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Kinetic and Calorimetric Considerations in the Scale-Up of the Catalytic Reduction of a Substituted Nitrobenzene

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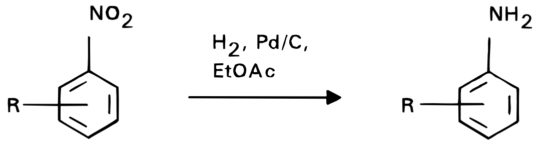
Abstract:

A reaction calorimetric investigation was conducted to assess proposed scale-up conditions (30 psig, 10 °C, initial reactant concentration = 0.69 M, catalyst concentration of 6.66 × 10^{-3} g/g of reactant) for the batchwise reduction of a substituted nitrobenzene to give the corresponding aniline in the presence of H_2, Pd/C catalyst, and ethyl acetate solvent. Heat evolution rates under these conditions were judged to be too large for safe plant operation. Alternative processing conditions were investigated, accounting for heat removal, pressure limitations, and gas−liquid mass transfer rates in the plant equipment as well as differences in reactivity between plant- and laboratory-prepared reactants. The recommended conditions (30 psig, 20 °C, and catalyst concentration of 7.53 × 10^{-3} g/g of reactant) were employed in the pilot plant, which resulted in conversion rates almost identical to those in the laboratory reactor, demonstrating the value of reaction calorimetry for scaling up a highly exothermic reaction without byproduct formation. Major improvements over the originally proposed process included operation at 20 °C to take advantage of the greater cooling capacity and decreasing the batch holding time by more than 35% with the additional constraints imposed by mass transfer. Additional experiments using nitrobenzene reactant demonstrated that water produced by the reaction promotes catalyst activity; in reactions where no water was initially present, a maximum was observed in the reaction rate, whereas a monotonically decreasing rate was observed for a 0.44 M initial water concentration.

Introduction

A key step in the manufacture of a pharmaceutical intermediate comprises the batchwise reduction of the nitro group on a substituted nitrobenzene to give the corresponding aniline in the presence of H_2, Pd/C catalyst, and ethyl acetate solvent:



Previous experiments showed that, at 10 °C and 30 psig H_2 pressure, the reaction is rapid and highly exothermic. Our goals in the present investigation were to (1) quantify the kinetics and the heat evolved at 10 °C and 30 psig, and thus assess safety aspects for an upcoming scale-up in a pilot plant; (2) assess the impact of gas-to-liquid mass transfer to obtain similar conversion rates and selectivities in the pilot plant reactor and laboratory; and (3) evaluate other process conditions that could lead to a safer and more economical process.

We discuss here a reaction calorimetric study performed to address these goals. Process conditions based on this work were selected for the scale-up. Comparison of the pilot plant run data with the calorimeter results indicates that the latter accurately predicted plant performance, demonstrating its great utility as a predictive tool for successfully scaling up this highly exothermic reaction.

Experimental Section

Calorimeter Principles. Reaction experiments were performed using a Mettler Toledo RC1 reaction calorimeter, comprising a 1-L jacketed glass vessel and a drafting agitator. The calorimeter operating principles are derived from an energy balance on the contents of the vessel, which can be expressed as follows:

$$\begin{pmatrix}\textit{Heat evolution}\\ \textit{rate by}\\ \textit{chemical reaction}\end{pmatrix} = \begin{pmatrix}\textit{Heat flow}\\ \textit{rate through}\\ \textit{vessel wall}\end{pmatrix} + \begin{pmatrix}\textit{Heat accumulation}\\ \textit{rate in vessel}\end{pmatrix}$$

The heat accumulation rate in the vessel includes accumulation by both the reaction mixture and the immersed reactor inserts (i.e., stirrer, temperature sensor, calibration probe; see below). Mathematically, the energy balance can be expressed as follows:

$$Q_{\mathrm{rxn}} - UA(T_{\mathrm{r}} - T_{\mathrm{j}}) + (m_{\mathrm{r}}C_{p_{\mathrm{r}}} + m_{\mathrm{i}}C_{p_{\mathrm{i}}})\frac{\mathrm{d}T_{\mathrm{r}}}{\mathrm{d}t} \qquad (1)$$

where

Q_{rxn} = heat evolution rate by chemical reaction, W

U = overall heat transfer coefficient between vessel contents and jacket fluid, W/(m^2·K)

A = wetted area of reaction vessel, m^2

T_{r}, T_{j} = temperatures of vessel contents and jacket, respectively, K or °C

m_{r}, $C_{p_{\mathrm{r}}}$ = mass (kg) and specific heat (J/(kg·K)) of reaction mixture, respectively

m_{i}, $C_{p_{\mathrm{i}}}$ = mass (kg) and specific heat (J/(kg·K)) of immersed reactor inserts, respectively

The quantity UA is determined by applying a known amount of power Q_{c} (i.e., heat per unit time) using a calibrated heater (calibration probe) immersed in the reaction mixture before the reaction begins (i.e., when Q_{rxn} is 0 and the temperature

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Table 1. **Feed and catalyst sources and experimental conditions**

run no.	feed source	catalyst source	temp, °C	pressure, psig	stirring speed, rpm	reactant concn, M	catalyst/reactant ratio, 10^3 g/g	reactor fill, L[a]
19603	lab	Aldrich, water added	10	30	1000	0.696	6.66	0.586
19604	lab	Aldrich, water added	10	30	1000	0.692	6.66	0.581
19605	lab	Aldrich, Lot No. 10324DN	20	10	1000	0.706	3.32	0.392
19606	lab	Aldrich, Lot No. 10324DN	20	30	1000	0.706	3.36	0.392
19607	lab	Aldrich, Lot No. 10324DN	20	40	1000	0.706	3.45	0.393
19609	lab	Aldrich, Lot No. 10324DN	20	30	500	0.706	3.25	0.393
19610	lab	Aldrich, Lot No. 10324DN	20	45	500	0.706	3.34	0.392
19614	pilot plant	Aldrich, Lot No. 10324DN	20	30	500	0.706	5.01	0.393
19615	pilot plant	Aldrich, Lot No. 10324DN	20	30	500	0.714	7.53	0.396
19616	pilot plant	Aldrich, Lot No. 10324DN	20	30	500	0.736	7.14	0.399

[a] Based on estimated density of 0.908 and 0.896 g/cm^3 at 10 and 20 °C, respectively for reactor contents.[1]

of the reactor contents in constant). The energy balance then reads

$$Q_c = UA(T_r - T_j) \tag{2}$$

and since Q_c is known and T_r and T_j are measured, UA can be determined.

Because the heat transfer coefficient changes with composition, an additional calibration is performed after completion of the reaction; interpolated values can thus be used during the reaction to account for heat transfer coefficient variation with composition.

The heat capacity of the reaction mixture is determined by performing a linear temperature ramp before reaction begins. The heat capacity is determined from the energy balance:

$$C_{p_r} = -\frac{UA(T_r - T_j) + m_i C_{p_i}\dfrac{dT_r}{d_t}}{m_r\dfrac{dT_r}{dt}} \tag{3}$$

with the heat capacity of the inserts presumed to be known. Variation of heat capacity with composition is estimated by performing an additional ramp after reaction is complete and interpolating between the two values.

