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Communications to the Editor

Safety Evaluation of an Unexpected Incident with a Nitro Compound

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Abstract:

An unexpected highly exothermic reaction followed by explosion has been studied by means of reaction calorimetry and adiabatic calorimetry. The investigation of the process shows that the incident took place by a local adiabatic temperature rise in the reactor vessel due to the presence of potassium carbonate, which activated the decomposition of a nitro compound with an unusual low temperature onset. The study is completed with an improved and safer procedure consisting of changing the order of chemicals addition as an alternative approach.

Introduction

In the past, Moehs Ibérica S.A. has produced Lansoprazol (a proton pump inhibitor indicated for gastric ulcer treatment) by a multistep synthesis from **1**. One of the intermediates is 2,3-dimethyl-4-(2,2,2-trifluoroethoxy)pyridine *N*-oxide (**2**), obtained by condensation of 2,3-dimethyl-4-nitropyridine *N*-oxide (**1**) with trifluoroethanol in MEK/water using triethylbenzylammonium chloride as a phase transfer catalyst (Figure 1).

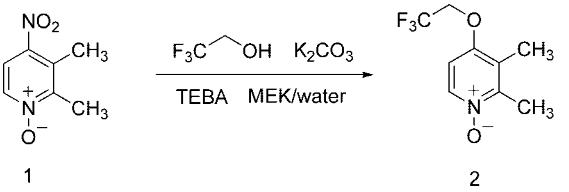

Figure 1. **Synthesis of 2,3-dimethyl-4-(2,2,2,-trifluoroethoxy) pyridine *N*-oxide (2).**

During the production of one batch, an incident occurred unexpectedly. The incident happened as follows. The vessel, at room temperature, was first charged with 450 kg of 2,3-dimethyl-4-nitropyridine *N*-oxide (**1**), then 720 kg of potassium carbonate and 15 kg of triethylbenzylammonium chloride (TEBA) were added without stirring, and finally 15 L of water was added. The incident started 10 min after the vessel was closed for alternate vacuum/nitrogen purge. A high increase of the internal temperature associated with fast gas evolution was detected (24 h after the incident, the temperature was 330 °C), generating a sudden pressure rise that ended up with the explosive breakage of the reactor (Figure 2). In view of the unexpected incident, an investigation was set up to clarify the origin of the severe system thermal runaway.

Results and Discussion

First, we evaluated the reactivity of **1** by differential scanning calorimetry to determine its explosive potential.[1] A sealed crucible was used, and a heating rate of 10 °C/min was applied in the DSC experiment. Compound **1** melts at 101 °C and shows a high severe decomposition beginning at 237 °C, with an associated heat of 1797 J/g, according to the results obtained directly from the DSC analysis (Figure 3). An adiabatic temperature rise of 998 °C has been calculated according to the equation $\Delta T_{\text{adiabatic}} = \Delta H/C_p$ (a heat capacity of 1.8 J/g °C has been estimated).

This result suggested the possibility that the other chemicals involved in the reaction mixture might affect the decomposition onset of **1**, since this value (237 °C) was too high to allow for the quick runaway observed. It has been described that pure organic nitro compounds decompose at high temperatures, exhibiting large exotherms, the reaction being violent or explosive in most cases. Moreover, reactants, solvents, and impurities may affect organic nitro compounds' thermal stability, lowering their temperature of decomposition.[2]

Therefore, we investigated the thermal stability of **1** in the presence of the other chemicals. Since DSC analysis is known to give results with a relative uncertainty regarding the decomposition onset as a result of the small sample size and high heating rates,[3] it was important to carry out screening experiments on a larger sample size. This was done in an accelerating rate calorimeter (ARC), which offers the possibility to prepare reaction mixtures, gives a more accurate determination of the onset temperature of the decomposition and makes it possible to determine the pressure rise during decomposition, which finally is what provokes the reactor breakage and explosion. It was observed that the mixture of **1** with triethylbenzylammonium chloride and potassium carbonate, analyzed by ARC, showed an slow exotherm from 72 °C, which became extremely fast at 89 °C with an adiabatic temperature rise higher

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(1) King, R.; Hirst, R. *Safety in the Process Industries*, 2nd ed.; Elsevier: Oxford, 2002.

