Thermal Hazards of the Vilsmeier-Haack Reaction on N,N-dimethylanilin.

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Abstract - Summary

From literature data and a preliminary calorimetric study it is clear that the Vilsmeier-Haack reaction poses specific thermal hazards as both the Vilsmeier-Haack intermediate (1) in N,N-dimethylformamide (2) and the reaction mixture with N,N-dimethylanilin (3) are thermally unstable and can generate high and fast temperature and pressures rises when heated. Therefore alternatives were investigated for their thermal hazards. The stability of Vilsmeier intermediates generated from a series of other formamides was investigated. In principle the Vilsmeier intermediate could be generated and converted *in-situ*, thus avoiding large amounts of an unstable intermediate in the process vessel and yielding the same reaction mixture. This concept could also be applied to the other formamides studied and this option was also included in the investigation.

Introduction

The Vilsmeier-Haack reaction[1,2,3] is a widely used for formylations. It can be applied to introduce an aldehyde group on activated aromatic compounds, but many other conversions can be achieved with this technology. In general N,N-dimethylformamide (DMF) and phosphorous oxychloride (OPCl$_3$, 4) are used to generate the Vilsmeier-Haack Intermediate. Within Agfa this reaction is used for the production of N,N-dimethylaminobenzaldehyde (DMAB, 5), from N,N-dimethylanilin (DMA), as an intermediate for dyes (Scheme 1).

Scheme 1. General reaction scheme of the Vilsmeier-Haack reaction on N,N-dimethylanilin
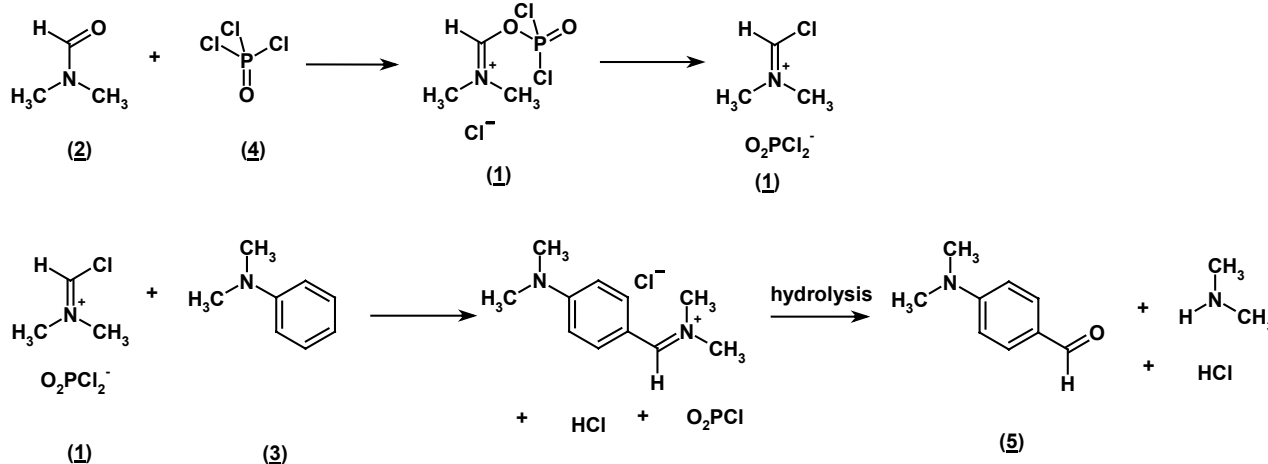
In the European Union the Seveso II directive requires that the hazards of chemical processes are identified in order to control the risks and avoid major incidents. One of the common hazards of chemical reactions performed in a (semi) batchwise process is a runaway resulting in a thermal explosion. It is imperative to have the appropriate experimental data to evaluate the risk of this possible event. Reaction and adiabatic calorimetry testing are the techniques used to acquire these data.