The heat evolution rate (HER) due to chemical reaction is thus determined by measurement of jacket and internal temperatures using eq 1.

Procedure. A weighed amount of Pd/C catalyst was transferred manually to the vessel. The substituted nitrobenzene, dissolved in ethyl acetate solvent, was subsequently added, followed by the additional solvent necessary to give the desired concentration. Reaction conditions are summarized in Table 1. The concentrations were calculated by assuming that the reaction mixture density is equal to that of ethyl acetate solvent, which was calculated using the method of Hankinson *et al.*[1]

After charging to the RC1 vessel, air was purged from the system by alternately applying house vacuum (70 Torr) and 5 psig of N_2 three times. A temperature ramp (typically 5 °C) to the desired reaction temperature was performed over a 10-min period to measure the heat capacity of the vessel contents, following which the calibrated heater was turned on to determine the quantity UA. N_2 was subsequently purged from the system and H_2 introduced into the head space by applying vacuum and H_2 pressure three times, with the stirrer turned off. The reaction was initiated by turning on the stirrer with the reactor at the desired H_2 pressure. At the end of the reaction, additional determinations of UA and the heat capacity of the reaction mixture were performed, as described above.

Table 2. **GC conditions**

oven temp program	60 °C for 0 min, 25 °C/min to 90 °C, 15 °C/min to 200 °C, hold for 2 min
injector temp	250 °C
detector temp	300 °C
carrier gas	He
column head pressure	25 psig
injection vol.	1 mL
split ratio	50/1

Ethyl acetate (99.9% purity) was obtained from Burdick and Jackson. Laboratory-synthesized batches of the substituted nitrobenzene were used in most experiments; the last three runs were performed with material made in the pilot plant (Table 1). All experimental materials were used as received.

Water was added to the Pd/C catalyst in the first few runs to obtain a 50% wet form. In subsequent runs, the pilot plant catalyst was employed; this catalyst was composed of a prewetted form (50% wet) and supplied by Aldrich (Table 1). In all cases, the Pd content of the catalyst was 10 wt % on a dry basis.

Several 2-mL samples taken from the reactor at various reaction times were analyzed using a Hewlett-Packard 6890 GC equipped with a capillary column (30-m × 0.25-mm i.d., HP-5MS 5% phenyl methyl siloxane phase, 0.25-mm film thickness) and a flame ionization detector. GC conditions are summarized in Table 2. The internal standard method of analysis was employed, with *n*-decane used as internal standard.

Results and Discussion

1. Evaluation of Initially Proposed Conditions. Experiments were first performed to evaluate the initially proposed conditions of 10 °C, 30 psig, initial reactant concentration of 0.69 M, and catalyst/reactant ratio of 6.66 × 10^{-3} (runs 19603 and 19604, Table 1). A high stirring

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(1) Reid, R. C.; Prausnitz, J. M.; Poling, B. E. *The Properties of Gases and Liquids*, 4th ed.; McGraw-Hill: New York, 1987.

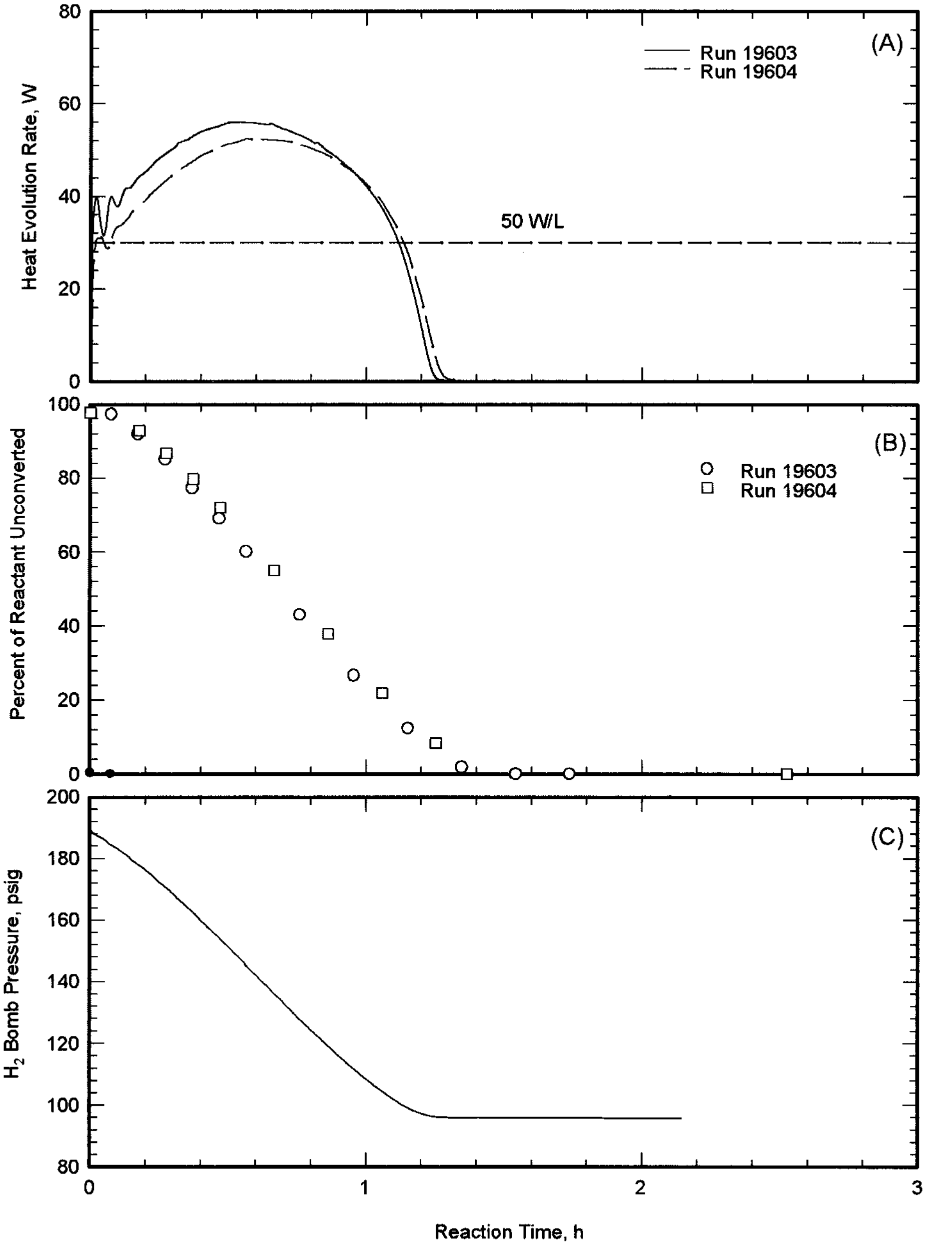

Figure 1. **Reproducibility and self-consistency of replicate RC1 runs (19603 and 19604, Table 1) performed at 30 psig, 20 °C, and a catalyst/reactant ratio of 6.66×10^{-3} g/g: (A) heat evolution rate, (B) reactant conversion, and (C) H_2 uptake (run 19604) as functions of time.**

speed (1000 rpm) was selected to obtain high gas−liquid mass transfer rates.

