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The role of reaction calorimetry in the development and scale-up of aromatic nitrations[1]

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Abstract

A Mettler RC-1 reaction calorimeter was utilized to investigate the thermochemistry of two aromatic nitrations prior to their scaleup. The calorimetry provided data that enabled the evaluation of alternative modes of operation and ultimately to intrinsically safer processes than were originally proposed. The results from this study and how they were used for pilot plant scale-up are discussed.

Keywords: Reactor calorimetry; Aromatic nitration; Scale-up

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1. Introduction

Aromatic nitrations are exothermic and give rise to products that have a propensity to be thermally unstable at elevated temperatures. Thermal runaways of nitrations, in fact, have been responsible for a number of industrial incidents [1]. It is important, therefore, to properly establish the heat flow potential when scaling nitrations to ensure sufficient cooling capacity. Reaction calorimetry is essential in providing information to aid in the development and safe scaleup of exothermic reactions in general but nitrations in particular. Two examples of aromatic nitrations that have been scaled up within our process development group will be discussed with an emphasis on the role of reaction calorimetry toward this effort. The first exemplifies the significance of reagent

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addition sequence while the second discusses an addition-rate strategy for improved control of reactor temperature. In both cases the organic substrate is a solid that is soluble in the acid media such that the reaction mixture is homogeneous. Complications in the kinetic descriptions due to liquid-liquid dispersions and mass transfer limitations are consequently eliminated. See, for example, the work of Albright et. al. [2] and Zaldivar et. al. [3] involving dispersed phase aromatic nitrations.

2. Calorimetric Principle

Heat flow calorimetry is accomplished by way of an energy balance around the reaction calorimeter. This enables the determination of the net heat flow produced as a result of a combination of reagents. Mathematically, the energy balance around the reactor is described by Eq. (1) for a semi-batch reaction under non-reflux conditions:

$$q_r(t) = UA(T_r - T_j) + m_r Cp_r \frac{dT_r}{dt} + \frac{dm_{dose}}{dt} Cp_{dose}(T_r - T_{dose}) \tag{1}$$

where U is the heat transfer coefficient, A is the the wetted area of the reactor, T_r and T_j are the reactor and jacket temperatures, m_r is the reaction mass, Cp is the heat capacity, and where the subscripts r and dose refer to the reactor contents and the feed stream respectively. Normally, U and Cp are determined before and after a reaction by way of a calibration procedure. To determine these two parameters, both a temperature ramp and the action of a precision heating probe (at constant temperature) are necessary. During the temperature ramp $q_r(t)$ is zero while dT_r/dt remains constant, and during the precision heater action $q_r(t)$ is a constant while dT_r/dt is zero. From these results, two equations in two unknowns are solved simultaneously to obtain both the heat transfer coefficent, U, and the heat capacity of the reactor contents, Cp_r. During a semibatch reaction, the energy balance must also account for the sensible heat of the feed which is the last term of Eq. 1. This term is zero for a purely batch reaction.

To obtain the total heat liberated for a reaction over an interval of time, the integral of Eq. 1 must be computed over the reaction limits according to the following equation:

$$\Delta H_{total} = \int_0^{tf} q_r(t)dt \tag{2}$$

where ΔH_{total} is the net heat liberated over the interval between zero and some final time, t_f. Another parameter that is useful when describing calorimetric results is thermal conversion, $X(t)_{thermal}$, which is the percent of the total heat liberated over the time interval 0 to t_f described by Eq. 3:

$$X(t)_{thermal} = 100* \frac{\int_0^t q_r(t)dt}{\Delta H_{total}} \tag{3}$$

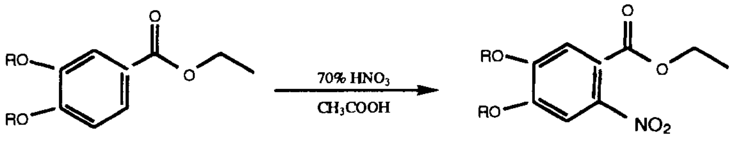
The thermal conversion in certain cases precisely follows the chemical conversion and thus provides information on reaction completion. For scaleup evaluation, it is often useful to report the extent of thermal conversion at the end of the dosing period for semibatch operations to indicate the thermal potential remaining in the so-called purely batch state.

