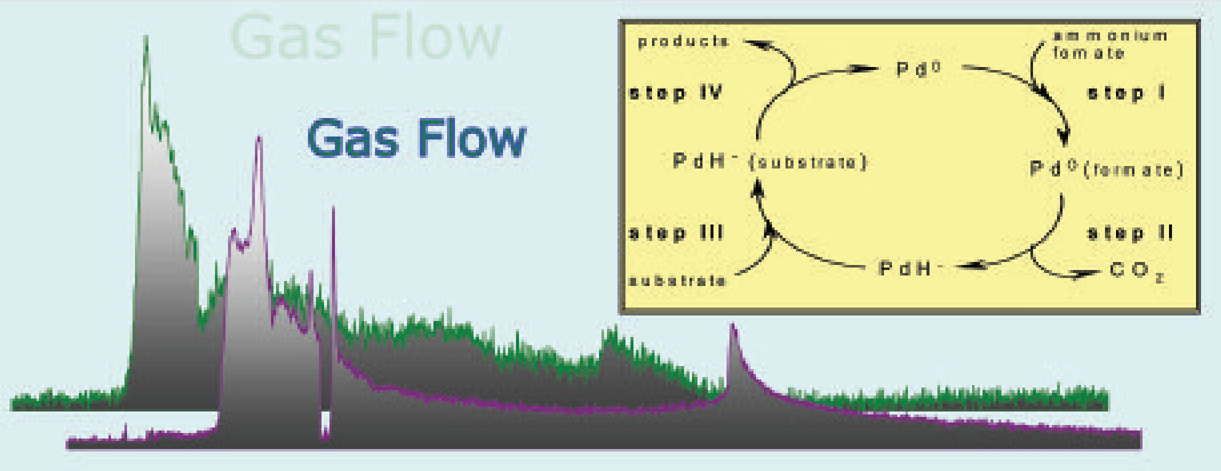

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PROCESS SAFETY ASSESSMENT OF A GAS GENERATING REACTION

Detailed knowledge of the hazards associated with chemical reactions is crucial to a successful and safe transfer of chemical processes from laboratory to plant. A case study, where reaction calorimetry was coupled with scale-down and mixing studies for the hazard assessment of a palladium catalysed transfer hydrogenation, is discussed.

A detailed chemical reaction hazard assessment must be undertaken for every chemical process prior to scale-up and, in particular, prior to transfer into a GSK chemical pilot plant. This assessment by process safety scientists is designed to identify, quantify and where possible eliminate safety issues in the transfer of chemical processes from laboratory to plant. Without knowledge of the hazards associated with a chemical process, no safe scale-up would be granted.

Central to the data-gathering necessary for the assessment is measuring the amount of heat and gas evolved from the chemical reactions. Understanding how best to control these and temper the rates is a key part of the chemical hazards assessment.

Case study

A case study of process safety assessment is presented below. Key to the safe scale-up of this process was the understanding of the chemical reactions involved and the generation of data to quantify the rates of evolution of heat and gas.

The process consisted of simultaneous debenzylation and CBz-deprotection (CBz=carboxybenzoyl) reactions followed by an intra-molecular cyclisation. The three chemical reactions all occurred under conditions of catalysed hydrogena-

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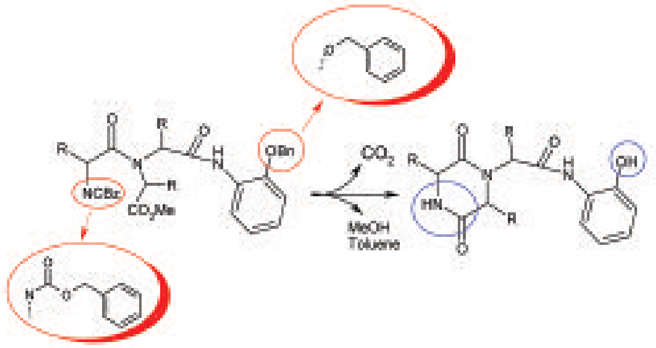


Fig. 1

tion (Fig. 1). The process generated carbon dioxide and toluene as by-products of the N-CBz deprotection and another equivalent of toluene in the O-debenzylation. Methanol was then liberated as a result of the spontaneous cyclization.