Results from replicate runs reproduced well, as evidenced by nearly coinciding heat evolution rate (HER) curves and GC-determined reactant conversions (Figure 1A,B). The self-consistency of the data was demonstrated by the nearly identical times (ca. 1.4 h) required to attain zero heat evolution and complete conversion for each run. Data self-consistently is also shown in Figure 1C, which indicates that the pressure in the H_2 supply cylinder to the RC1 vessel decreased and attained a constant value at a time coinciding with the attainment of zero HER and complete reactant conversion. The extent of reaction could thus be monitored in three different ways.

Figure 1A also shows that the HER curve, which is proportional to the reaction rate, increased from a nonzero initial value, attained a maximum, and then decreased to zero at long reaction times. This profile, which was reproduced in subsequent experiments, is clearly more complex than the monotonically decreasing heat evolution curve expected for a reaction forming one product and obeying simple (e.g., first-order) kinetics. We address the shape of the heat evolution curve later.

The initially proposed conditions gave a reasonable reaction time (ca. 1.4 h). Furthermore, the substituted aniline product was formed in almost 100% yield, with the yield of substituted toluidine byproduct being <1%. Representative product chromatograms at ca. 50 and 100% conversion are given in Figure 2. (Formation of a substituted toluidine byproduct was a concern because of the possibility of the hydrogenolysis of a benzylic bond in the presence of the Pd/C catalyst and hydrogen.) The reaction was also highly exothermic, as expected, with a heat of reaction of 395 kJ/kg of reactant, corresponding to a theoretical adiabatic temperature rise of 197 °C (i.e., the temperature rise expected if loss of cooling were to occur). Under isothermal condi-

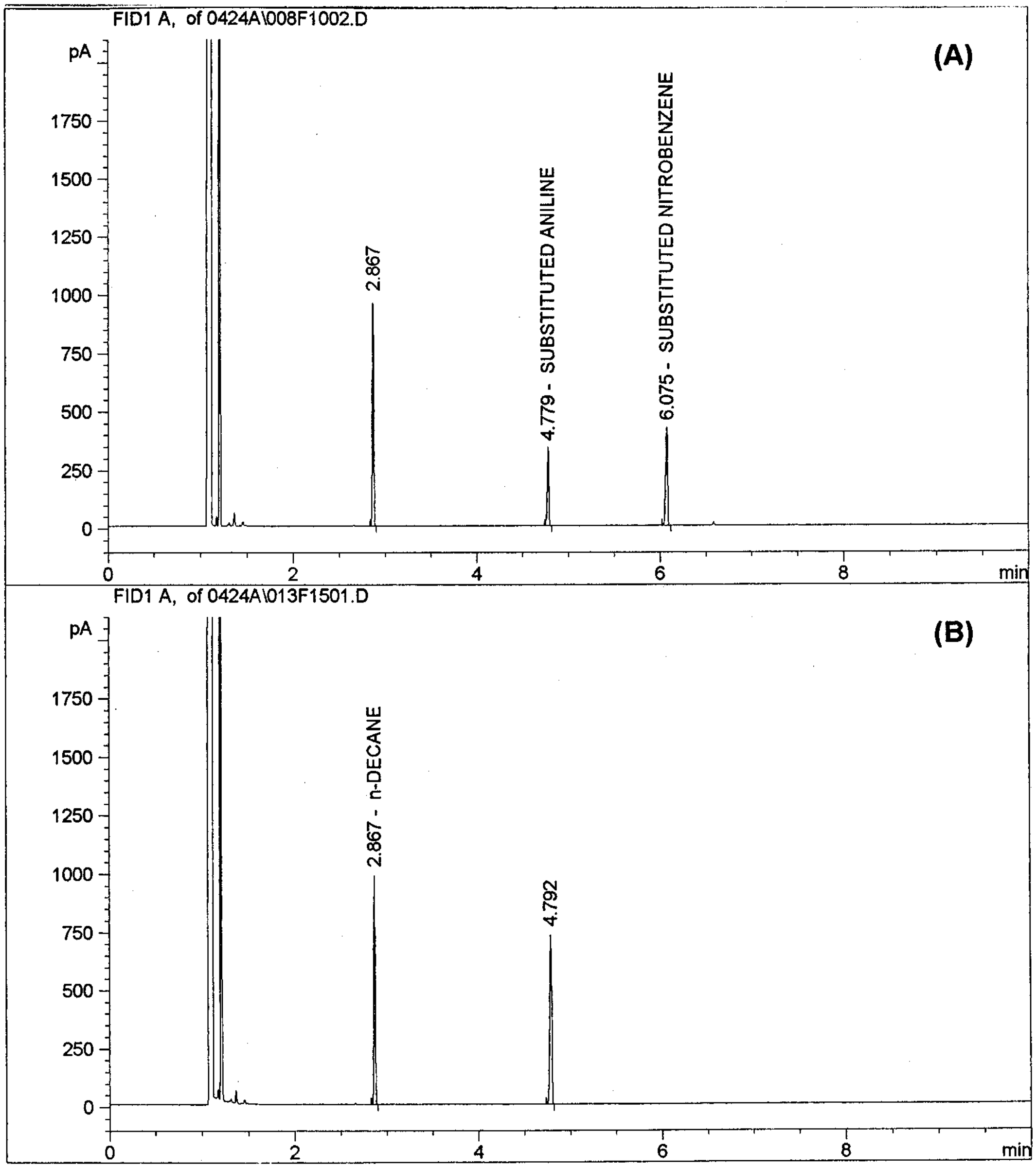

Figure 2. **Representative product chromatograms at (A) approximately 50% and (B) 100% reactant conversion.**

tions, the heat evolution rate per unit volume (hereafter referred to as the intensive HER) exceeded 80 W/L (Figure 1A). An intensive HER of 50 W/L has been used as an estimate of the upper bound of heat removal capability for the targeted pilot plant vessel. As the intensive heat flow exceeded 50 W/L for a significant fraction of the reaction time (Figure 1A), the heat flow is deemed greater than the plant reactor's heat removal capability based on this criterion. Before proceeding with additional results, we address briefly the premise and applicability of the 50 W/L criterion.

2. Examination of 50 W/L Criterion for Maximum Heat Removal Rate in Targeted Pilot Plant Vessel. To avoid uncontrolled temperature excursions, all the heat generated by chemical reaction must be removed through the reactor wall, or

$$Q_{rxn} = UA(T_r - T_j)$$

Dividing by the reaction phase volume V gives

$$\frac{Q_{rxn}}{V} = \frac{UA}{V}(T_r - T_j)$$

Therefore, for a given T_r value and a minimum jacket temperature, the product of the heat transfer coefficient and the heat transfer surface area must be known to determine the maximum intensive heat evolution for avoiding temperature excursions.

Because the overall heat transfer coefficient U includes heat transfer resistances between reactor wall and bulk fluid on both the batch and jacket sides, its value depends on the compositions of the vessel contents and the jacket fluid; Table 3 shows U values supplied by the vessel manufacturer[2] for various reactor and jacket fluids.

In the pilot plant campaign, ethyl acetate solvent was employed with Dowtherm J as jacket fluid, suggesting that 200 W/(m^2•K) is a reasonable estimate for U (Table 3). With the heat transfer area in the 100-L vessel employed estimated at 0.9 m^2, a value of UA/V of 1.8 W/(L•K) is obtained.