The adiabatic temperature rise calculation provides an estimate for the final temperature a reaction would reach if the all the heat liberated went to raising its temperature. There are different levels of sophistication for calculating adiabatic temperature rise. For example, the temporal dependencies of Cp, and m_{rxn} with extent of reaction can be considered in its description [4]. A simpler form is the one shown in Eq. 4.

$$T_{\text{adiabatic}} = T_{\text{rxn}} + \frac{\Delta H_{\text{rxn}}\, n}{Cp(m_{\text{rxn}})} \tag{4}$$

where T_{rxn} is the desired processing temperature (°C), ΔH_{rxn} is the heat of reaction (kJ/mol of n), n is the number of moles of n, Cp is the heat capacity of the reaction mixture (J/kg °C), and m_{rxn} is the reaction mass (kg). The adiabatic temperature rise is useful in evaluating whether potential decomposition reactions could be reached during a thermal runaway.

3. Nitration of a substituted ethylbenzoate in Acetic Acid



A synthetic procedure was presented to our safety lab for the nitration of a 3,4 disubstituted ethylbenzoate to establish the usual calorimetric parameters prior to scale-up in our pilot plant.

In the original process description, concentrated nitric acid was fed to a solution of 3,4-disubstituted ethylbenzoate (EB) in glacial acetic acid. The experimental procedure, as received by our Process Safety Laboratory, was performed in a reaction calorimeter to determine the heat flow and potential adiabatic temperature rise. The heat flow profile obtained from the experiment, shown in Fig. 1, revealed that there was a significant induction period observed with this reaction and that less than 10% thermal conversion was achieved during the 60 minute addition period. Furthermore, the maximum heat flow occurred well after the entire addition was complete. Thus the process resembled a purely batch reaction since very little reaction occurred until all of the reactants were combined.

The heat of reaction was measured to be −120 kJ/mol of EB while the adiabatic temperature rise associated with the process was 35°C above the desired processing temperature of 40 °C so $T_{\text{adiabatic}} = 75$ °C. In this case, almost all of the thermal potential remained at the end of the addition period.

Thermal stability experiments in a Radex showed that the onset temperature for thermal decomposition of the reaction mixture initiated near 72° C when a 1.8 g sample was heated from ambient to 150 °C at 0.5° C/min. The maximum pressure rate occurred

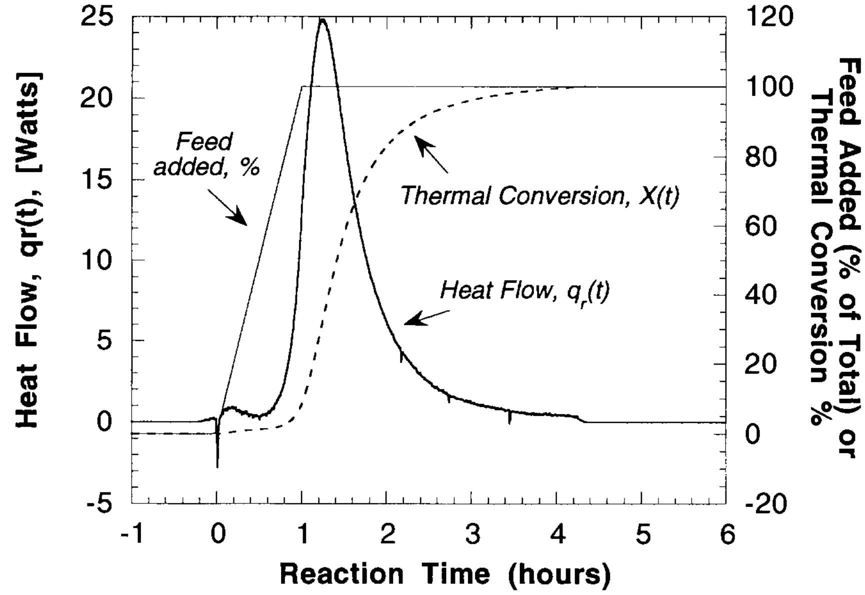


Fig. 1. Heat flow profile and thermal conversion for the nitration of 3,4 disubstituted ethylbenzoate (EB). Nitric acid was added over 60 minutes to a solution of EB in acetic acid at 40°C. Note the induction period and the very little conversion achieved during the dosing period.

at about 115 °C. Based on the low onset temperature for decomposition and the unfavorable heat flow profile from the calorimetry an alternative was sought. In particular, a dose-controlled process was sought such that better temperature control could be obtained on scale. More important is that the process is safer when the dosing rate can be used to control the exotherm. To achieve the desired dose-controlled process we had to speed up the reaction kinetics during the dosing period.