Batch and semi-batch processes can be classified into five types of runaway scenarios[4,5] (Figure 1)[7] depending on the relative position of the following parameters : process temperature (Tp), boiling temperature of the reaction mixture (Tb), maxiumum temperature of the synthesis reaction (MTSR) and the temperature with a time to maxiumum rate of 24 hour (TMR$_{24}$ or MaxTsafe 24[6]).
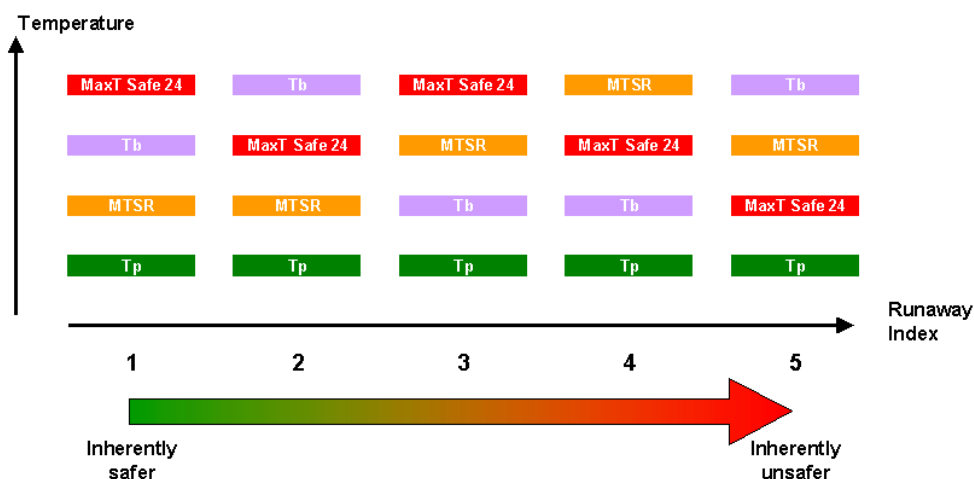
Figure 1. Classes of thermal runaway scenarios.

Process temperature and boiling point can quite easily be obtained but MTSR should be calculated from calorimetric data and Max Tsafe 24 values come from adiabatic thermal stability testing. For the readers not familiar with reaction calorimetry : the heatflow (Qr) is a measure for the heat generated by the process(ess) at any time; integrating this signal over the whole process yields the total process enthalpy (ΔH). The combination of these data with other process information allows the calculation of other parameters which are important for risk assessment of the process. These comprise :

- MAT : Maxiumum Adiabatic Temperature that can be achieved when all the process enthalpy is converted to temperature rise,
- MTSR : Maxium Temperature of the Synthesis Reaction is the calculated temperature that will be achieved when the dosing is stopped at the time of a cooling failure, it is a measure for the accumulation in a semi-batch process during the process,
- FHR : Fraction of Heat Released is a measure for the accumulation of reagent at the end of the dosing.

This concept is used in the risk assessment of all our chemical processes. In this report we discuss the results of the study of the process for DMAB production.

Literature information

There is only limited literature data on the thermal hazards of the Vilsmeier-Haack reaction[8,9]. Both articles have been examined and although the interesting information, this data was not sufficient to identify the hazards of a similar process. Other references on this topic were unavailable in the time allowed for this study.

Thermal Hazard Evaluation of Vilsmeier Reaction with DMF and MFA[8]

In this article the authors studied the Vilsmeier reaction under specific experimental conditions : short addition times (less than 2 minutes) and high dilution (DMF/OPCl$_3$ = 24/1 MFA/OPCl$_3$ = 15/1 in mass ratio). Both these parameters are outside of the operations range of our proces. In our opinion it is required that calorimetric data are obtained under conditions as close as possible to plant conditions and the conditions mentioned are quite different from our process. A reaction enthalpy value of –57 kJ/mol is reported. The authors state that there is a high potential hazard of thermal decomposition of the Vilsmeier complex in the cases where this is formed without substrate present. This can be avoided by running the process in a different way : mix the substrate with DMF and feed OPCl$_3$ to it and the Vilsmeier complex is consumed as soon as it is formed.

Scale-up of a Vilsmeier Formylation Reaction : Use of HEL Automate and Simulation Techniques for Rapid and Safe Transfer to Pilot Plant from Laboratory[9]

In this article the Vilsmeier reaction is run with DMF/OPCl$_3$ and an additional solvent at a temperature of – 5 °C either with or without the substrate in the reaction mixture at the time of addition. It is claimed that the best chemical results are obtained with preformed Vilsmeier complex

in the solvent mixture. Calorimetric data was used to model the reaction to support the scale-up of the process. A comparison of the data obtained from the AutoMate and Simular was also discussed. The potential of decomposition of the reaction mixture is not mentioned.

The literature information presented here was not sufficient to identify all the hazards associated with our process. Therefore an initial calorimetric study was performed in the RC1 according to the parameters of the production process. This intitial study indicated that high-energy potentials were involved therefore a more in depth study was required to fully characterize the thermal hazards of this process.

Results and discussion

Our intitial objective for studying the DMAB process was to measure the reaction heat and determine the thermal stability of the reaction mixture at different stages in order to establish the 'runaway index'. The results confirmed the findings of previous studies in that there is a significant problem with thermal instability. This prompted us to investigate the thermal hazards of potential alternative methodologies : integration of the process stages, use of other formamides and a combination of both.