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[2] The Pfaudler Company, Sales Bulletin SB95-500-1, Rochester, NY.

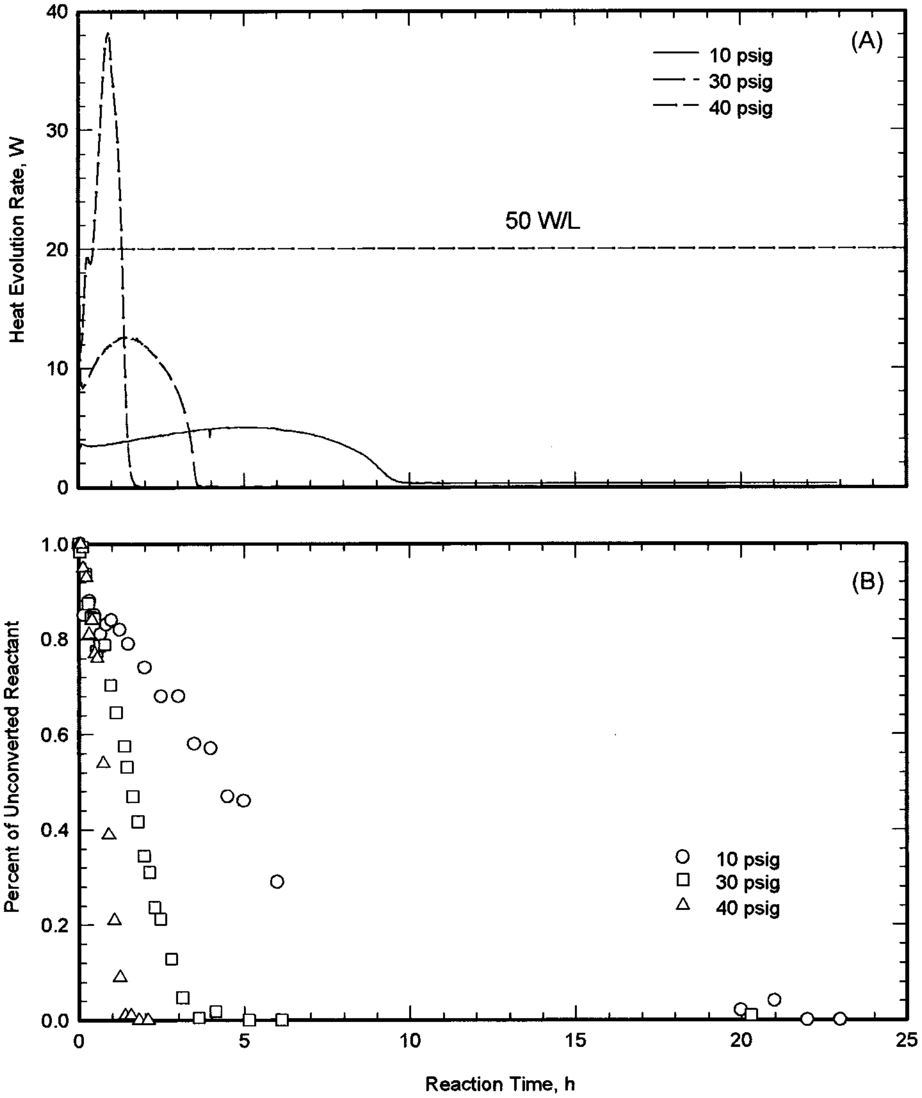

Figure 3. **Impact of pressure on (A) heat evolution and (B) reactant conversion at 30 psig, 20 °C, 1000 rpm stirrer speed, and a catalyst/reactant ratio of 3.3−3.5 × 10^{-3} g/g (runs 19605, 19606, and 19607, Table 1).**

Table 3. **Selected values of overall heat transfer coefficient (W/(m^2·K)) between bulk reactor contents and jacket fluid for 0.66-in. stainless steel reactor wall**[2]

heating water with steam	514
heating water with heat transfer oil	355
cooling organic liquid with water	200
cooling viscous organic liquid with water	95.2

Because the minimum achievable jacket temperature is −15 °C, with the reactor at 10 °C, the maximum value of Q_{rxn}/V is thus 45 W/L, which is close to the 50 W/L criterion. More typically, reactor temperatures of at least 20 °C are employed, so that maximum values of Q_{rxn}/V exceed 50 W/L, implying that the 50 W/L criterion for maximum heat removal capability is reasonable for the targeted pilot plant vessel.

3. Experiments at 20 °C and 1000 rpm. Subsequent experiments were conducted at 20 °C to increase the heat removal capability. At this temperature, the maximum temperature driving force is 35 °C (vs 25 °C at 10 °C), increasing the maximum heat removal capability by 40% for the same heat transfer coefficient, reaction volume, and heat transfer area. But because the reaction rate and, thus, heat release rate are greater at higher temperature (with catalyst concentration kept constant), it was necessary to slow the reaction by reducing catalyst concentration. A ~50% reduction in catalyst concentration was selected, giving a value of 3.32 × 10^{-3} g of catalyst/g of reactant (Table 1). In addition, the same 50 wt % wet Pd/C catalyst used in the plant campaign was employed (Table 1) in these experiments along with a lower fill (0.4 L) to reduce reactant consumption.

The impact of pressure was examined at 20 °C (Figure 3), all other process variables being kept constant (Table 1). The reaction rate increased monotonically with pressure (Figure 3). At the highest pressure, despite a reaction time of under 2 h, the HER was large, with the maximum 40-W value corresponding to a maximum intensive HER of 95 W/L, almost double the 50 W/L criterion. In contrast, the reaction time for complete conversion at 10 psig was over 20 h and thus impractically long. The 30-psig reaction pressure gave the best compromise, giving a reasonable reaction time of about 4 h with a maximum intensive HER of only 28 W/L.

More importantly, the yield of substituted *o*-toluidine byproduct was inferred to be very low, being below the GC detection limit. Operation at the safer 20 °C temperature

