

# Process Safety Evaluation To Identify the Inherent Hazards of a Highly Exothermic Ritter Reaction Using Adiabatic and Isothermal Calorimeters

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**ABSTRACT:** This paper describes the process safety studies that were carried out prior to the scale-up for the initial process containing the reaction of 1,3-dimethyladamantane with sulfuric acid and acetonitrile. The reaction temperature is set at 13 °C followed by heating to 23 °C for progress of the reaction. Thermal screening studies showed the exotherm onset to occur at 30 °C, which is very close to the desired final process temperature, with high rate of temperature rise and pressure rise. Also understood was the better option for selecting the sequence of reagent addition, i.e., either acetonitrile or sulfuric acid. These thermal hazard evaluation results helped to redesign the process temperature at  $38 \pm 2$  °C, which was evaluated for safety aspects to prevent the untoward situation using an adiabatic calorimeter and an isothermal reaction calorimeter.

## INTRODUCTION

Understanding a chemical reaction provides the greatest opportunity in identifying the inherent hazards<sup>1</sup> associated with the process. Process chemistry greatly determines the potential impact of the critical reactions which affect the people, equipment, and environment. Process safety issues are quite common in batch reaction systems in the pharmaceutical industry. Batch reaction<sup>2</sup> processing plants are often designed for general use rather than dedicated to a specific process, which frequently involves manual intervention, modifications based on the demands of the current process, common utilities piping for many types of equipment, etc. Therefore, understanding the behavior of the chemicals individually (i.e., raw materials, intermediates, reaction mixtures, products) and also an evaluation of the reaction thermodynamics are key aspects for determining the process safety issues in a given process. Most chemical reactions are exothermic because of the reactivity of the chemicals by their very nature. Generally, thermal runaway<sup>3</sup> reactions are due to the lack of knowledge about the reaction hazards involving undesired thermal instability of the reaction mixtures or compounds. However, a safer design may perhaps be found even for highly exothermic reactions by detailed experimental evaluation of the thermal behavior of the reaction using calorimetric methods. Most of the thermal runaway situations are due to instability of the reaction mixtures or compounds at higher temperatures. The safe margins for process parameters must be assessed to avoid an untoward scenario instead of a desired outcome.

To design a safer reaction, a systematic risk analysis<sup>4</sup> approach should be practiced in any chemical industry. Risk analysis is not only an objective but also one of the key elements of the design of a technically efficient process. It reveals the inherent hazards of the process, providing the corrective actions to be taken before the plant scale is attempted. The first step in the risk analysis is to understand the process and information on materials and processing

conditions followed by literature sources, thermal screening, reaction thermodynamics, etc.

During the course of understanding the hazards<sup>5</sup> of an intermediate which involves the Ritter reaction<sup>13–17</sup> of 1,3-dimethyladamantane (1,3-DMA) with 98% sulfuric acid and acetonitrile was evaluated. As per the available resources, 1,3-DMA undergoes a bromination reaction to form 1-bromo-3,5-DMA, which is to be further reacted to give 1-acetamido-3,5-DMA. This process necessitates the addition of bromine at reflux temperature, which evolves toxic bromine vapors and produces an excess of effluent which is not eco-friendly and difficult at commercial scale.<sup>16</sup> Hence, in view of the difficulties, a new process was developed without the bromination reaction, in which 1,3-DMA is reacted with 98% sulfuric acid and acetonitrile directly to give 1-acetamido-3,5-DMA. Early in the process development, the reaction was tried with lower molar ratios, but the conversion time was approximately 20 h, whereas with 18 molar equiv of sulfuric acid and 9 molar equiv of acetonitrile the reaction requires only 6 h. The process was developed at 13 °C where acetonitrile is added to a precooled mixture of 1,3-DMA and 98% sulfuric acid. In a later stage, the reaction temperature is to be raised to 23 °C sparingly for progress of the reaction conversion, but a sudden temperature rise was observed at the laboratory stage. As per *Bretherick's Handbook of Reactive Chemical Hazards*<sup>6</sup> notes, a mixture of acetonitrile and sulfuric acid on heating to 53 °C undergoes an uncontrollable exotherm to 160 °C. Considering the available information about the mixture, detailed process safety studies were carried out to understand the thermal hazards of the reaction.<sup>7</sup> The experimental studies consisted of thermal screening studies of the reaction mixture from a lower temperature to a higher temperature to know the thermal