It was hypothesized that the nitration was of higher order in nitric acid concentration than in substrate concentration and that the reaction rate may be increased if the nitric acid concentration was higher throughout the addition period. The hypothesis was reasonable based on the literature for aromatic nitration in solvents such as acetic acid which report that reaction orders can vary depending on the solvent, the reactivity of the substrate, as well as the concentration of nitric acid in the system of interest [5][6][7]. Increasing nitric acid concentration relative to substrate was achievable by simply reversing the order of addition so that the substrate would be fed into the nitric acid. This way the nitric acid concentration would be at its maximum level at the commencement of the substrate addition.

In the revised procedure, two-thirds of the acetic acid and all of the nitric acid was initially charged to the reaction vessel and maintained at 40 °C while the remaining acetic acid was used to dissolve the substrate (EB) for the feed stream. The reaction was initiated by charging the feed solution (EB in acetic acid) to the nitric-acetic acid mixture over a 90 minute period. The resulting heat flow profile for the new procedure is shown in Fig. 2. In contrast to Fig. 1, the heat flow profile is markedly different. In the

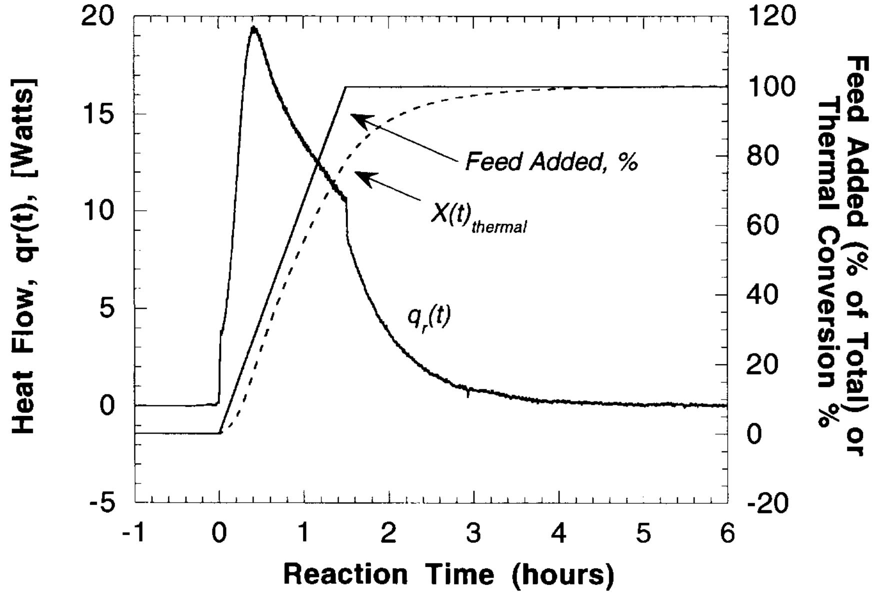


Fig. 2. Heat flow profile for the nitration of 3,4 disubstituted ethylbenzoate (EB). EB in acetic acid was fed to a solution of nitric and acetic acids over 90 minutes at 40°C. Note the thermal conversion achieved during the dosing period.

revised process, as seen by the profile of Fig. 2, there is no appreciable induction period and the maximum heat flow occurred during the first half of the dosing period. The heat of reaction, ΔH, was − 130 kJ/mol of EB with an adiabatic temperature rise of 36°C. More important, was that 80% of the total heat had been liberated (i.e. $X(t)_{\text{thermal}} = 80\%$) with only an adiabatic potential of 7° C remaining by the end of the substrate-acetic acid addition. Slightly different heats of reaction resulted between the two scenarios due to slightly different volumes of acetic and nitric acids used (see experimental).

As verification of conversion, samples were removed from the calorimeter and analyzed via HPLC to monitor the reaction completion. The HPLC assays of the reaction samples confirmed that the reaction went to completion in addition to verifying that the thermal conversion measured from the calorimeter was equivalent to the HPLC-measured extent of reaction. A plot of the thermal conversion of the reaction versus reaction completion was linear between 0 and 100%. In this case, selectivity to desired product was high so reaction completion was calculated from the ratio of the area% of the product peak to the sum of the area% of the product and the starting material peaks (as measured by HPLC).