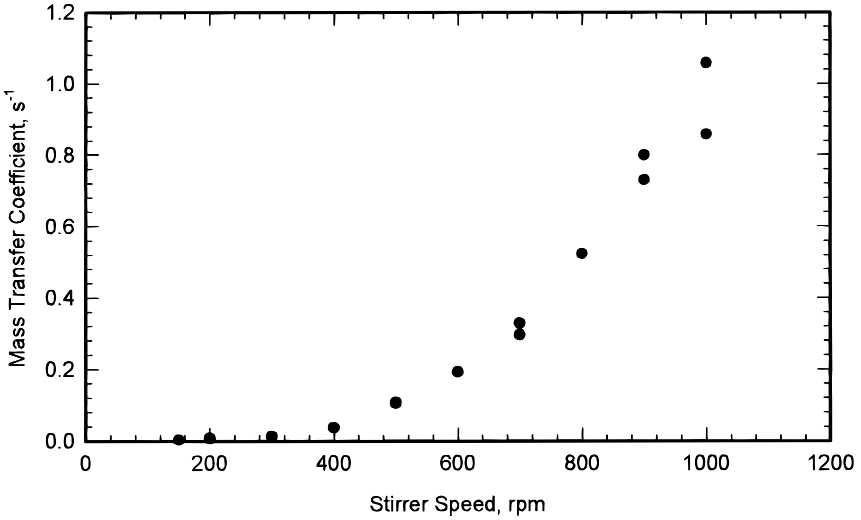

Figure 4. **Variation of mass transfer coefficient with stirrer speed in RC1.**

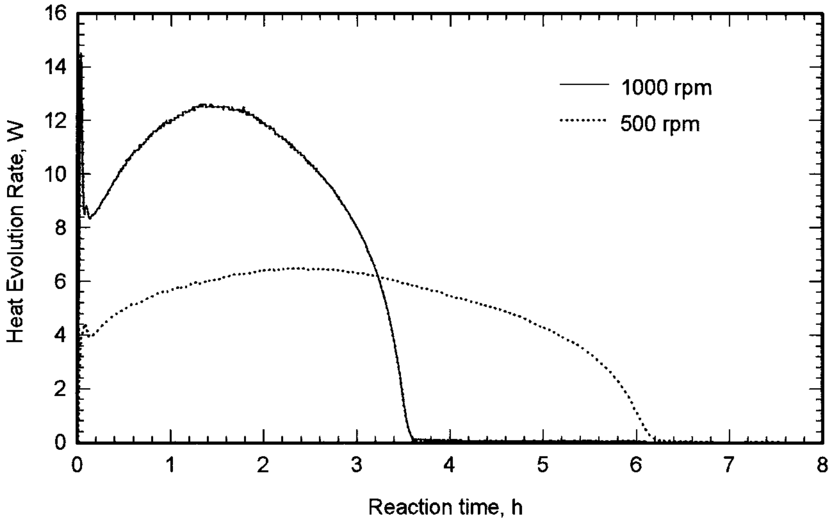

Figure 5. **Impact of stirrer speed on heat evolution and reaction rate (runs 19606 and 19609, Table 1). Reaction conditions: 30 psig, 20 °C, catalyst/reactant ratio ~3.3×10^{-3} g/g.**

without byproduct formation was thus demonstrated by using a lower catalyst concentration.

4. Mass Transfer Implications. A stirrer speed of 1000 rpm had been employed in all the experiments performed so far (Table 1). At this high speed, hydrogen transfer into the liquid phase is expected to be rapid. The mass transfer coefficient in the plant reactor was determined to be approximately 0.1 s^{-1} based on earlier measurements.[3] To compare the latter value to corresponding values in the RC1, the mass transfer coefficient in the RC1 was measured as a function of stirrer speed (Figure 4) using the procedure of Delmling *et al.*[4] In this procedure, H_2 is applied to the vessel head space with the vessel containing solvent and the stirrer off. The vessel is then isolated from the H_2 supply. The stirrer is subsequently turned on, and the pressure decrease in the head space due to H_2 absorption into the liquid is monitored as a function of time. The mass transfer coefficient is then calculated from a material balance. As indicated in Figure 4, the RC1 mass transfer coefficient at 1000 rpm exceeded the plant reactor value by about 1 order of magnitude.

To obtain similar conversion rates upon scale-up, mass transfer rates between laboratory and pilot plant reactors should be similar, particularly if rapid reaction occurs. To establish the relative magnitude between reaction and mass transfer rates, an RC1 experiment was performed at 30 psig, but at 500 rpm, corresponding to the same mass transfer coefficient as that of the pilot plant reactor (Figure 5). As the figure shows, the conversion rate was much smaller at early reaction times, resulting in a substantially longer reaction time for complete conversion (6.4 vs 3.6 h). The strong impact of stirrer speed on the conversion rate implies that, in this case, the intrinsic reaction rate was rapid relative to the mass transfer rate (i.e., mass transfer is rate-controlling). The 500 rpm results thus represent the expected conversion rate in the pilot plant reactor.

5. Optimization at Same Mass Transfer Rates as Those of Plant Reactor. The relatively long 6.4-h reaction time in the 500 rpm run (Figure 6) and its low corresponding heat flow motivated a search for conditions giving more rapid reaction at 20 °C and 500 rpm. Although higher pressure

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(3) Landau, R. N. Unpublished work.

(4) Delmling, A.; Karandikar, B. M.; Shah, Y. T.; Carr, N. L. *Chem. Eng. J.* **1984**, *29*, 127−140.

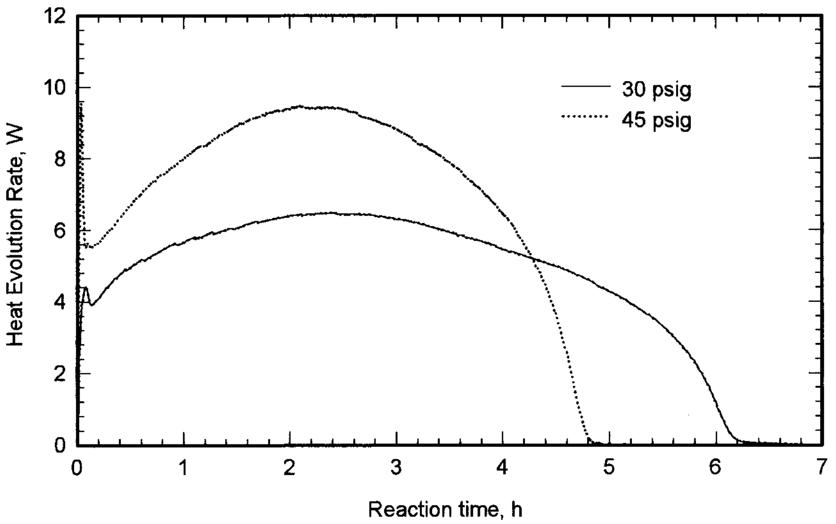

Figure 6. **Impact of pressure on heat evolution and reaction rate at stirrer speed representative of plant mass transfer rate (runs 19609 and 19610, Table 1). Reaction conditions: 20 °C, 500 rpm, catalyst/reactant ratio 3.3 × 10^{-3} g/g.**

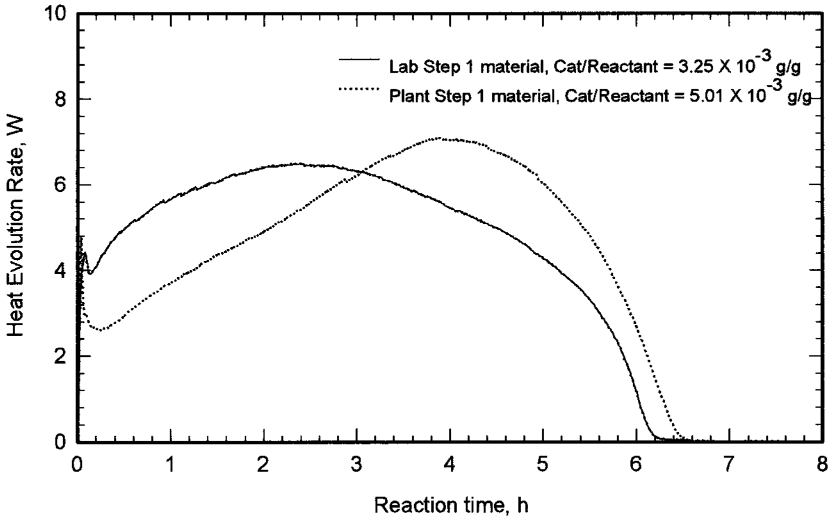

Figure 7. **Lower reactivity of plant-produced feed material as evidenced by similar conversion rate at higher catalyst loading (runs 19609 and 19614, Table 1). Reaction conditions: 30 psig, 20 °C, 500 rpm.**

(45 psig) reduced the reaction time to 4.5 h (Figure 6) with a maximum intensive heat flow of only 24 W/L, operation of the plant reactor above 35 psig was not feasible. Higher reaction rates at 20 °C, 30 psig, and 500 rpm were thus sought using larger catalyst concentrations.