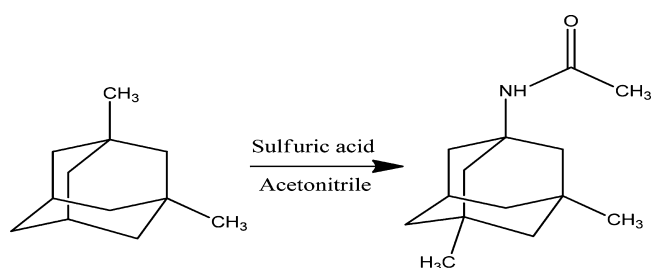
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stability, sequence of addition, and rate of temperature rise comparison between acetonitrile addition and sulfuric acid addition, the heat of reaction, and other thermodynamic<sup>5</sup> parameters for acetonitrile addition by using the Advanced Reactive System Screening Tool (ARSST) and a reaction calorimeter (RC1e).

## RESULTS AND DISCUSSION

It is very important to go with a systematic approach for better understanding of the hazards of any chemical reaction by considering the reactants used in the process, their physical and chemical properties, the process conditions, and observations by the laboratory scientists during the development stage. As per the initial development process, the reactants consist of 18 molar equiv of sulfuric acid and 9 molar equiv of acetonitrile with 1 molar equiv of 1,3-DMA at  $13 \pm 2$  °C followed by a gradual temperature rise to  $23 \pm 2$  °C over a period of 2 h (Figure 1). This may be impractical to bring up the



**Figure 1.** Reaction of 1,3-DMA with sulfuric acid and acetonitrile to produce 1-acetamido-3,5-DMA.

temperature sparingly without engineering controls. As mentioned in *Bretherick's Handbook*, a mixture of acetonitrile and sulfuric acid on heating undergoes an uncontrollable exotherm. Indeed, enough experimental information is required to know the exact onset temperature of the exotherm and the thermal behavior as per our desired process conditions.

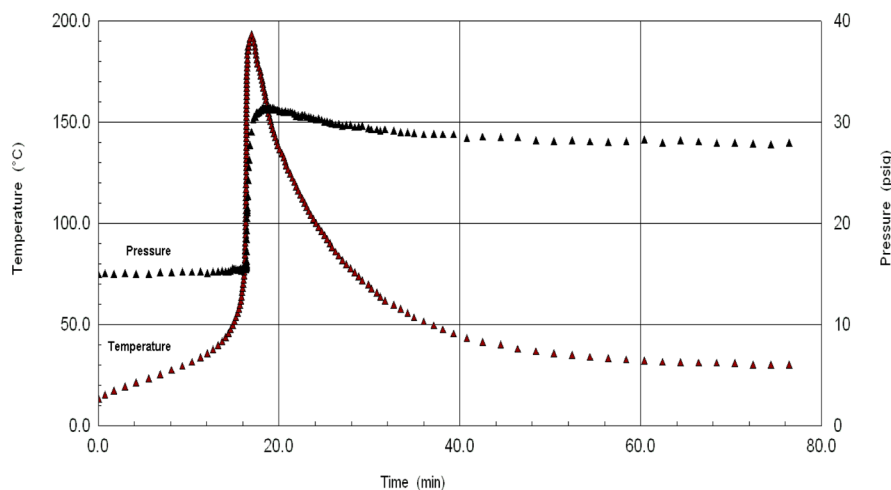
Initially a thermal screening<sup>8</sup> experiment was conducted in an adiabatic calorimeter<sup>9</sup> for the reaction mixture of 1,3-DMA, sulfuric acid, and acetonitrile which was prepared under cooling slowly at around 13 °C. On heating after 15 min, an exothermic

event was observed at 30 °C and reached a maximum temperature of 193 °C and a maximum pressure of 31.4 psig within a few seconds (Figure 2). The maximum self-heat rate was 1277 °C/min (Figure 3), and the maximum rate of pressure rise was 192 psi/min. The exotherm onset temperature of 30 °C is very close to the desired highest process temperature of  $23 \pm 2$  °C. Because of the thermal instability of the reaction mixture, heating of the reaction mixture from  $13 \pm 2$  to  $23 \pm 2$  °C may not be safe. Also it recommends that the reaction temperature should be higher than the onset temperature of 30 °C where it was reacted instantly as per the experiment.