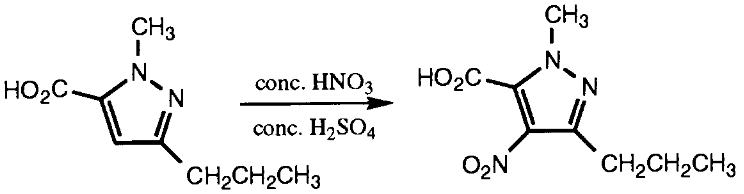
The revised and preferred process (Fig. 2), investigated in the RC-1, was scaled for a 378 L (100 gal) tank in the pilot plant where it was performed without incident. As a result of our calorimetric investigation, we successfully modified the process that was essentially a batch reaction to one that was almost entirely dose-controlled resulting in an inherently safer process. Additionally, we provided the pilot plant with projected heat removal requirements that ensured adequate temperature control of the reaction.

3.1. Experimental

Heat flow measurements were obtained with a Mettler RC-1® [8] reaction calorimeter equipped with a 2 Liter AP01 reactor vessel with anchor stirrer. For the experiment shown in Fig. 1, 194 g of 3,4 disubstituted ethyl benzoate (EB) was dissolved in 675 ml (3.5 volumes) of reagent grade glacial acetic acid and brought to 40.0°C. To this solution, 270 g (4.6 equivalents) of a 70% reagent grade nitric acid was fed linearly over 60 minutes while the temperature was maintained at 40 °C. The agitation rate was constant at 150 rpm with the glass anchor stirrer. In the modified process (Fig. 2), 210 g of 3,4 disubstituted benzoate was dissolved in 210 ml of acetic acid (1 vol) in a separate dosing bottle. This solution was added linearly over 90 minutes to a solution of 4.0 equivalents of nitric acid and 420 ml of acetic acid(2 volumes with respect to EB).

A Radex-Solo® [9] (Astra Scientific) was employed to measure thermal stabilities of reaction mixtures and to monitor pressure rise associated with thermal decompositon. The nitration mixture used for Radex testing was the same as used in the initial calorimetry experiment but simply scaled down to about 2 ml and mixed at room temperature. At room temperature, all the materials could be combined without significant reaction occurring. The Radex sample vial was sealed in the stainless steel-pressure vessel equipped with pressure transducer. For thermal stability tests, the temperature was ramped from ambient to 150° C at 0.5° C/min while the temperature and pressure data were acquired by the Radex computer system.

4. Aromatic Nitration of a Substituted Pyrazole in Sulfuric Acid



A reaction calorimeter was again used to evaluate the nitration of a substituted pyrazole (1-Methyl-3-propyl-1H-pyrazole-5-carboxylic acid) in sulfuric acid prior to scaleup in our pilot plant. This compound and its nitration product are process intermediates of the drug sildenafil [10] which is a highly selective GMP phosphodiesterase inhibitor.

The original process description that was received in our Process Safety Lab involved a 2 hour addition of concentrated nitric acid (70 wt%) to a solution of the pyrazole and sulfuric acid. The procedure prescribed a reaction temperature of 60° C to insure rapid conversion to product without accumulation of substrate. The heat flow profile obtained from the RC-1 experiment for the reaction, as recieved, is shown in Fig. 3. Here the reaction ocurred quite rapidly and, in fact, the thermal conversion was 90% at the end of the nitric acid addition. This is an added safety measure, as seen in the

