

# CALORIMETRIC STUDIES IN EARLY STAGE OF CHEMICAL PROCESS DEVELOPMENT



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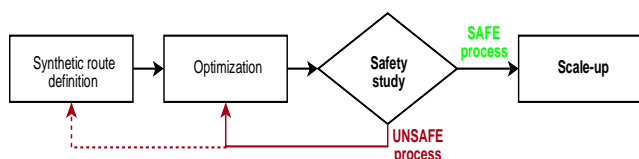
## Introduction

According to the internal company policy about process safety, it is not allowed to proceed with the scale up of a reaction unless its thermodynamic and thermokinetic parameters are determined; considering the whole process, it includes investigation about thermal stability of all fractions involved in<sup>1</sup>. The safety study is always performed before proceeding with the pilot or industrial process.

Such practice, essentially based on safety criteria, aims to obtain a more complete and objective overview of the process before the industrial scale-up.

Making a safe process means that it has to be fully characterized in order to highlight critical points and correct them according to the appropriate criteria.

The result is a deep process optimization, also intended in terms of yield, quality and running time: that means “costs optimization”.



**Figure 1 – Cycle of development of a chemical process**

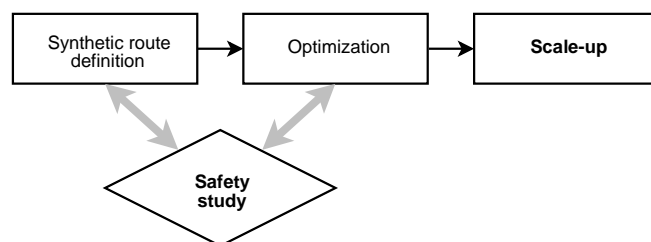
If during the early phase of a chemical process development, critical parameters are not considered before the pilot phase, then serious problems may arise after the execution of the safety study and this could compromise the execution of the scale-up procedure.

It may also happen at this point that corrections of critical parameters will require substantial changes to the process that could make the previous efforts spent for optimization worthless. In very severe cases, the process has to be reviewed and re-optimized and, if problems cannot be corrected, then the synthesis route has to be redefined: that is not easily acceptable in today's context where the strict development schedule is essential to be attractive on the market.

Due to these reasons, Procos set-up an internal organization for R&D process

development where the result of the safety study no longer represents a barrier (YES or NO) to the industrial scale-up of the synthetic method. To increase the efficiency in the production of good results, the use of calorimetric techniques have been introduced from early phases of the process development, starting from the definition of the synthetic route (discovering phase). Results from calorimetric study can be used not only for safety but also for the optimization of the process; this kind of integration makes the calorimetric study a core activity of process development.

Based on these considerations, calorimetric data increase the speed of further development and optimization phases, they will take up the process from preliminary phases through suitable and straighter routes for industrial execution.



**Figure 2 – Process development concurrent to the safety study**

To support this strategy, the R&D structure has to be “adapted”, both in terms of technical skills of human resources, and of available calorimetric equipment.

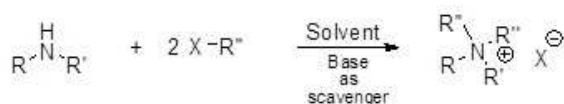
In our case for example, if we consider the Mettler-RC1 calorimeter, it was necessary to purchase a smaller reactor (SV01 / 100±1000 mL) than the standard one (2 Lt) to operate with small amounts of raw materials. Furthermore, we use automatic reactors that assist researchers in the preparations of the substances to be used for calorimetric studies (ex: Mettler-LabMax), DSC & TGA instruments and Systag-RADEX calorimeter for the thermal stability analysis of the reaction mixtures.

Through this new approach, whose implementation is still ongoing in our structure, we obtained a strong reduction of the scale-up time for new developed projects,

reducing necessary resources in term of pilot/industrial timing and human resources (less critical processes, more straight). Thermochemical data collected in early phases of development give valuable support in understanding reaction dynamics and degradations, and help researchers to define a more robust and optimized processes during the synthesis route definition.

The following examples are some real case studies performed in our laboratory in the last year.

## 1. N-Alkylation Reaction



The first case is the scale-up of a process where an N-Alkylation reaction of a secondary amine produces the corresponding quaternary ammonium salt. After the preliminary phase, where the process synthesis route was defined, the recipe indicated to perform the process in batch mode at 50°C. Using 8 moles of the Halogen derivative for 1 eq. of amine and a double molar amount of scavenger vs. amine (1 mole of ammine: 8 moles di Halogen derivative: 2 moles scavenger); the concentration of the substrate (secondary amine) into the reaction mixture was 30 g/l.