(2) Gustin, J-L. *Org. Process Res. Dev.* **1998**, *2*, 27–33.

(3) Steinbach, J. *Safety Assessment for Chemical Processes*, Wiley-VCH: Weinheim, 1999; pp 29–26.

(4) Townsend, I. *J. Therm. Anal.* **1991**, *37*, 2031–2066.

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Figure 2. **View of the facilities after the incident.**

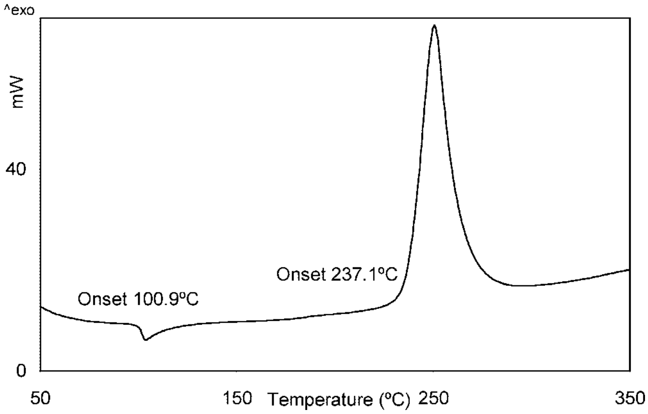

Figure 3. **DSC curve of 1 carried out at a heating rate of 10 °C/min.**

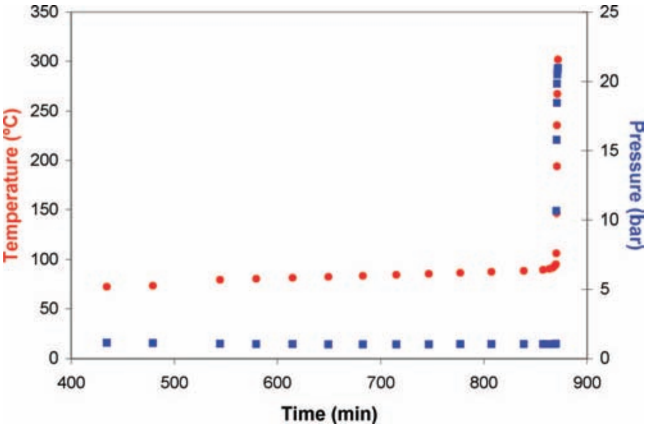

Figure 4. **Temperature and pressure as a function of time of a mixture of 1 with triethylbenzylammonium chloride and potassium carbonate, analyzed by ARC.**

than 364 °C and an internal pressure rise higher than 21 bar (Figure 4). So, a dramatic lowering of the decomposition onset was observed.

Since the onset temperature of the decomposition observed by ARC is above the operating temperature of the loading process (room temperature), we decided to study the cause of the thermal runaway activation. Our hypothesis was that an initial heating of the reaction mass activated the severe decomposition of compound **1**. The order of addition of reactants suggested the possibility of a local temperature increase due to the dissolution of potassium carbonate in water. So we tried to determine the temperature rise provoked by this phenomenon of dissolution in a 1-L automatic laboratory reactor in the absence of any other reactants. A local temperature rise from 22.3 to 81.5 °C was observed by a temperature sensor located on the carbonate surface when water was added. These data show that the exothermic dissolution of potassium carbonate in water generated enough heat to locally increase the temperature of the reaction mass and to trigger the decomposition of the nitro compound **1**, generating the observed thermal runaway.

The synthesis under study has been repeated many times at large scale in industry, but the incident occurred only once. So this suggests that the heat transfer is not usually easy, but depending on the particular conditions of charging (i.e., the way solids were deposited), it could occur.