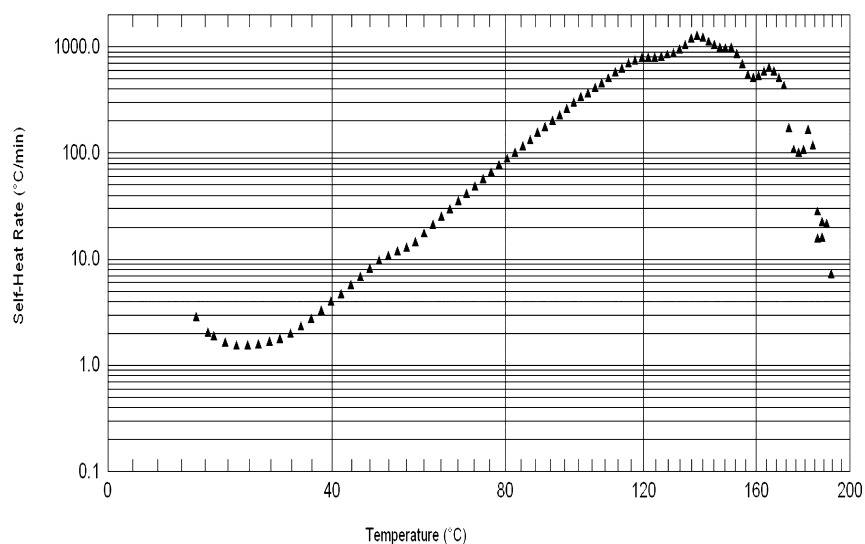
Two more experiments were conducted in adiabatic calorimeter to identify the severity of risk for a sequence of additions. Sulfuric acid was added to a mixture of 1,3-DMA and acetonitrile at room temperature ( $\sim 28$  °C). As a result, the temperature immediately increased to 130 °C with a maximum self-heat rate of 369 °C/min (Figure 4). Similarly, when acetonitrile was added to a mixture of 1,3-DMA and sulfuric acid, the temperature reached a maximum of 100 °C with a maximum self-heat rate of 16 °C/min (Figure 5). Even though both reactions are instantaneous, acetonitrile addition is the better option instead of sulfuric acid addition on the basis of the self-heat rates. The boiling temperatures for 1,3-DMA, sulfuric acid, and acetonitrile are 201.5, 335, and 81.6 °C, respectively. The presence of a high-boiling reagent as the initial fill is safe to avoid boiling or the formation of vapors due to the reaction heat for this process.

Table 1 presents a summary of all three experiments, which also suggest the severity of the risk based on the maximum temperature values attained as a result of the reaction heat and self-heat rate. Heating of the reaction mixture is not recommended because of its strong exotherm with a self-heat rate of 1277 °C/min. From the other experiments, sulfuric acid addition showed a maximum temperature of 193 °C with a self-heat rate of 369 °C/min, whereas acetonitrile addition showed a maximum temperature of 100 °C with a self-heat rate of 16 °C/min, which is lower in risk.

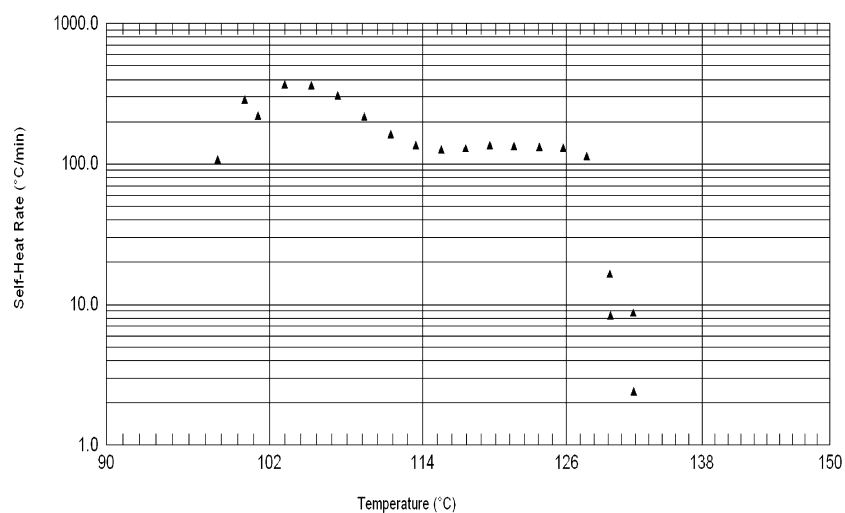
However, in view of the risk involved as per the thermal stability results, isothermal reaction calorimetry<sup>10–12</sup> experiments were conducted for the reaction in which acetonitrile was added to the 1,3-DMA and sulfuric acid mixture. The