Just after the synthesis route was defined (including definition of molar ratios of the reagents), and before the optimization phase of the process, the reaction was performed using the Mettler-RC1 calorimeter (Figure 3).

The reaction was quite slow, and in these conditions, it lasted about 22 hours. The scavenger used was slightly nucleophilic, and the heat emissions towards the end of the reaction were partially caused by the heat of its alkylation (very slow reaction, slower than the main one but exothermic).

The resulting  $\Delta T_{ad}$  was 31.4K and the MTSR<sup>2</sup> resulted to be 81.4°C. The boiling point of the solvent is above this temperature.

The thermal stability of the final MXR at the MTSR is not a problem (RADEX Calorimeter determination).

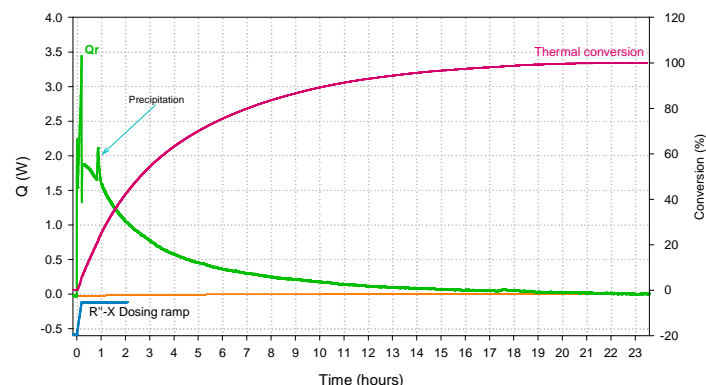


Figure 3 – RC1 Thermogram of the alkylation reaction 30g/l, batch process

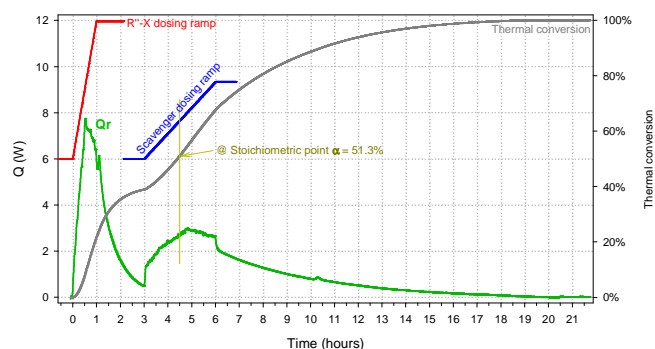
Before starting the next optimization step, we suddenly realized that, to set up a productive process, the reaction batch had to be concentrated and had to operate at a substrate concentration to alkylate of about 170 g/l (5.7 times more than the concentration used in the preliminary recipe).

Starting from the thermodynamic data of the reaction batch at 30 g/l, the  $\Delta T_{ad}$  for the concentrated system was estimated to be 180K. A value no longer manageable by a batch system (MTSR 230°C).

In the optimization phase, we immediately proceeded in developing a semi batch method for controlling the heat emission. The situation was more difficult than expected because the reaction speed at 50 °C was not fast enough to allow a good process control. At higher temperature, a significant amount of impurities formed.

The solution was using a “hybrid” dosing system batch/semi batch where the Halogen derivative was added faster at the beginning (over 1 hour, practically batch) with no scavenger. At this point only 50% of the reaction could take place since the substrate, that had to be alkylated, also acted as a scavenger and its protonated form resulted not nucleophilic. After an appropriate ageing time, we proceeded dosing the scavenger that, being more alkaline than the substrate, freed it as base to give the desired alkylation reaction.

The RC1 diagram of the modified process is shown in Figure 4:



**Figure 4 – RC1 Thermogram of final process at 170 g/l, semi-batch**

For industrial scale it was decided to perform the addition of the halogen derivative in the batch (single portion, no dosage). The adiabatic temperature increase, associated to this addition, resulted 51.1K and the MTSR 101°C.

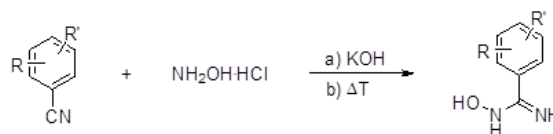
During the addition of the scavenger, performed in 3 hours, the adiabatic temperature, due to the accumulation of the reactive, was 60.8K corresponding to a MTSR of about 111°C (value below the boiling point of the solvent).