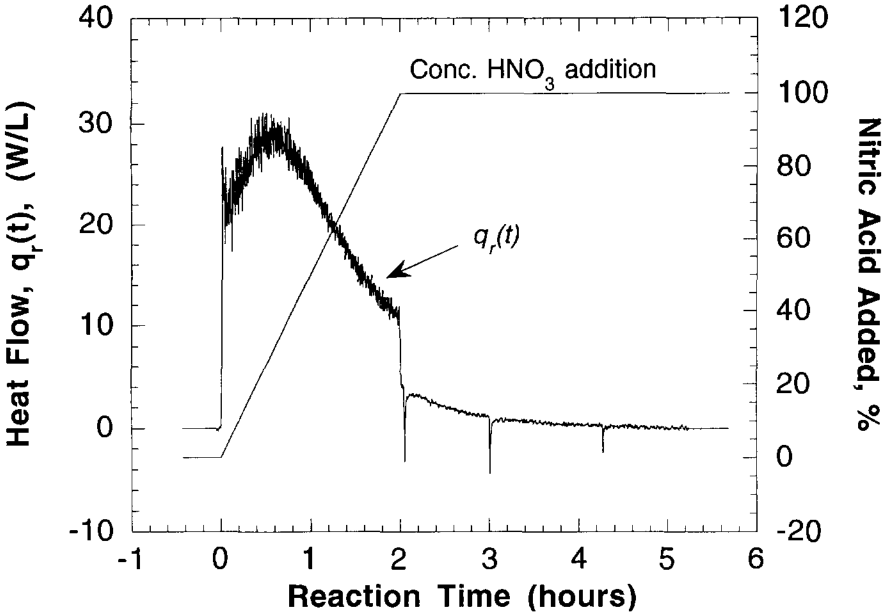


Fig. 3. Heat flow profile obtained from the RC-1 for the nitration of substituted pyrazole at 60°C. The heat flow is shown as Watts/Liter while the 2 hour addition of nitric acid is shown as a percent of the total added.

previous example, because in the event of a cooling loss the feed can be simply be halted to eliminate further exothermic potential. If the cooling loss occurred after the addition was complete then a relatively small potential would remain.

The nitration of the pyrazole was targeted for a scale of 227 L (60 gal) in a 378 L (100 gal) reactor. Prior to the scaleup, cooling experiments were performed in this reactor to measure the heat transfer coefficient and response time of the cooling jacket. An example of the temperature profiles observed during a cooling experiment for 208 L (55 gallons) of acetone is shown in Fig. 4. The experiment was carried out by allowing the solvent to equilibrate at 50° C before a manual change in setpoint to $-25\,^{\circ}C$ was performed. After the change in setpoint, time and temperature data were collected. The cooling rate, plotted in Fig. 4, was calculated by taking the derivative of a polynomial fit to the reactor temperature, T_r, versus time data. In this case, cooling rate was calculated from Eq. 5 and the $T_r(t)$ data.

$$-q_c(t) = \frac{M_{\text{acetone}}}{V_{\text{acetone}}} Cp \frac{dT_r}{dt} = \rho_{(\text{acetone})} Cp \frac{dT_r}{dt} \tag{5}$$

Here M, V, and ρ refer to the mass, volume, and density, of the acetone. From the jacket temperature obtained during the cooling experiments, U was computed from linear plots of Eq. (6) and found to be 225 W/m^{2}K for acetone and 290 W/m^{2}K for water.

$$\text{Log}_e \left[\frac{T_r(i) - T_{j,\text{avg}}}{T_r(t) - T_{j,\text{avg}}} \right] = \frac{UA}{Cp} t \tag{6}$$