1. The two-stage DMF process

In the standard production process the Vilsmeier intermediate is generated in and from DMF by dosing $OPCl_3$ to excess. Subsequently this is reacted with a feed of DMA. The product is then transferred to a mixture of water and sodium acetate to hydrolyse and isolate the DMAB. This is called the two-stage process since there are two feed sequences.

Reaction Calorimetry

In order the facilitate the interpretation and avoid extrapolation of the results, the reaction calorimetry was performed using, as far as possible, the production conditions – see Experimental Section. The reactor was charged with DMF, cooled to the process temperature and $OPCl_3$ was dosed to it, followed by the DMA. As shown, aging period was used to ensure complete reaction. This yielded the following results for the formation of the Vilsmeier intermediate.

Table 1. Calorimetry results DMF + $OPCl_3$ at 5°C		
Parameter	Value	Comments
Qr	22 W/mol 5 W/mol	At the start there is an interaction with the water present in the technical grade DMF (0.3 %)
ΔH	- 46 kJ/mol	Total reaction enthalpy, including the interaction with water which has a contribution of about – 10 kJ/mol, leaving about - 36 kJ.mol for the Vilsmeier reaction
MAT	73°C	MAT including the interaction with water, MAT = 61°C for the Vilsmeier reaction
MTSR	6 °C	Indicates an addition limited process
FHR	98 %	Nearly no accumulation

The graphical representation of measured and calculated parameters allows more in depth interpretation of the calorimetry information and results.
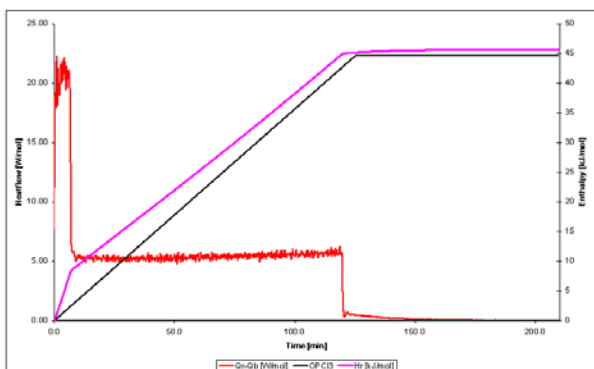
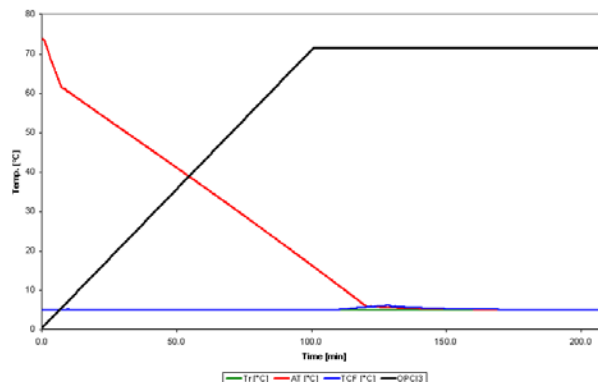*Figure 2.* DMF + OPCl$_3$ ⇨ Vilsmeier profile

Figure 3. DMF + OPCl$_3$ ⇨ Vilsmeier safety parameters

It can be concluded that the reaction is fast compared to the dosing rate and generates only a moderate amount of heat. The conversion is essentially complete at the end of the dosing and within 60 minutes of this all heat production has ceased.

Adiabatic Calorimetry

A sample taken from a reaction mixture after the dosing of OPCl$_3$ to DMF was transferred to the ARC (ARC = Accelerating Rate Calorimetry) test cell (usually called ARC bomb) and the 'heat-wait-seek' profile was applied. The measured data are summarised in *Table 2*.