The stability of the reaction mixture at the MTSR was verified by RADEX calorimeter and no problems occurred.

## Comments

In this case, thanks to the preliminary calorimetric analysis made by the RC1, prior to the optimization step, we are focused on the potential thermal problem of the batch system in concentrated conditions and, at this early stage, it was decided to develop a semi batch process, optimizing the charging ramps as a function of the process safety. This fact, discovered just before the scale-up, would have required more experiments to define the safe conditions, however, these probably would not have been optimized in function of the requested productivity criteria.

## 2. Formation of an Amidoxyme



The second case refers to a scale-up of a reaction for the synthesis of an Amidoxyme through the reaction of the Hydroxylamine free base on a substituted Benzonitrile. This method, not optimized in our laboratory but developed by the customer, has referred to a laboratory scale production.

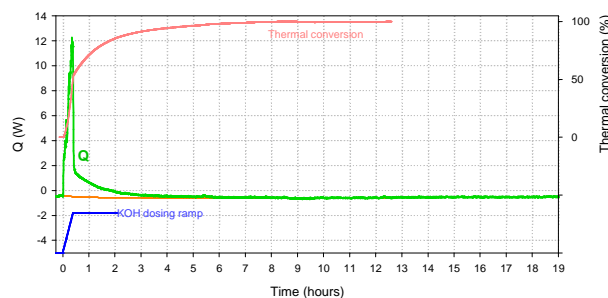
In that recipe, the Benzonitrile was charged into the reactor with the Hydroxylamine HCl (1.5 eq vs. Benzonitrile) and the solvent. At this point, KOH was dosed and the temperature increased by 30K because of the exothermic reaction, due to the base liberation.

At the end of the addition, the system heated to 40°C for about 18-20 hours. A further increase in the reaction temperature for precautionary reasons was not foreseen to prevent the thermal degradation of the Hydroxylamine free base during the reaction.

The customer warned us to pay attention to the possible metallic catalysis that could cause Hydroxylamine decomposition, recommending the synthesis conduction and scale-up in glass lined reactors<sup>3</sup>.

From a preliminary RC1 trial (Figure 5), performed in isothermal conditions at 40°C, it was determined that the heat of neutralization of Hydroxylamine HCl caused an adiabatic temperature rise of about 25K.

At the end of KOH addition, the observed conversion was 55% and the adiabatic  $\Delta T$  due to accumulation was 24K.



**Figure 5 - RC1 Thermogram of the reaction**

Examining the thermal stability of various fraction involved in the synthesis process, the main problem of this reaction system was the stability of the mixture Hydroxylamine base / Hydroxylamine HCl during the addition of KOH. Even if the adiabatic  $\Delta T$  associated with the addition of the KOH was rather low, to maintain the system under isothermal conditions, a controlled dosing ramp was required.

During that dosage, that could take a relevant time, the Hydroxylamine HCl and the free base coexist into the reaction mixture. This was the most severe situation in terms of thermal stability because that mixture became less stable compared to the starting one (100% hydrochloride, quite stable) and also less stable than the final one, where only the complete freed base was contained. The two following RADEX diagrams (figure 6 and 7) evidence such instability; the interpretation of diagrams could be made as a DSC.