With the plant campaign approaching, subsequent experiments were performed with pilot plant produced substituted nitrobenzene material which would be used in the pilot plant campaign. The impurity profile of this material was expected to differ from that of laboratory preparations because of variations in purity grades for reagents and solvents. While the impact of catalyst concentration was being evaluated, it was found that the plant-produced material had a much lower reactivity. For example, similar conversion rates were obtained in a run using laboratory-prepared feed and another run performed with the plant-produced feed but with 50% greater catalyst concentration (Figure 7). Unfortunately, it was not possible to ascribe the reactivity difference to specific inhibitors or impurities, despite rigorous GC internal standard analyses. It was thus decided to use only the plant-produced material in remaining experiments in order to best mimic plant operation.

Reduction of the reaction holding time by increasing the catalyst loading was again explored, but this time with the plant-generated material. Using a catalyst concentration of 7.53 × 10^{-3} g of catalyst/g of reactant, the batch holding time was decreased to a reasonable value (2.5 h), with a maximum intensive heat evolution of 50 W/L (Figure 8). The conditions used in run 19615 were recommended for the pilot plant campaign.

6. Pilot Plant Campaign. The pilot plant reactor comprised a 114-L vessel equipped with a four-pitched-blade impeller. Reaction conditions were 30 psig, 20 °C, and catalyst concentration of 7.53 × 10^{-3} g of catalyst/g of reactant. The plant run results are compared with the RC1 results in Figure 9. In the figure, the RC1 heat flow is plotted on the right-hand-side axis, and the plant's H_2 flowmeter reading is given on the left-hand axis. Both of these quantities are directly proportional to the conversion rate, providing instantaneous rate data as a function of time.

The conversion data from the plant and laboratory reactor are very similar at early reaction times. At about 1.25 h, the jacket temperature in the plant reactor could not be decreased further because of a fault in the plant cooling

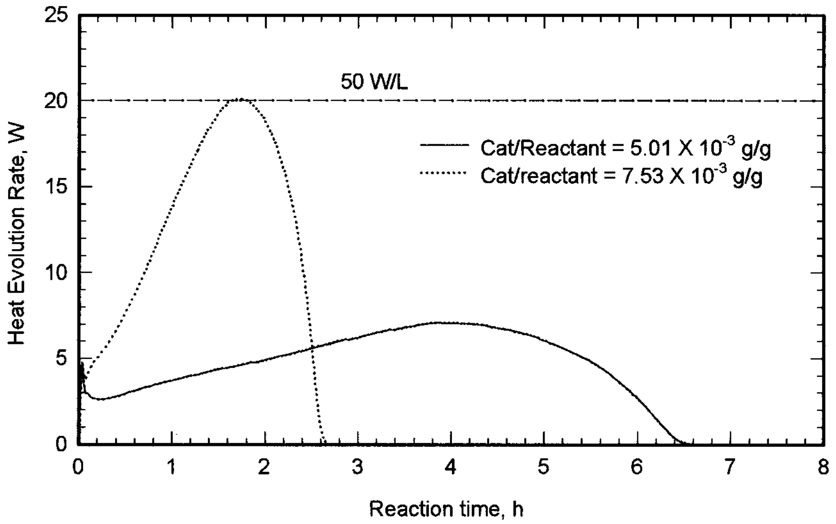

Figure 8. **Final optimization of reaction conditions by variation of catalyst loading using plant-generated feed material (runs 19614 and 19615, Table 1). Reaction conditions: 30 psig, 20 °C, 500 rpm. The horizontal dashed line indicates that heat evolution corresponding to the 50 W/L intensive heat evolution value.**

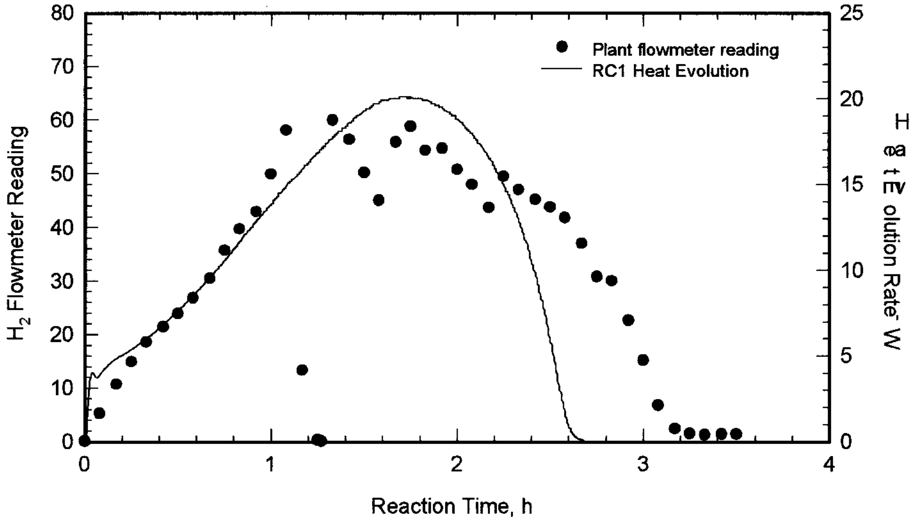

Figure 9. **Conversion rate comparison between plant reactor and RC1. Plant reactor and RC1 conversion rates are expressed in terms of H_2 flowmeter reading (left-hand axis) and heat evolution (right-hand axis), respectively.**

system. It was thus necessary to halt the reaction temporarily by stopping the impeller for a few minutes. The impeller was also stopped at 1.6 h reaction time for the same reason. But despite these minor upsets, the conversion rate in the plant reactor matched the RC1 results very well, with the lower rate in the plant due to the upsets resulting in a longer reaction time as expected.

Figure 9 illustrates clearly the excellent predictive capability of the reaction calorimetry technique, which allowed the successful scale-up and optimization of a highly exothermic reaction. The major improvement over the initially proposed process is the higher safety margin obtained by operating at 20 °C and thus taking advantage of the greater cooling capacity for this exothermic reaction. Furthermore, the higher catalyst concentration selected relative to the initially recommended value (7.5 vs 6.7 × 10^{-3} g of catalyst/g of reactant) resulted in reduction of the batch holding time to 2.8 h vs an estimated 4.4 h (based on linear interpolation of Figure 8 results), a decrease of more than 35%. We also emphasize that these processing savings were realized with no byproduct formation (Figure 10).

7. Shape of Heat Flow Curve. The attainment of a maximum in the HER profile (Figures 1, 3, and 5−9) can indicate autocatalytic behavior. With a catalytic reaction, such behavior could result because the catalyst is not in a fully active state at the start of the reaction and becomes more active during the course of the reaction.