To eliminate the potential secondary reaction of the mixture K_2CO_3/H_2O/TEBA as the cause of the incident, we performed an adiabatic calorimetry experiment (data not shown) in the same molar rates as in the original methodology. We did not detect any exotherm neither a significant pressure increase.

We decided to develop a safer process, and an alternative method that avoided the initial heat evolution was designed. The process was divided in two steps: in a first step, the reaction mass was prepared by adding successively at room temperature all of the reagents except **1** into the reaction vessel and letting the system release all of the evolved heat. In a second step, the nitro compound **1** was added and then heated up to 85 °C. To check the safety of this procedure, reaction calorimetry and adiabatic calorimetry experiments[5] were performed with the following results.

Reaction Calorimetry (RC). The heat flow analysis[6] applied to this dynamic process shows an exothermic event during heating up to 85 °C (Figure 5). The obtained data are shown in Table 1.

The adiabatic temperature rise is calculated to be 18 °C according to the equation $\Delta T_{\text{adiabatic}} = \Delta H/mC_p$ while the MTSR is 103 °C in the worst case (total accumulation). This moderate value demonstrates that safe conditions can be obtained if **1** is added to the reaction mixture maintained at room temperature once the previous exothermic (mixture and dissolution) events have ceased.

Adiabatic Calorimetry (ARC). To define the scenario of criticality, an ARC experiment of the reaction mass was performed in the following manner. Potassium carbonate and water were introduced into the calorimetric bomb, and a

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[5] (a) Landau, R. N.; Blackmond, D. G. *Chem. Eng. Prog.* **1994**, *90* (11), 43–48. (b) Landau, R. N. *Thermochim. Acta* **1996**, *289*, 101–126.

[6] Coates, C. F. *Thermochima Acta* **1985**, *85*, 369–372.