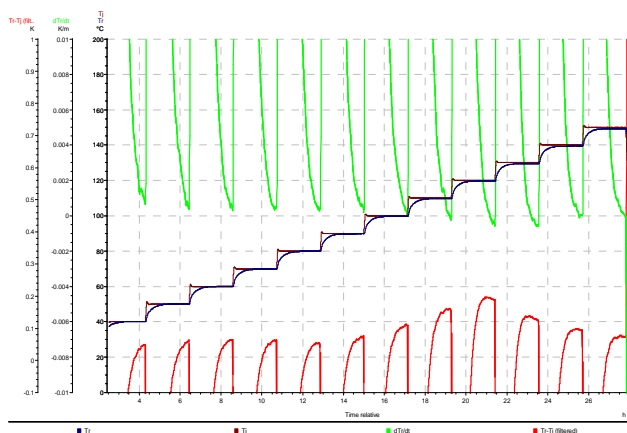


Figure 6 - RADEX Thermogram, solution of the free base

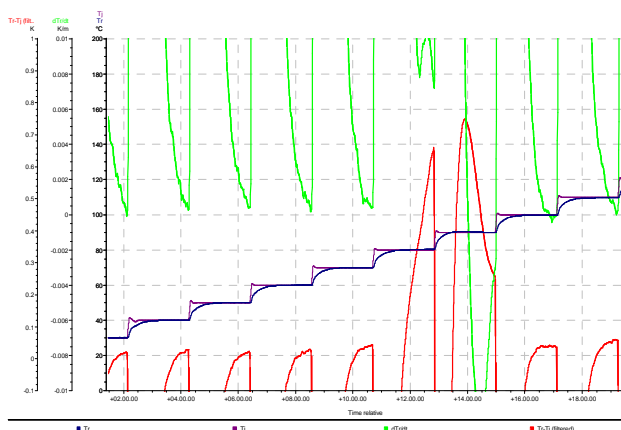


Figure 7 - RADEX Thermogram mix base/HCl 1:1 mol/mol

The final reaction mixture resulted thermally stable up to 120°C.

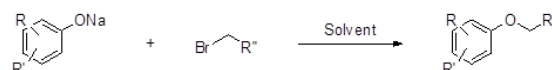
To safely operate this synthesis, a dosage of KOH at low temperatures (5-10°C) must be considered to minimize the risk of the decomposition of the solution of Hydroxylamine base/HCl. Before heating the system at the optimum temperature for the synthesis, the pH must be controlled to verify that the base freeing was correctly performed. Considering the thermal stability of the final reaction mixture, to speed-up the reaction, the temperature may be increased (from 40°C to, for example, 55-60°C) with no further safety issues.

### Comments

This example shows how calorimetric techniques applied during the preliminary screening phase of a process can highlight possible criticalities, suggesting the correct direction of process optimization.

The reaction calorimetry data are very useful in the scale-up, but must be integrated by complementary techniques that allow a more complete risk evaluation. The thermal stability analysis allows optimization of temperature and time.

### 3. Alkylation of a Phenate



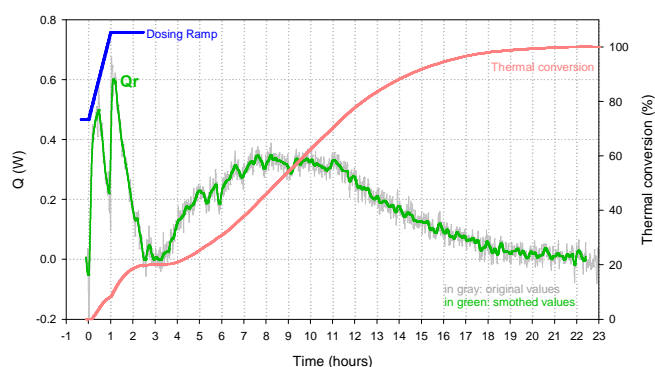
The third case presented is an O-Alkylation of a Sodium Phenate by a primary Bromo derivative with a *complex* structure. In this case the method was not optimized in our laboratory.

The preliminary method (laboratory scale) was provided by the customer who initiated the project for a kilo-lab scale production. In that recipe formula the Phenate and the Bromo derivative (twice the moles of phenate) were charged at room temperature into the reactor with an appropriate solvent.

In the original recipe a further amount of  $\text{K}_2\text{CO}_3$  (20% molar on Phenate) was added. The batch was then heated to 107-110°C for

about 18 hours to obtain the desired conversion of the Phenate.

A preliminary experiment made by RC1 was performed to evaluate the thermal potential of the reaction. For this determination we decided to execute the reaction in semi batch mode by dosing the Bromo derivative in 1 hour at the temperature of 110°C. The reaction was then maintained at the optimum temperature of synthesis. The resulting thermogram is reported in Figure 8:

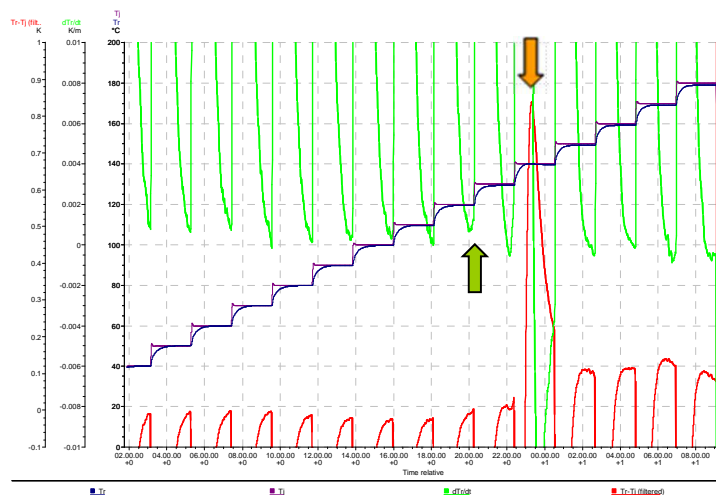


**Figure 8 - RC1 Thermogram of the O-alkylation reaction**

The thermal profile of the reaction is not easily interpreted. Probably the kinetics of the reaction is in function of the solubility of the Phenate that in the reaction solvent is not high enough but increases with the conversion. The adiabatic  $\Delta T$ , considering a batch conduction, is 42K and the MTSR is 149°C (its value is below the boiling point of the solvent).