Reaction under gaseous hydrogenation conditions

This process was first developed as a gaseous hydrogenation and successfully scale-up to a 10 kg scale. 5% Palladium on carbon catalyst and 0.5 barg of hydrogen afforded the desired product at ambient temperature in N-methylpyrrolidinone (NMP) as solvent.

Process safety assessment of this process showed that the reaction was moderately exothermic (heat of reaction: -247 kJ/mol of substrate) with a mild associated predicted adiabatic temperature rise. Also, no particular thermal stability issues were associated with the chemistry. The basis of safe operation for this process was therefore simply centred on safe handling of the catalyst, control of the rate of reaction via control of the hydrogen flow and safe venting. It may be said that similar basis of safety would generally be shared by most standard gaseous hydrogenation reaction.

The process did, however, possess some drawbacks: the build up of carbon dioxide in the headspace required periodic venting of the gases to allow the hydrogenation to continue giving typical reaction times of approximately 16 hours on plant. Long reaction times and the limited availability and sizes of hydrogenation vessels restricted the throughput of the process.

Development of a new transfer hydrogenation process

A new process was then developed in the chemistry laboratory using a transfer hydrogenation process rather than gaseous hydrogenation. Ammonium formate was chosen as the hydrogen source and the process again utilised 5% palladium on carbon catalyst. This process could then be run in general plant equipments allowing for a more efficient production of batches which made the new process highly desirable. During the process development however, reaction initiation time showed to be inconsistent and associated with vigorous liberation of gas once the reaction had finally started. At the same time, some liberated carbon dioxide was reacting further to generate ammonium bicarbonate which was subliming from the reaction mixture. In some cases the process even failed entirely to initiate.

It was also shown in the chemistry laboratory that the variation in the incubation time for the process initiation was partially to be attributed to different quality of input solutions which were being carefully filtered at the end of the previous step. Producing a robust process and, at the same time, establishing safe operating conditions for taking this chemistry onto plant was now a challenge for the project team.

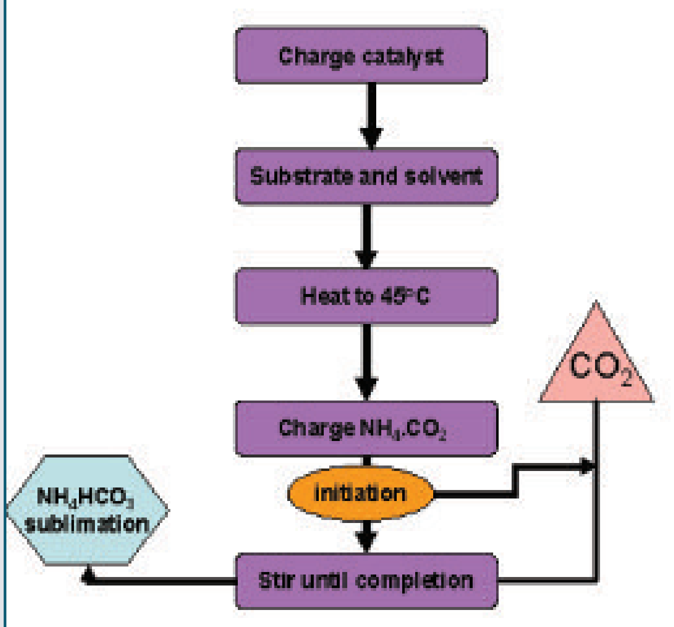


Fig. 2 - First semi-batch process

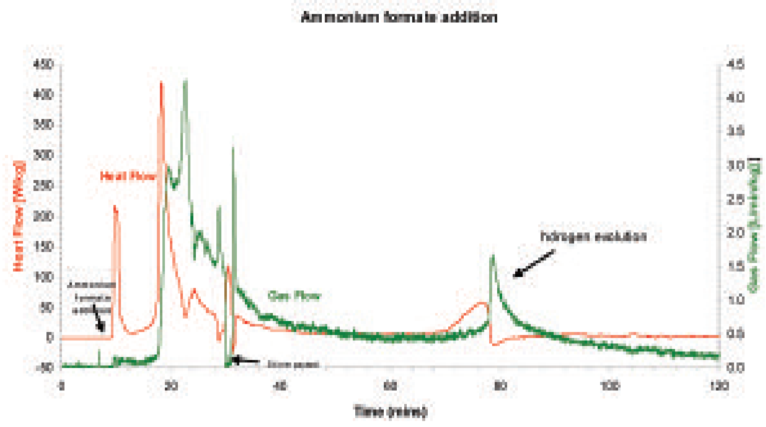
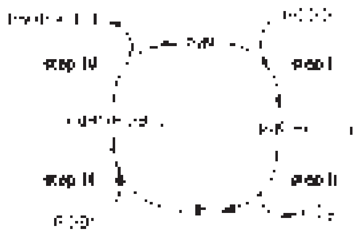