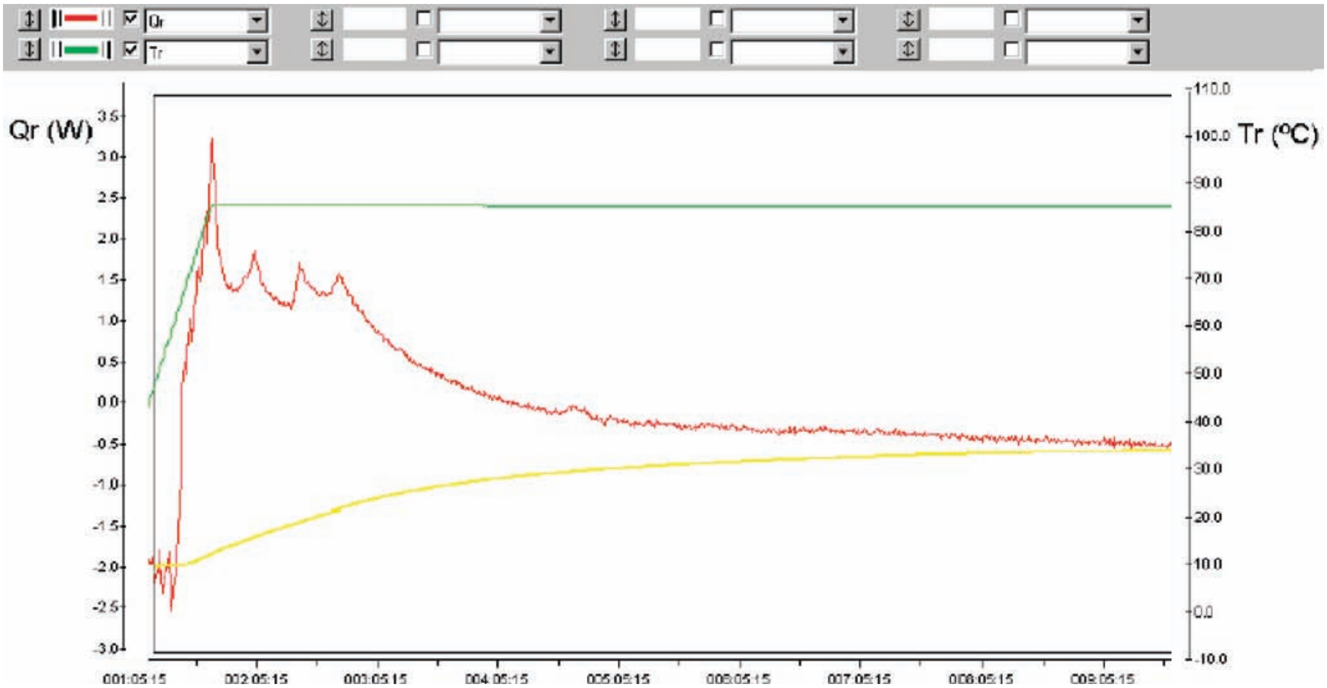

Figure 5. **Heat power (Q_r) and reaction temperature (T_r) as a function of time associated with heating up to 85 °C.**

Table 1. **Results of reaction calorimetry investigation**

heat of reaction (kJ/kg)	35.4
maximum heat flow (W/kg)	7
ΔT_{ad} (K)	18
heat accumulation when reaching 85 °C (%)	91
maximum temp of the synthesis reaction MTSR (°C)	103
heat capacity of reaction mass (kJ/kg K)	2.0

temperature increase was observed. Once the temperature reached room temperature again, triethylbenzylammonium chloride, MEK, 2,2,2-trifluoroethanol and 2,3-dimethyl-4-nitropiridine *N*-oxide were added without stirring. The bomb was introduced into the calorimeter, and the “heat-wait-seek” method was applied.[6] A high severity exothermic phenomenon starting from 173 °C was detected, with a maximum self-heating rate of 4.8 °C/min and an adiabatic temperature rise higher than 200 °C (Figure 6). A value for the heat of decomposition higher than 360 J/g was calculated according to the equation $\Delta H = \Delta T_{\text{adiabàtic}} \cdot C_p$ (estimated value for $Cp = 1.8$ kJ/kg K). The pressure rise due to decomposition was higher than 86 bar, and the time to maximum rate at the final reaction temperature of 85 °C was 1000 h, while at the maximum temperature of the desired reaction (MTSR = 103 °C) it was 300 h.

Finally, to classify the criticality of the process, the well established methodology by Stoessel can be used.[7] We must consider the relative position of four temperature levels: process temperature (85 °C), MTSR (103 °C), temperature at which TMR_{ad} is 24 h (145 °C) and boiling point (85 °C). This allows us to classify our process in a risk class 3 (Figure 7), that is, after loss of control of the synthesis reaction, the boiling point will be reached but the decomposition reaction cannot be triggered. The safety of the process depends on the heat release rate of the synthesis reaction at the boiling point.

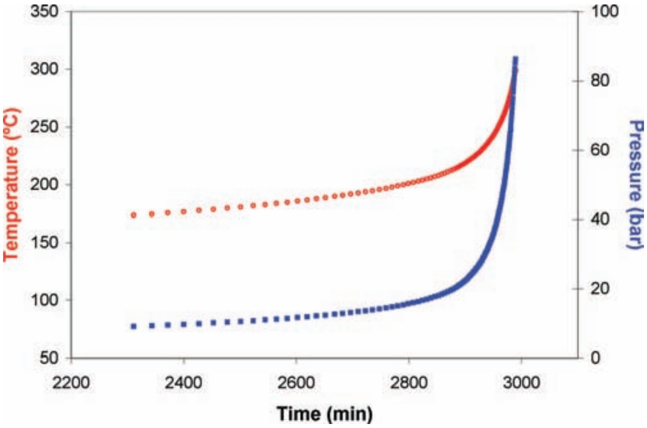

Figure 6. **Temperature and pressure as a function of time of a mixture of potassium carbonate, water, triethylbenzylammonium chloride, MEK, 2,2,2-trifluoroethanol and 1 analyzed by ARC.**

Conclusions

Our investigations have demonstrated that potassium carbonate accelerates the decomposition of **1**, increasing the probability of runaway of the reaction mass in the original methodology. The incident occurred because a local temperature increase took place during water addition, leading the reaction mass to heat up to a runaway activation temperature followed by explosion. An improved process changing the order of addition of the chemicals as an alternative approach has been safely designed, evaluated and successfully scaled-up.