The reaction is quite slow and the instantaneous associated power is modest, also considering a scale-up on pilot or industrial scale.

Further serious problems were highlighted by the thermal stability analysis of the final reaction mixture.

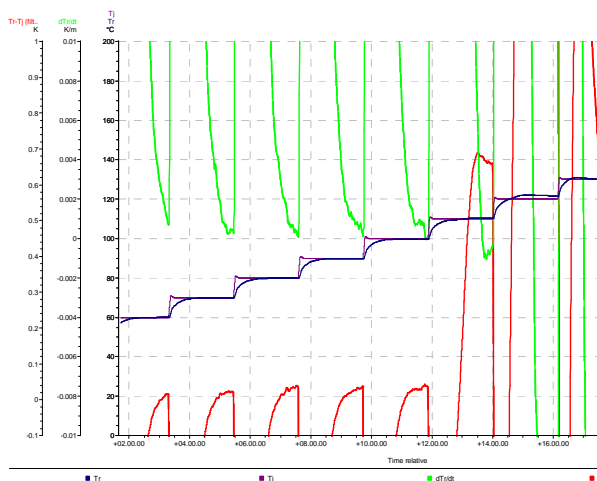


**Figure 9 - RADEX Thermogram, final reaction mixture**

From the reported RADEX thermogram (Figure 9), the reaction mixture could give a thermal decomposition starting from 120°C. The decomposition heat measured by DSC was 320 J/g. The onset of the decomposition reaction is below the MTSR of the reaction: during a batch process, if the thermostat of the industrial equipment had some problems, then the system, even if slowly, could evolve to a dangerous condition of runaway.

We promptly shared this problem with the customer, who was initially quite skeptical, “we have performed the reaction many times but with no problems” – finally was persuaded to evaluate an alternative method.

From further studies we confirmed that the stability problem of the final reaction mixture was not caused by the final product (that is thermally stable both as pure isolated product and in reaction solvent), but was caused by the excess of residual not reacted Bromo derivative. Such compound concluded a strong thermal instability, even in the pure state, starting from 120°C. (figure 10).



**Figure 10 - RADEX Thermogram of the Bromo derivative**

The theoretical evaluation of the thermal stability of this molecule in function of its chemical structure, performed by the ASTM-CHETAH software<sup>4</sup>, gave no warnings.

The change of the current synthesis, to make it safe, is still under study and, at this point, two different routes are under evaluation. The first uses a semi batch method, changing the concentration of the Phenate in

the reaction solvent, furthermore reducing the excess of the Bromo derivative without varying the conduction temperature.

The second considers a different method, using a PTC catalyst in order to reduce the temperature of synthesis and the use of a solvent whose boiling point temperature is lower than the onset of the decomposition of the Bromo derivative; in this manner the reflux of the system can act as barrier for reaching the onset of thermal decomposition.

## Comments

In this case, it has been highlighted how a preliminary calorimetric analysis allows for the reduction of time and resources wasted to optimize a method that, if considered from a safety point of view, may have such severe problems that it is impossible to scale it up.

## References:

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<sup>2</sup> Lerena P.; Wehner W.; Weber H.; Stoessel F. - Assessment of hazards linked to accumulation in semi-batch reactors *Thermochimica Acta*, Volume 289, Number 2, 1 December 1996, pp. 127-142(16)

<sup>3</sup> Gigante L.; Lunghi A.; Pasturezzi C.; Rubiliani B.; Cardillo P.; Bielli A.; Rota R. - L'idrossilammina e i suoi sali: studio termooanalitico e di sicurezza - *La rivista dei combustibili*, Vol. 58, fasc. 4, 2004

<sup>4</sup> Shanley E.S.; Melhem G.A. - A review and critique of ASTM CHETAH 4th edition - *Journal of Loss Prevention in the Process Industries*, Volume 13, Number 1, January 2000, pp. 67-68(2)