Fig. 3 - RC1® trace of heat and gas evolution

Step I: Adsorption of formate ion on catalyst
Step II: Abstraction of "hydride" by the catalyst with generation of carbon dioxide
Step III: Adsorption of substrate onto catalyst "hydride" species
Step IV: Formation of desired product



Scheme 1

Initial process safety assessment

Process safety assessment of this process was promptly initiated and reaction calorimetry data collected. The Mettler Toledo Reaction calorimeter, RC1®, coupled with a thermal mass-flow-meter and mass spectrometer for gas stream analysis were used. A semi-batch procedure where the substrate and catalyst slurry were firstly heated to temperature before introducing the aqueous ammonium formate solution was tested (Fig. 2).

Initial calorimetry results showed that the reaction was not very exothermic however accurate heat measurement was being negatively affected by the high degree of foaming in the vessel. The reaction, in fact, was liberating a large amount of gas and, as described above, this was accompanied by copious sublimation of ammonium bicarbonate. Analysis of the gas stream showed that although carbon dioxide was the major component, hydrogen was also being evolved in the latter stages of the reaction.

Despite the mixture being heated prior to ammonium formate addition, reaction initiation would still only occur several minutes after addition completion. The reaction was behaving as a batch process. Upon initiation, rapid heat and gas evolution would be detected. This was followed by several uncontrolled gas spikes throughout the reaction profile including a delayed surge of gas towards the end of the reaction. Although relatively low heat and gas rates were being detected, a considerably larger total amount of gas was being produced as a result of this new transfer hydrogenation process (2 eq of carbon dioxide rather than 1 eq).

Also, a large batch size, approximately 100 kg, was planned for the following plant campaign. Typical heat and gas profiles are shown below (Fig. 3). Uncertainties over the scalability of the above gas evolution profile had also become an area of great concern. It was therefore clear at this point that a further mechanistic understanding of the transfer hydrogenation reaction together with some process optimisation were required.

Process understanding: mechanism of transfer hydrogenation

The hydrogen-donating abilities of various formates and in particular of ammonium formate with palladium catalysts are well described in the chemical literature (V.S. Rajagopal, A.F. Spatola, *Applied Catalysis A: General*, 1997, **152**, 69).

The reaction path can generally be divided into steps reported in Scheme 1. Kinetic studies have shown that abstraction of "hydride" (step II) from the ammonium formate by the catalyst is generally considered to be the rate limiting step. This is then followed by a rapid adsorption of the substrate as well as reaction to afford the desired product. Literature data also highlighted that the initial rate of reaction (step I) was dependant on ammonium formate concentration as well as total number of active sites on the catalyst. The kinetics of this transfer hydrogenation reaction were thus suggesting that a slow addition of ammonium formate may have helped gaining control over the reaction initiation. An increased catalyst loading was also adopted and this contributed, together with quality of substrate, to a more consistent reaction initiation profile.

Reaction calorimetry investigations then resumed.

Development of a basis for safe operation

A controlled slow addition, over approximately 45 min., of the solution of ammonium formate was established as the preferred process for plant scale operation. It was this process that was further investigated with the use of reaction calorimetry.

For all future reaction investigations a more accurate representation of the plant set-up was adopted. A round bottom 2 L RC1® vessel (AP01®) equipped with an upflow propeller stirrer was used for all subsequent experiments. Baffles were also introduced to reduce the level of foaming and improve accuracy of heat and gas measurements. Thermal mass flow meter and mass spectrometer were still being used for gas stream analysis. As described above, the new "scaled-down" process that was now being investigated consisted of a slow addition of aqueous ammonium formate to the substrate and increased catalyst loading as a slurry in NMP at 45 °C (Fig. 4).