| *Table 2.*		
Parameter	Value	Comments
Onset temp.	67°C	Temperature at which the first heat production above the sensitivity threshold is detected
Temp @ max rate	173°C	Temperature at which the maximum rate of temperature rise is detected
Max. T. rate	28°C/min	The maximum temperature rate. This value can be considered as a high rate
Max. P.rate	48 bar/min	The maxiumum pressure rate This value can be considered as a high rate
MaxTsafe 24	49°C	This rather low value is the result of the low onset temperature and the short time to thermal explosion.
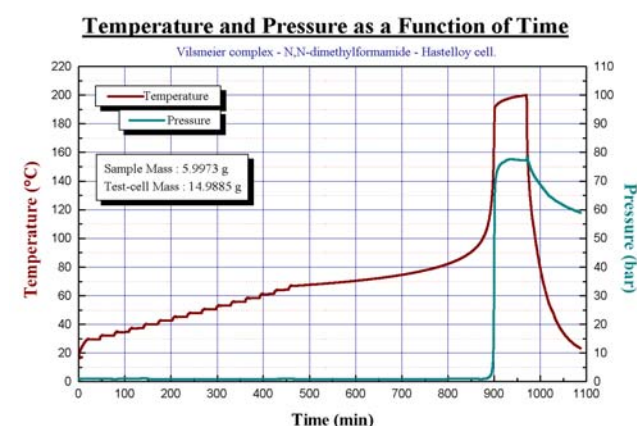
Figure 4. ARC – T,P-graph
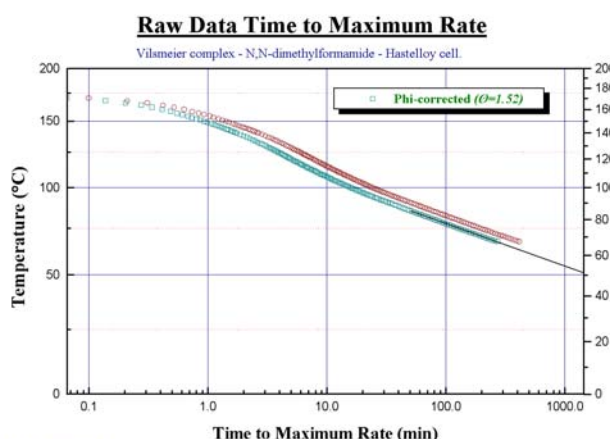
Figure 5. Max T Safe 24 graph

The sample starts to self-heat above the threshold value from 67°C. This exotherm continues to around 195°C where the temperature and pressure stalls. Around 140°C there is a rapid temperature increase accompanied with a sharp pressure rise, comparable to an explosion. A MaxTSafe 24 value of 49°C is obtained after extrapolation to 1440 minutes and correction for the phi-factor (the phi-factor is the ratio of the total mass (bomb + sample) over the mass of the sample; the lower the value, the better).

Runaway index Vilsmeier intermediate formation
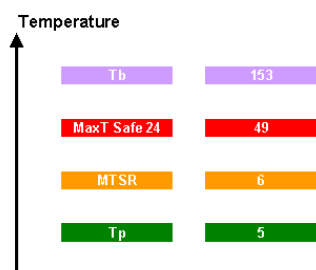
Although the MaxTSafe 24 value is quite low, this is still a class 2 process because of the slow dosing, the strong feed control and the low temperature rise in case of cooling failure.

Figure 6. Runaway index for the formation of the Vilsmeier intermediate in DMF

For the reaction calorimetry of the Vilsmeier intermediate with DMA the following results were recorded by the RC1.

| *Table 3.* Calorimetry results Vilsmeier intermediate + DMA at 15 ⇨ 40°C		
Parameter	Value	Comments
Qr	± 12 W/mol	The heatflow starts at 4 W/mol and increases to ± 12 W/mol after 20 minutes.
ΔH	107 kJ/mol	This value includes the phase at higher temperature, required to finish the process
MAT	112 °C	This high value is the result of the high reaction enthalpy and the high concentration of the process, but for a semi-batch process this is not particularly significant
MTSR	46 °C	A 30 °C increase due to accumulation in the process can be considered as a high value
FHR	70 %	This also indicates a substantial accumulation of the energy potential of the process. The reaction is slower than the feed.
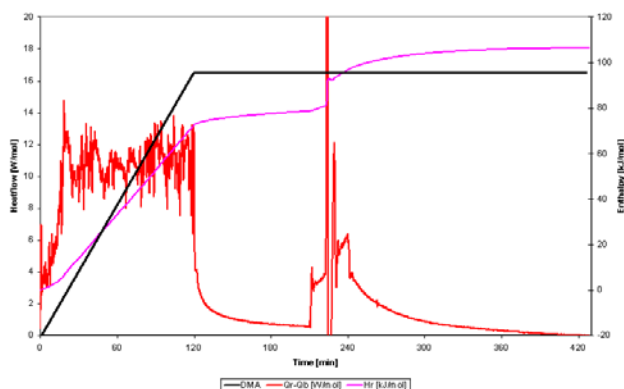
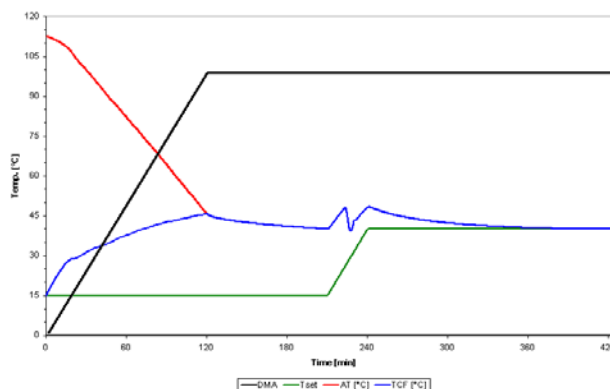*Figure 7.* **Vilsmeier + DMA profile**