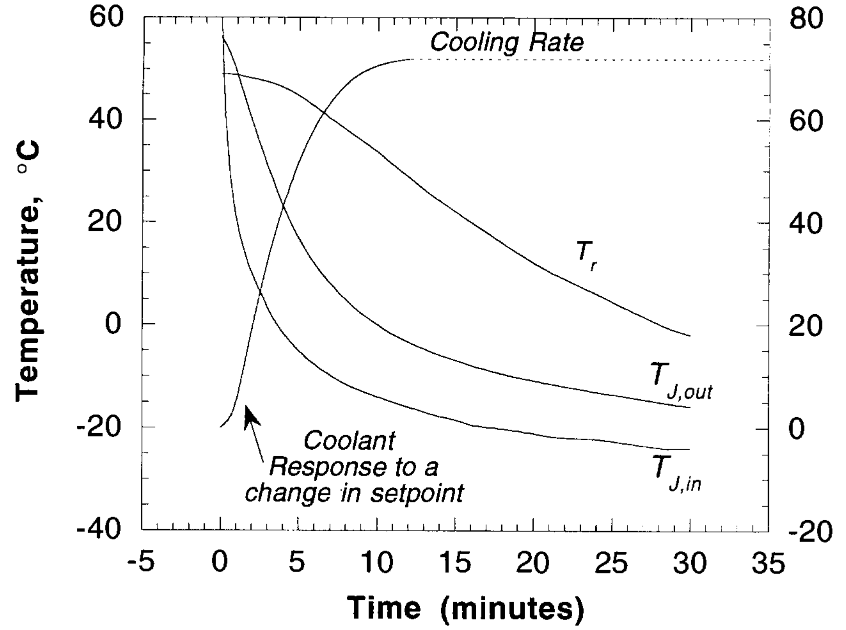


Fig. 4. Cooling curve for 55 gallons of acetone in a 378 L (100 gal) Dietrich vessel. The cooling jacket consisted of a closed system of syltherm distributed between brine and steam heat exchangers.

In Eq. 6, $T_{j,Avg}$ is the average jacket temperature determined from the jacket inlet and outlet temperatures and $T_r(i)$ is the initial pot temperature. The heat transfer area, A, was calculated from the geometry of the reactor for any desired liquid volume.

Although the ultimate cooling capacity was sufficient for this nitration, it was insufficent during the first few minutes of the nitric acid addition. This is evident by examining the initial heat flow of Fig. 3 and comparing with cooling rate of Fig. 4 during the initial minutes of the reaction. The cause for concern was that the transient response of the cooling jacket (i.e $T_{j,Avg}$) is too slow during the first few minutes of the nitric addition to maintain the 60°C setpoint. To further illustrate the situation on scale the projected jacket-temperature profile was calculated from Eq. 7 and plotted in Fig. 5.

$$T_{j,avg} = T_r - \frac{(q_r(t)/V)_{RC1} V_{pp}}{(UA)_{pp}} \tag{7}$$

In Eq. 7, $q_r(t)_{RC1}$ is the heat flow removed by the cooling jacket of the RC-1 experiment, and where U, A, and V_{pp} are the heat transfer coefficient, area, and volume on the pilot plant scale. Here a conservative estimate for the heat transfer coefficient, U of 200 W/m^2K, was used for the calculations while the area ($A = 1.5\,m^2$) was determined for the 227 L scale. Of importance in Fig. 5 is the instantaneous 15°C drop in jacket temperature once the feed was initiated. This type of cooling demand is unrealistic on a large scale and would result in an increase in reactor temperature above the desired

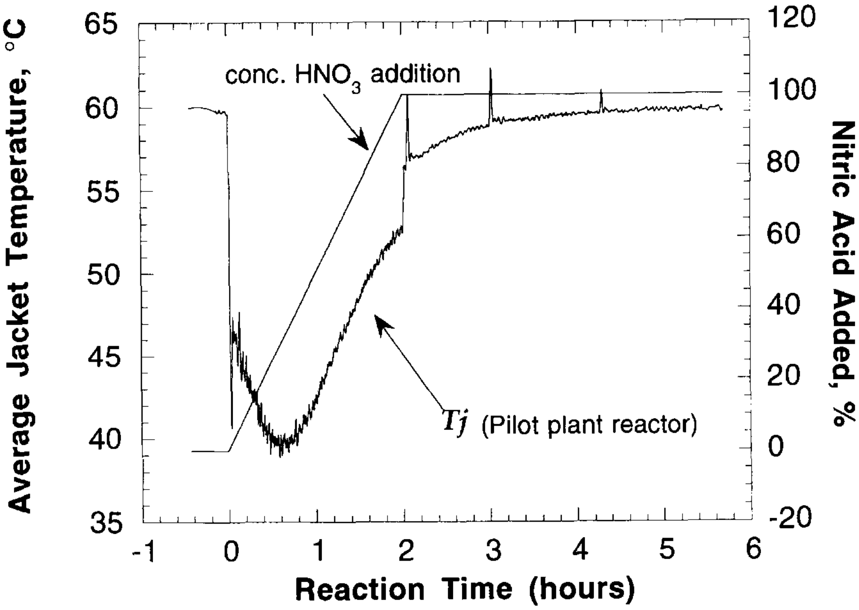


Fig. 5. Projected jacket temperature required to maintain a 60°C setpoint for the nitration of substituted pyrazole determined from the heat flow shown in Fig. 3.

setpoint possibly approaching a hazardous situation. The spike seen initially in the $q_r(t)$ curve occurs at the beginning and end of the addition period and are due to sudden changes in the reagent addition profile. Mathematically, they are discontinuities of dm/dt of Eq. 1 [11].