Experimental results were now showing a heat output of -230 kJ/mol of substrate, with a moderate associated predicted temperature rise. A surge of heat and gas associated with reaction initiation was consistently observed during the addition of the first 20% (1 eq) of ammonium formate solution. Significantly lower rates of both heat and gas would then accompany the remainder of the addition. Copious sublimation could not be avoided however it was demonstrated to be occurring only after the main heat and gas evolution spikes. This was then representing a minor risk of line blockage during the key part of the reaction. A typical experimental profile is shown in Fig. 5.

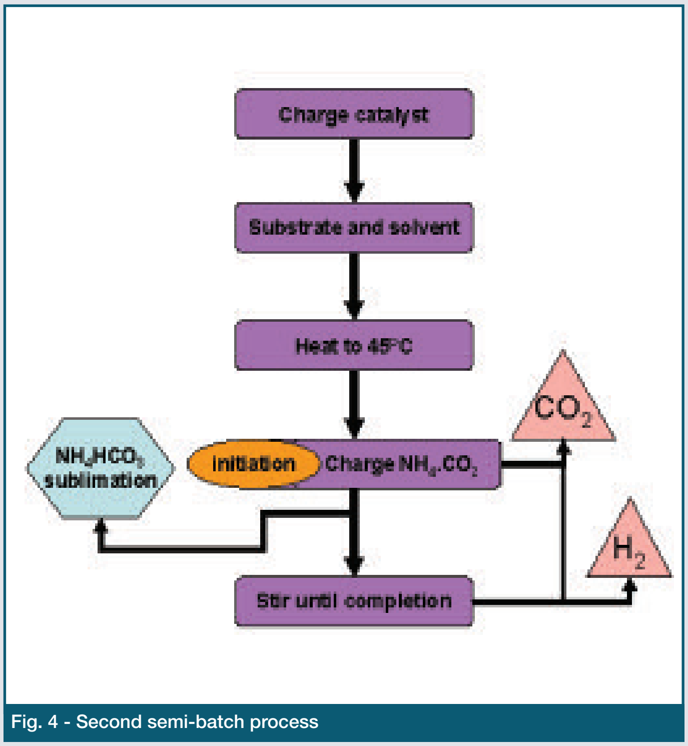


Fig. 4 - Second semi-batch process

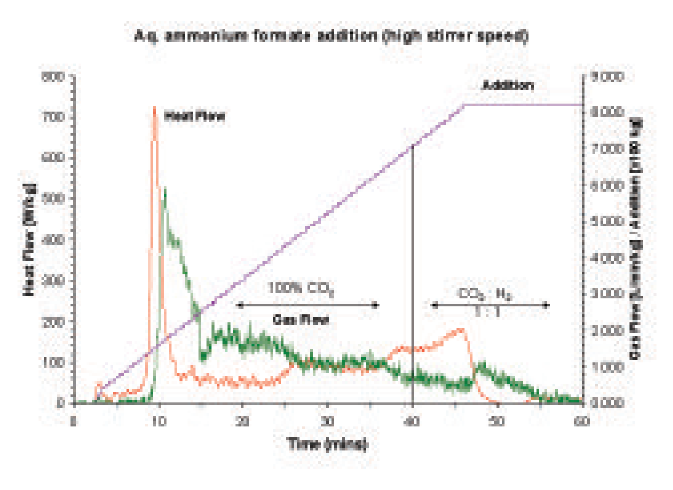


Fig. 5 - RC1® trace of heat and gas evolution

Analysis of the gas stream with the use of a mass spectrometer confirmed what was already suggested in the literature. As long as the substrate was available competitive decomposition of ammonium formate to afford hydrogen, carbon dioxide and ammonia was non-existent. This meant that until reaction was complete, no risk of hydrogen evolution existed. The problematic initial surge of gas was composed solely of carbon dioxide. Decomposition of excess ammonium formate would then begin once the substrate was consumed thus causing the delayed surge of gas.

Mass spectrometer analysis of the gas at this point confirmed that at by that point the gas stream composed of hydrogen and carbon dioxide approximately on a 1:1 ratio. This unwanted decomposition of the excess ammonium formate however was occurring during the final part of the addition meaning that only very minor accumulation of gas was being observed. Further reaction optimisation could ultimately eliminate this issue.

Although a better reaction profile and accurate calorimetry data were now available, it was still obvious that no control on the initial heat and gas evolution rates could be established. Investigations of the effect of stirring rates on the gas evolution were therefore necessary in order to safely run the process on a 100 kg scale.