Experimental Section

Equipment Used. Differential scanning calorimetry equipment: Mettler-Toledo DSC-30 differential scanning calorimeter; high pressure crucibles with a capacity of 30 μL. Automatic laboratory reactor: Mettler-Toledo LabMax equipped with a temperature sensor and with a glass anchor stirrer. Reaction

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(7) (a) Stoessel, F. *Chem. Eng. Prog.* **1993**, *89* (10), 68–75. (b) Stoessel, F.; Fierz, H.; Lerena, P.; Killé, G. *Org. Process Res. Dev.* **1997**, *1*, 428–434.

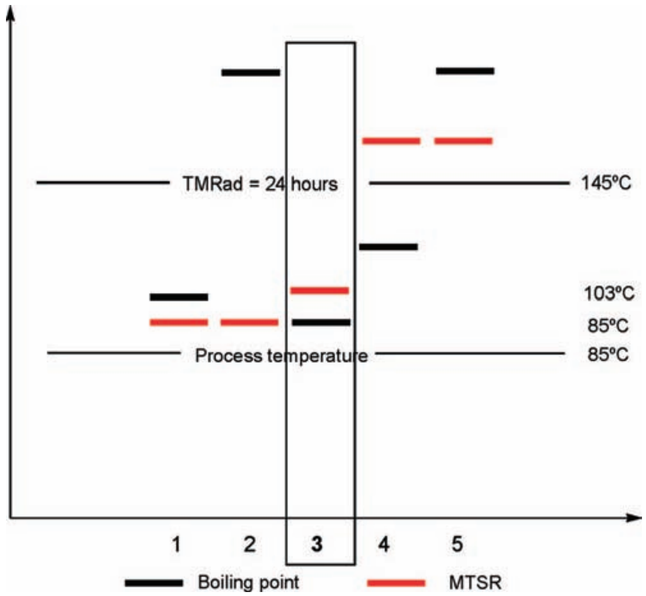

Figure 7. **Evaluation of the thermal risk of the improved process, according to the criticality classes of scenarios.**[7]

calorimetry equipment: Mettler-Toledo RC-1 reaction calorimeter was equipped with a 1-L medium pressure reactor (MP10) and with a hastelloy anchor stirrer. Adiabatic calorimetry equipment: accelerating rate calorimeter was from Thermal Hazard Technology; ARCTC-HC-MCQ (Hastelloy) test cells were used; sensitivity threshold was set to 0.02 °C/min.

General Procedure for RC-1 Experiment. In the reaction vessel at 20 °C were charged potassium carbonate (128.0 g), water (73.7 g), MEK (124.5 g), TEBA (2.6 g) and 2,2,2-trifluoroethanol (157.4 g). The reaction mass was stirred at 150 rpm. Then, at 20 °C, 80.0 g of **1** were added slowly. Finally, the reaction mass was pressurized with nitrogen (1.5 bar), and it was heated up to 85 °C and stirred for 10 h.

General Procedure for ARC Experiments. *Original Methodology*. 2,3-Dimethyl-4-nitropiridine *N*-oxide (2.21 g), TEBA (0.08 g) and potassium carbonate (3.56 g) were introduced into the calorimetric bomb at room temperature, without stirring. The bomb was introduced into the calorimeter, and the "heat-wait-seek" method was applied. *Improved Methodology*. Potassium carbonate (1.37 g) and water (0.72 mL) were introduced into the calorimetric bomb. Once the temperature reached room temperature again, TEBA (27.2 mg), MEK (1.63 mL), 2,2,2-trifluoroethanol (1.12 mL) and 2,3-dimethyl-4-nitropiridine *N*-oxide (0.78 g) were added successively without stirring. The bomb was introduced into the calorimeter, and the "heat-wait-seek" method was applied.

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