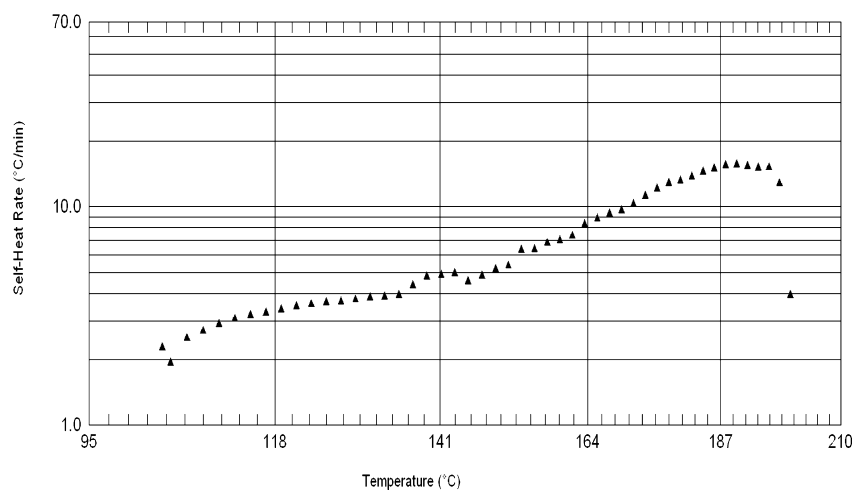
**Figure 2.** Thermal instability profile of the reaction mixture consisting of 18 equiv of sulfuric acid and 9 equiv of acetonitrile for 1 equiv of 1,3-DMA (ARSST data).



**Figure 3.** Rate of temperature rise profile during thermal instability of the reaction mixture consisting of 18 equiv of sulfuric acid and 9 equiv of acetonitrile for 1 equiv of 1,3-DMA (ARSST data).



**Figure 4.** Rate of temperature rise profile for sulfuric acid addition to a 1,3-DMA and acetonitrile mixture (ARSST data).



**Figure 5.** Rate of temperature rise profile for acetonitrile addition to a 1,3-DMA and sulfuric acid mixture (ARSST data).

reaction temperature ( $T_r$ ) increased to  $38 \pm 2$  °C, which is higher than the onset of the exotherm of the reaction mixture at

30 °C to avoid the accumulation of energy due to instantaneous reaction. To replicate a batch reaction system, initially

Table 1. Summary of the ARSST Results

sample	$T_{\text{initial}}$ (°C)	$T_{\text{onset}}$ (°C)	$T_{\text{max}}$ (°C)	self-heat rate (°C/min)
reaction mixture (1,3-DMA, acetonitrile, and sulfuric acid)	10	30	193	1277
sulfuric acid addition to 1,3-DMA and acetonitrile	30	instantaneous	130	369
acetonitrile addition to 1,3-DMA and sulfuric acid	30	instantaneous	100	16

acetonitrile was added at 38 °C in 3.5 h at a controlled feed rate (Figure 6). This RC1e experiment indicated that the reaction is safely scalable in the case of a controlled feed rate. The adiabatic temperature rise ( $\Delta T_{\text{ad}}$ ) for the batch reaction is 193 °C on the basis of the total heat of reaction ( $Q_r$ ), and the maximum temperature of a synthesis reaction mixture (MTSR)<sup>5</sup> is 231 °C, which indicates that the reaction is highly exothermic. In the worst-case scenario for this reaction (i.e., failure of controlled addition), the temperature rise of the reaction mixture would be very quick and may be greater than the boiling points of 1,3-DMA (201.5 °C) and acetonitrile (81.6 °C) as per the MTSR value, considering the thermal accumulation and no thermal conversion.<sup>5</sup> Thus, it needs to be further divided in terms of liberation of energy, which reduces the adiabatic temperature rise as well as the MTSR. It is always advised to have lotwise additions for highly exothermic reactions for safe commercial-scale operations, as noncontin-

uous addition of the reagent should minimize the risk in the worst-case scenario. In the case of lotwise additions, the total amount of heat can be divided, which leads to lower  $\Delta T_{\text{ad}}$  and MTSR values. On the basis of this consideration, another RC1e experiment was conducted for the same reaction with the acetonitrile addition in four equal lots to determine the enthalpy values (Figure 7).