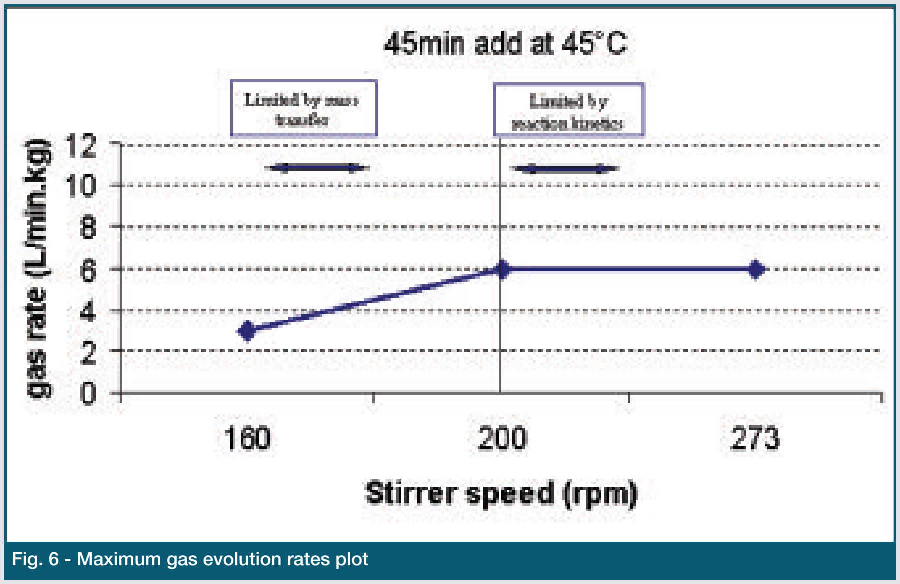


Fig. 6 - Maximum gas evolution rates plot

Establishing whether the gas evolution profile, for the chosen addition time, was determined by the intrinsic reaction kinetics or by the gas-liquid mass transfer was key to a successful reaction hazards assessment. A set of experiments, in collaboration with the chemical engineering group, were therefore carried-out to answer this question. Detailed analysis of the data collected soon showed that slower stirring regimes would cause the process to fall into a gas-liquid mass transfer limited zone. In such a case, accurate scale-up prediction of gas evolution rates would have not been possible without detailed knowledge of plant gas-liquid mass transfer data. However, as the stirring speed was gradually increased the maximum gas evolution rates reached a plateau. At this point, the system had transitioned to a point where the gas evolution rates were solely governed by the intrinsic reaction kinetics (Fig. 6).

These measurements demonstrated that, as long as the addition time and the reaction temperature were kept constant, a maximum gas flow of 6 L/min./kg of substrate could be expected for any type of vessel configuration. This rate of gas flow would then represent a "worst case scenario" for scaling up this process onto plant. Additionally, detailed engineering calculations and vessel calibration were carried-out in the pilot plant in order to establish accurately the maximum venting capacity for the proposed vessel and scrubber set-up. With all these data and process knowledge to hand, the team was now in a position to establish a basis for safe plant operation of this process. The newly developed transfer hydrogenation process could now be run on plant scale as long as implementation of the following key controls was ensured:

- control of the batch size to ensure max rates of gas falls within the plant venting capability;
- slow controlled addition of aqueous ammonium formate solution via a fail-safe device;
- confirmation of reaction initiation after 20% of addition;
- headspace of at least 50% available in the vessel to contain any foaming.

Summary and conclusions

In order to safely transfer the new process from laboratory to plant scale it was necessary to establish a basis of safe operation for the plant.

The key to this exercise was initially in selecting the semi-batch process and then in understanding the fundamental chemical reactions underlying the heat and gas-flow data generated using reaction calorimetry. The key differentiation between the mass-transfer limited process and the reaction kinetics was essential in establishing the worst-case scenario of gas evolution rates. This process was successfully run on plant on a 50 kg scale.

Acknowledgements: This work was carried out in collaboration with the Synthetic Chemistry and the Chemical Engineering project team members.

ABSTRACT

Valutazione della sicurezza di processo di una reazione di generazione di gas

La conoscenza dei pericoli associati alle reazioni chimiche è cruciale per il trasferimento sicuro dei processi chimici da scala di laboratorio all'impianto. Nell'articolo viene descritto un processo in cui la calorimetria di reazione viene accoppiata al ridimensionamento e allo studio della valutazione del rischio di un'idrogenazione tramite catalizzatore di palladio.