To explore the possibility of water activation of the catalyst, two experiments were performed at 20 °C, 30 psig, and a stirring speed of 1000 rpm using nitrobenzene reactant (substituted nitrobenzene was no longer available). In one experiment, a nitrobenzene concentration of 0.660 M was employed. In the other, a 0.654 M nitrobenzene concentration was used, but with water in the feed at a concentration of 0.435 M, the latter concentration corresponding to 66% of the final concentration of water in the reaction mixture without nitrobenzene in the feed. The same catalyst/reactant ratio (4.53 × 10^{-3} g/g of reactant) was employed in each experiment.

As shown in Figure 11, the HER profile with water in the feed decreased monotonically with reaction time from an initial high value. In contrast, with water absent from

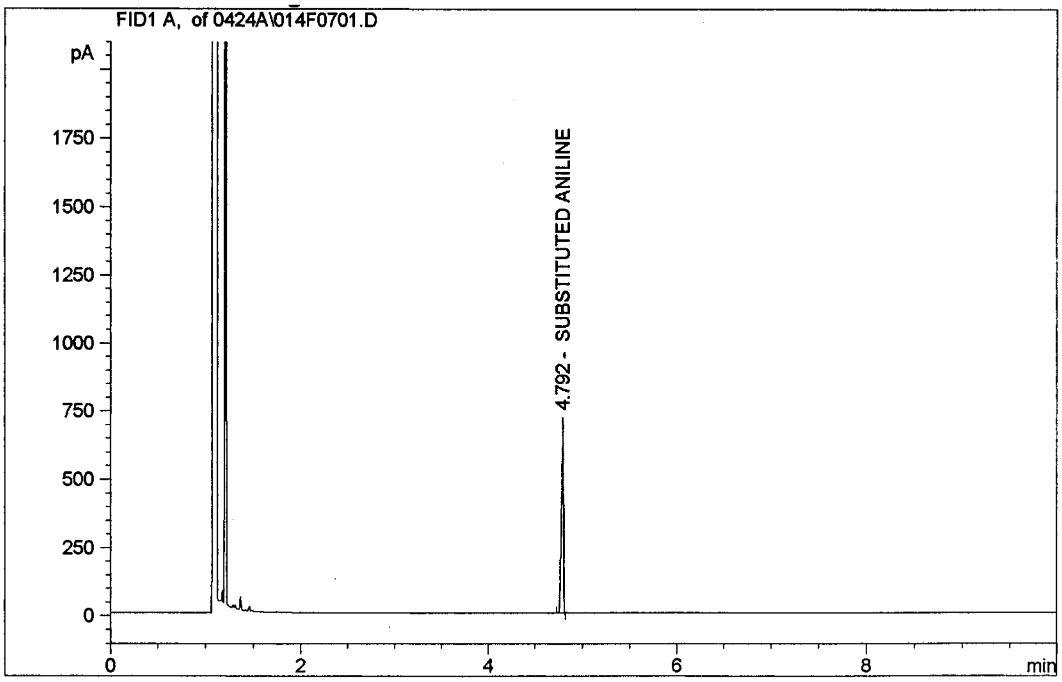

Figure 10. **Product chromatogram from pilot plant run.**

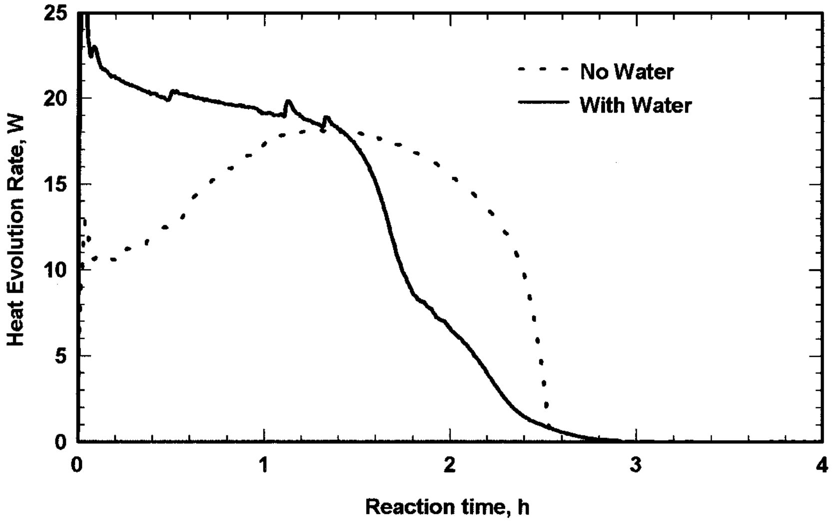

Figure 11. **Impact of 0.435 M water in feed on HER profile for nitrobenzene reduction (0.65 M) to aniline at 20 °C, 30 psig, 1000 rpm, and a catalyst/reactant ratio of 4.53 × 10^{-3} g/g.**

the feed, the HER profile increased to a maximum value from a lower initial value than that observed with water in the feed, as seen previously (Figures 1, 3, and 5−9). The results of Figure 11 thus indicate a greater initial reaction rate with water in the feed, implying a promotional effect by water on the Pd/C catalyst. Furthermore, no byproducts were formed in any significant yield with water in the feed (Figure 12).

The possibility that catalyst activation might occur due to Pd metal reduction during reaction was evaluated by performing an experiment in which the Pd/C catalyst was exposed to H_2 for a time period comparable to the total reaction time. Specifically, the Pd/C catalyst was placed in the reactor with ethyl acetate solvent. The reactor was pressurized to 30 psig with H_2, and the stirrer was turned on for 1 h to contact the catalyst with H_2. The substituted nitrobenzene reactant was then pumped into the reactor over 4 min. As Figure 13 shows, a maximum in the heat evolution profile was again observed similar to that observed without catalyst pretreatment. We conclude that incomplete reduction is not the main cause for the maximum in the heat flow profile.

We note finally that examination of the literature reveals that the mechanism for reduction of aromatic nitro groups involves three consecutive two-electron steps,[5−7] with elimi-

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(5) Streitwieser, A.; Heathcock, C. H. *Introduction to Organic Chemistry*; Macmillan: New York, 1976.

(6) Pascoe, W. The Selective Hydrogenation of Bromonitrobenzenes to Bromoanilines. In *Catalysis of Organic Reactions*; Rylander, P. N., Greenfield, H., Augustine, R. L., Eds.; Marcel-Dekker: New York, 1988.

(7) Kosak, J. R. Hydrogenation of Nitroarenes; The Hydroxylamine Intermediate. In *Catalysis of Organic Reactions*; Rylander, P. N., Greenfield, H., Augustine, R. L., Eds.; Marcel Dekker: New York, 1988.

