a function of agitation speed. This approach could form the basis of the scale-up strategy for successfully and safely scaling both this and other classes of highly exothermic reactions.

ASSOCIATED CONTENT

S Supporting Information

Further details on the equipment setup, a general experimental procedure for the determination of $k_{\rm L}a$ via the batch-absorption method, and a more detailed discussion of the development of the statistical model for the prediction of $k_{\rm L}a$. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We would like to thank Wilfried Hoffmann of Scale-up Systems for his invaluable help and advice throughout the course of this work and Neil Faiber without whose support this project would not have been possible.

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