As per the RC1e values summarized in Table 2 for acetonitrile addition in four equal lots, the heat of reaction for the first lot is greatest, and the heat gradually decreases for all of the remaining lots. The adiabatic temperature rise values for the first, second, third, and fourth lots are 65, 46, 42, and 39 °C, respectively. MTSR values for the first, second, third, and fourth lots are 103, 84, 80, and 77 °C, respectively. During the lotwise addition, the reaction mixture mainly contains 1,3-DMA and sulfuric acid. The MTSR values for all four lots are less than the boiling points of 1,3-DMA (201.5 °C) and sulfuric acid (335 °C).

## CONCLUSIONS

Risk evaluation is not simply just an assessment; it also helps in the safer design of chemical reactions. Even highly exothermic reactions may be made into scalable processes by knowing the reaction rate characteristics and thermal stability behavior. In our process, the risk evaluation indicated what can go wrong in the worst-case scenario as determined by the thermal instability of the reaction mixture, which was very close to the desired

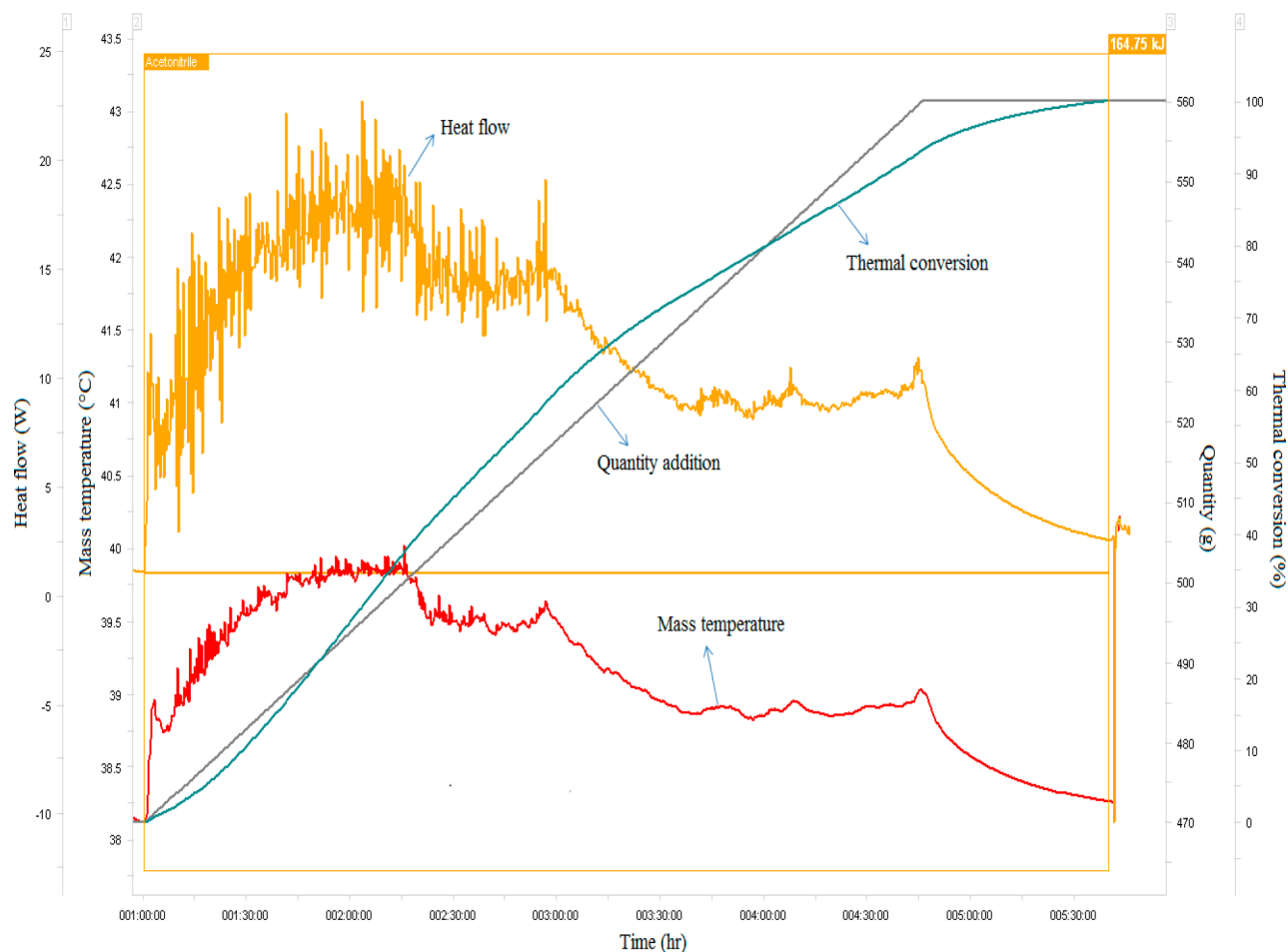


Figure 6. Rate of reaction profile for acetonitrile addition in a single lot (RC1e data).

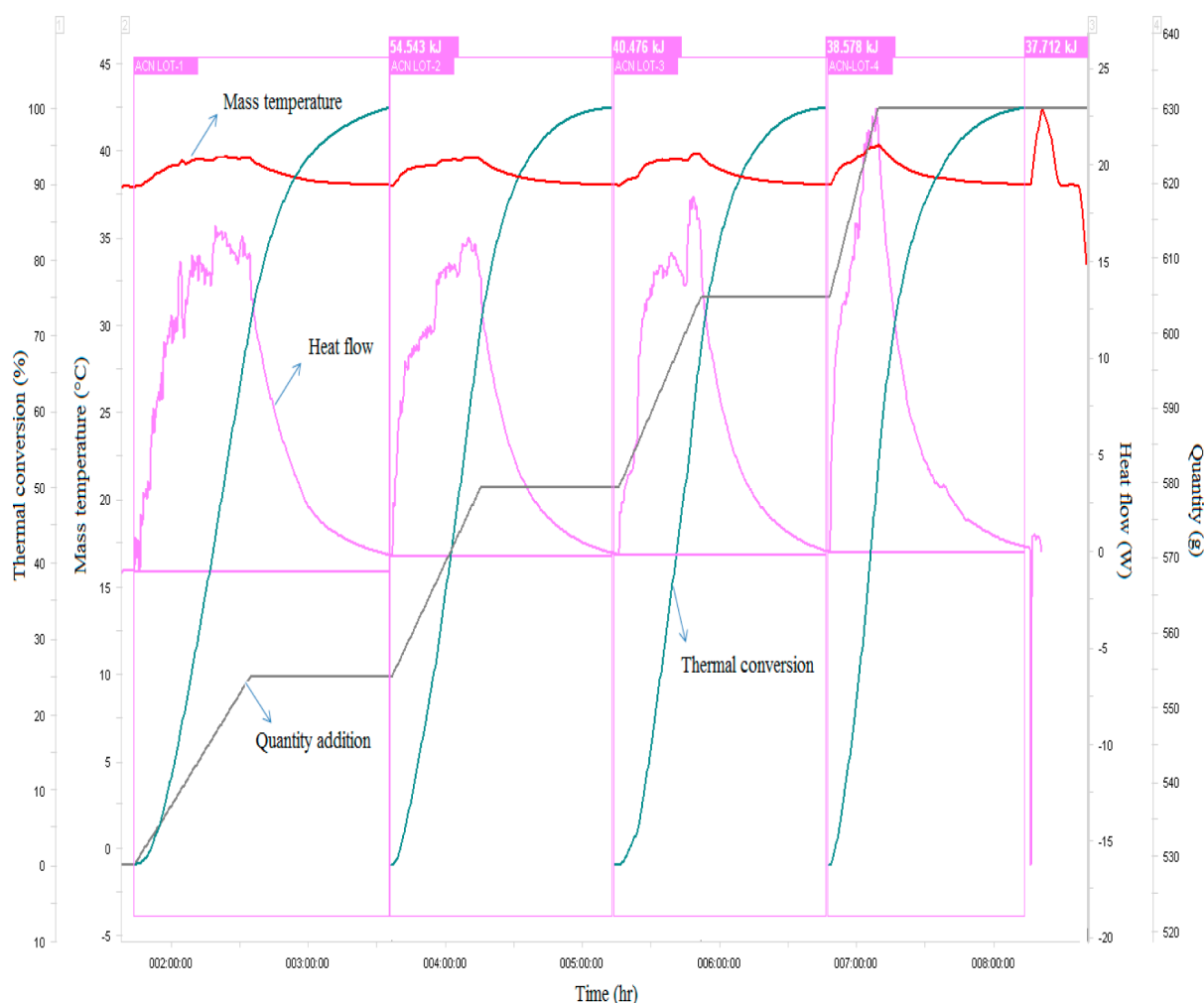


Figure 7. Rate of reaction profile for acetonitrile addition in 4 lots (RC1e data).