Practically, the temperature control of this nitration reaction could be achieved during a manual-controlled operation, by simply starting and stop the feed in order to maintain the setpoint temperature. For eventual operation in an automated plant, however, it is desirable to have an addition strategy so as to always stay within the cooling capacity of the reactor; which is the approach taken here. Further, Radex tests for this reaction mixture show that exothermic decomposition reactions occur in the neighborhood of 100 °C. Thus, adequate temperature control of this reaction is important.

The RC-1 data was used to aid in the development of an addition rate strategy to better accomodate the cooling dynamics of the reactor on scale. Further examination of Fig. 3 shows that the first one-third of the nitric acid addition, which corresponds to the first equivalent, has the highest heat flow. After that the heat flow is significantly less. By slowing the feed rate for relatively fast reactions, the instantaneous heat flow $q_r(t)$ is reduced because the rate of reaction is limited by the rate of addition. As a result, the instantaneous demand on the cooling jacket is reduced. The strategy developed here involved adding the feed non-linearly; slow at first and progressively faster during the latter stages of the addition. The results of this approach were obtained from the RC-1 and are presented, in part, in Fig. 6. Here the heat flow profile is shown in which

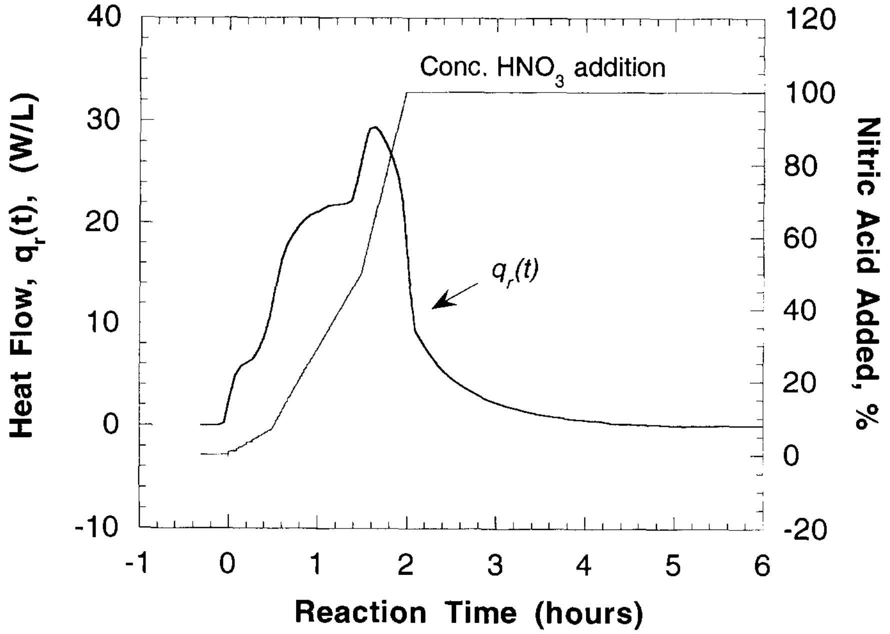


Fig. 6. Heat flow profile for the non-linear addition of 2.0 equivalents of nitric acid fed over 2 hours to a solution of substituted pyrazole in sulfuric acid. The heat flow is noisy due to the intermittent pulses of the pump and has been smoothed here to show the actual profile.

the nitric acid was added over a period of 2.0 hours but at 3 different rates (right axis of Fig. 6). The initial phase was 0.2 g/min followed by 0.5 g/min and 1.1 g/min which when contrasted with Fig. 3 shows that the change in heat flow is more gradual rising only to 6 W/L during the first few minutes as compared to the instantaneous 22 W/L seen in the former case.

Fig. 7 illustrates the projected jacket temperature for the new strategy using the same UA values that were used in Fig. 5. The jacket temperature for the 3-stage addition does not have to respond nearly as fast as the linear profile shown in Fig. 5 and is consequently more amenable to temperature control especially on larger scale.