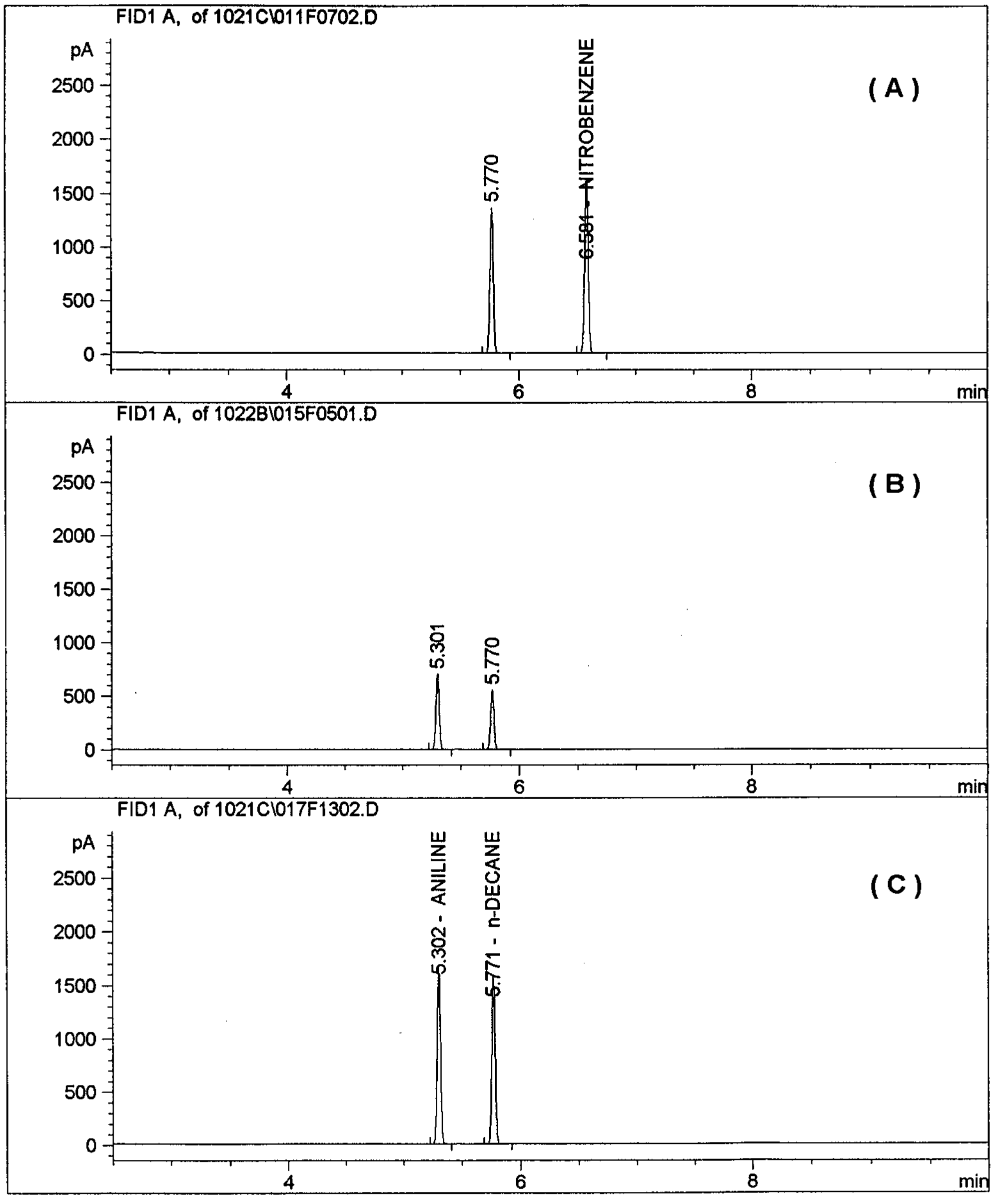


Figure 12. **Chromatograms corresponding to experiments using nitrobenzene reactant: (A) feed, (B) product at 100% nitrobenzene conversion without water in feed, and (C) product at 100% nitrobenzene conversion with water in feed.**

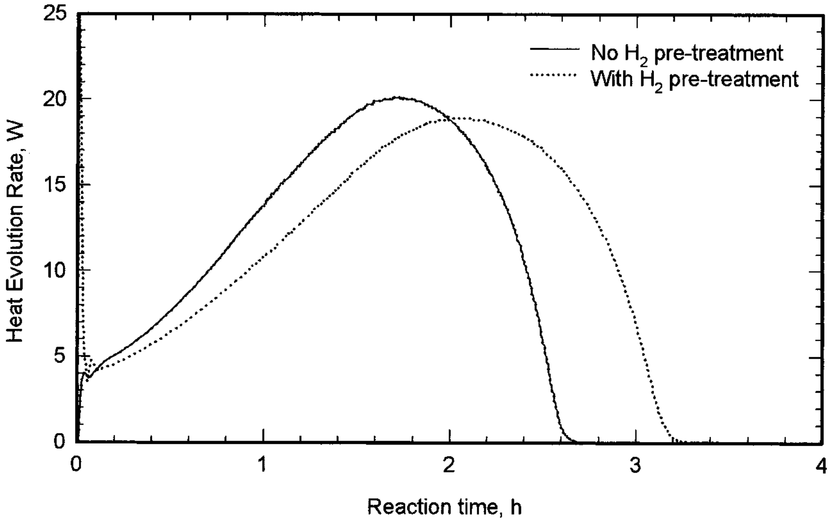
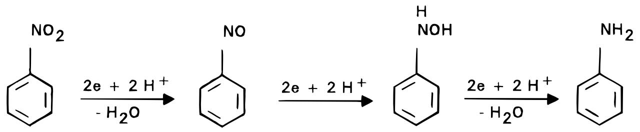


Figure 13. **Similarity of heat evolution profiles and thus conversion rates regardless of Pd/C catalyst pretreatment with H_2 (runs 19615 and 19616, Table 1). Reaction conditions: 30 psig, 20 °C, 500 rpm, catalyst/reactant ratio of 7.1−7.5 × 10^{-3} g/g.**

nation of water in two of these steps:



However, intermediate nitroso or hydroxylamine products were not detected in significant amounts using the rigorous the GC internal standard technique, which gave material balance closures >95% (Figures 2, 10, and 12). The activating effect of water (Figure 11) is thus implicated as the primary cause of the apparent autocatalytic behavior observed.

Conclusions

Reaction calorimetry experiments were performed to evaluate proposed conditions for scale-up of the catalytic reduction of a substituted nitrobenzene. Heat evolution rates under the proposed conditions were estimated to be beyond the safe operating limits of the pilot plant reactor. A comprehensive evaluation of alternative conditions was performed taking into consideration plant heat removal and pressure constraints, plant reactor gas−liquid mass transfer, and reactivity differences between plant- and laboratory-prepared reactants. The evaluation led to the selection of reaction conditions for the pilot plant campaign (30 psig, 20 °C, and catalyst concentration of 7.53×10^{-3} g of catalyst/g of reactant) incorporating safety improvements and batch holding time savings. Very good agreement between conversion data from the pilot plant and laboratory reactor was obtained, demonstrating the capability of reaction calorimetry in successfully scaling up a highly exothermic reaction without byproduct formation. Major improvements over the initially proposed process include (a) increasing the safety margin by operation at 20 °C and thus taking advantage of the greater cooling capacity and (b) decreasing the batch holding time by more than 35%.

The maximum in the observed HER profile was attributed to the activating effect of water on the Pd/C catalyst by comparing HER profiles from experiments with and without water in the feed. This insight also demonstrates the potential of reaction calorimetry for elucidating catalyst promotional effects.

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