Table 2. Enthalpy Results from the RC1e Experiment for Acetonitrile Addition in Four Equal Lots

acetonitrile addition	$T_r$ (°C)	$Q_r$ (kJ)	$\Delta T_{ad}$ (°C)	MTSR (°C)
1st lot	38	54.43	65	103
2nd lot	38	40.48	46	84
3rd lot	38	38.58	42	80
4th lot	38	37.6	39	77

process temperature, and enthalpy values for the reaction. The evaluation showed that the adiabatic temperature rise could be reduced by lotwise addition of the reagent. On the basis of all the experimental results using adiabatic and isothermal calorimeters, lotwise addition of acetonitrile to a mixture of 1,3-DMA and sulfuric acid at  $38 \pm 2$  °C is recommended as a safe and controllable reaction.

## EXPERIMENTAL SECTION

As we discussed in the Introduction, the Ritter reaction involves the transformation of a nitrile compound into an *N*-alkyl amide using an alkylating reagent such as a strong acid. The Ritter reaction is most useful in the formation of new carbon–nitrogen bonds, especially in the formation of amides in which the nitrogen has a tertiary alkyl group. Acetonitrile and sulfuric acid were used as the nitrile group and strong acid, respectively. Three experiments in an adiabatic calorimeter and two

experiments in an isothermal calorimeter were conducted as described below.

**Adiabatic Calorimeter Experiments.** The Fauske ARSST is the low-thermal-inertia calorimeter used to obtain information for a variety of safety applications, including characterization of material compatibility, thermal stability, and reaction chemistry. Test data including adiabatic rates of temperature and pressure changes can be directly applied to the process scale because of the low thermal inertia. The testing sample is added to a 10 mL glass test cell placed inside the 350 mL stainless steel containment vessel with magnetic stirring facility. The thermal inertia<sup>18</sup> is about 1.08 (i.e., quite adiabatic). For all of the thermal stability experiments, 0.0043 mol of 1,3-DMA, 0.077 mol of sulfuric acid, and 0.039 mol of acetonitrile were used.

**Isothermal Calorimeter Experiments.** A Mettler Toledo 1 L capacity reaction calorimeter (RC1e) was used to measure the reaction heat and thermal conversion characteristics.  $T_r$  mode (constant reaction mass temperature) was selected, and the quickcal method was used to determine the specific heat of the reaction mass.

A mixture of 0.243 mol of 1,3-DMA and 4.384 mol of sulfuric acid at room temperature ( $\sim 28$  °C) was heated to 38 °C, and 2.192 mol of acetonitrile was added at 38 °C in 3.5 h using a peristaltic pump. In another experiment with the same process conditions, the addition of acetonitrile was split into four

lots (0.616 mol of acetonitrile for each lot), which were added to 0.274 mol of 1,3-DMA and 4.933 mol of sulfuric acid that had been initially placed inside the reactor.

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### Notes

The authors declare no competing financial interest.

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## LIST OF SYMBOLS AND ABBREVIATIONS

- ARSST, Advanced Reactive System Screening Tool  
RC1e, reaction calorimeter  
1,3-DMA, 1,3-dimethyladamantane  
psig, pounds per square inch (gauge)  
 $T_{\text{initial}}$ , initial temperature ( $^{\circ}\text{C}$ )  
 $T_{\text{onset}}$ , onset exothermic temperature ( $^{\circ}\text{C}$ )  
 $T_{\text{max}}$ , maximum temperature attained as a result of the exotherm ( $^{\circ}\text{C}$ )  
 $T_r$ , reaction mass temperature ( $^{\circ}\text{C}$ )  
 $\Delta T_{\text{ad}}$ , adiabatic temperature rise ( $^{\circ}\text{C}$ )  
 $Q_r$ , heat of reaction (kJ)  
MTSR, maximum temperature of a synthesis reaction ( $^{\circ}\text{C}$ )

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