During the development of this work we found significant exotherm due solely to the heat of mixing of the concentrated nitric acid into the concentrated sulfuric acid. This was not unexpected since the nitric acid was 30wt% water while the sulfuric acid was 96 wt% (4% water) which when combined is exothermic due to the heat of solution. A reduction in nitric acid would consequently lower the total exotherm by reducing this heat of solution. Based on these results, a reduction in the usage of nitric acid from 2.8 equivalents to 2.0 equivalents (roughly a 30% reduction) was investigated. When this was examined, the total heat flow was lowered by only about 5% but had the added benefit of lowering the amount of nitrating agent in the vessel. Reaction calorimetry revealed that the reaction still went to completion with less nitric acid but with an increase in reaction time from 3.75 hr to 4.75 hr.

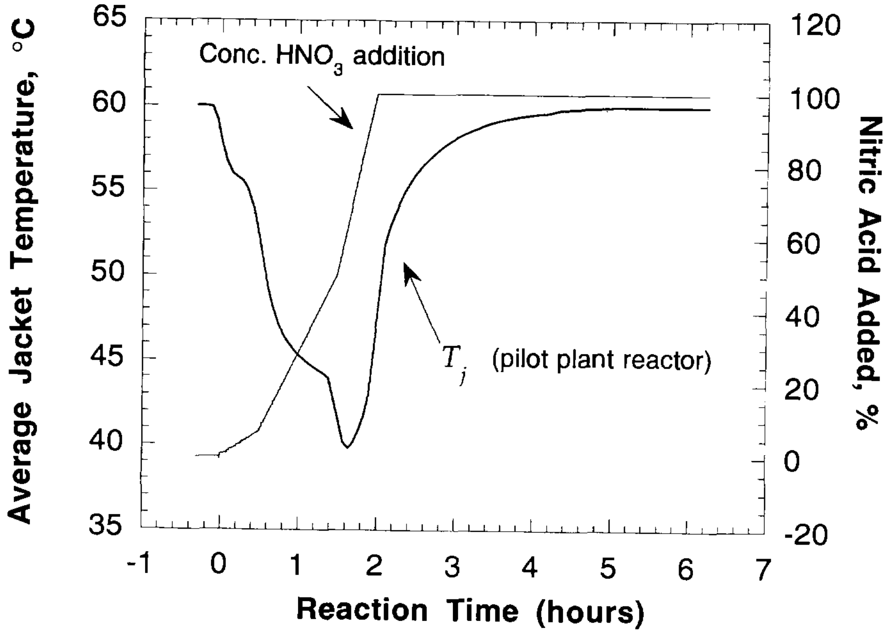


Fig. 7. Projected jacket temperature required to maintain a 60°C setpoint for the the nitration of the substituted pyrazole; $T_{j,Avg}$ determined from the heat flow profile shown in Fig. 6.

The nitration of the substituted pyrazole was successfully performed in our pilot-plant facility without incident. The pilot-plant stategy employed was based, in large part, on the results obtained from the reaction calorimetry studies performed in our Process Safety Laboratory such as using aliquots of nitric acid at different addition rates as well as reducing the amont of nitric acid charged. There were some minor modifications however. For example, the nitric acid was divided into four aliquots (instead of 3 used here) and placed into pressure cans. This way, the nitric acid delivered could be controlled more easily without the possibility of overcharging.

4.1. Experimental

Heat flow measurements for the nitration of substituted pyrazole were obtained with a Mettler RC-1 reaction calorimeter equipped with a 1 Liter SV01 reactor vessel. To the SV01 vessel, 63.2 g of substituted pyrazole was dissolved in 335 ml of reagent grade (96wt%) sulfuric acid and brought to 60.0° C. To this solution, 93.8 g of a 70% reagent grade nitric acid (2.8 equivalents) was fed linearly over 120 minutes while the temperature was maintained at 60° C. The agitation rate was constant at 600 rpm with the glass propeller stirrer. In the revised process, 68 g of nitric acid (2 equivalents) was added in 3 linear stages over 120 minutes. The rates of addition were 0.16 g/min for 30 minutes, 0.49 g/min for 60 minutes, and 1.1 g/min for 30 minutes.

5. Conclusions

In addition to possessing significant exothermic potential, the nitration reactions discussed above posed extra thermal hazards; namely, onset temperatures for thermal decomposition were within the potential adiabatic temperature rise of the nitration reactions. These issues motivated the need to carefully characterize the thermal and heat flow profiles to explore and develop alternative processes or strategies to minimize the thermal risk. The role of the automated reaction calorimeter was essential toward the development and scale-up of the described aromatic nitrations.

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