Figure 8. **Vilsmeier + DMA safety parameters**

This reaction profile is more complex as there seems to be some induction period before the heat production reaches a constant value. Although the heatflow drops substantially at the end of the dosing, after 90 minutes there is still heatflow and during the temperature rise from 15 to 40°C. Further reaction is observed, including a sharp peak possibly due to crystallisation. At the final temperature an aging time of 180 minutes is required to complete the thermal conversion. It seems that 15°C is too low a temperature to maintain full control on the process via the dosing. This is both indicated by the MTSR and FHR results. A higher process temperature could avoid this accumulation, but it should be confirmed that this change leaves the product quality unaffected.

A sample of the final reaction mixture was subjected to the same ARC test procedure as the intermediate and yielded the following data.

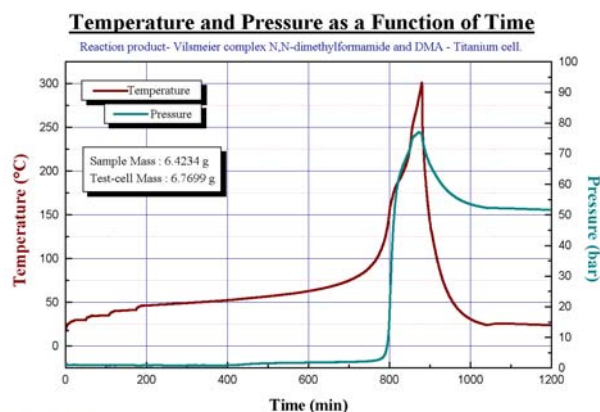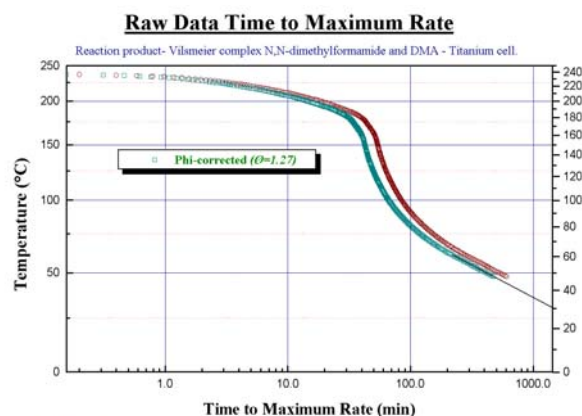| Table 4. ARC results on the reaction mixture Vilsmeier + DMA		
Parameter	Value	Comments
Onset temp.	48°C	The start of the exothermic activity in the sample
Temp @ max rate	238°C	
Max. T. rate	4.6°C/min	
Max. P.rate	4.2bar/min	
MaxTsafe 24	30°C	This rather low value comes from the low ontset temperature and the high velocity of the decomposition.

Figure 9. ARC – T,P-graph

Figure 10. Max T Safe 24 graph

The exothermic activity in the sample starts at 48°C and proceeds to a temperature of 300°C, which terminated the test, and a pressure of 77 bar. From 120°C on there is a strong pressure increase over a short period. The first exotherm switches to a second one around 175°C.

A runaway index of 5 is obtained for the reaction of the Vilsmeier intermediate with DMA.
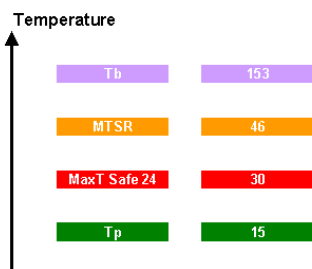
Figure 11. Runaway index

The combination of the high accumulation during the feed and the low onset temperature for the reaction mixture result in a runaway index of 5. It is recommended to avoid this type of process which therefore should be revised.

2. The one-pot DMF process

From both in-house experience and literature information[8] is was clear that an alternative method of running the same process should be possible. As indicated earlier $OPCl_3$ could be added to a mixture DMF and DMA at the required process temperature. Since the reaction between DMF and $OPCl_3$ is fast it can be assumed that the Vilsmeier intermediate is generated in situ and could already start to react with the DMA. In this way the build up of large amounts of the Vilsmeier intermediate could be avoided. It is difficult to predict if this would also result in a more thermally stable reaction mixture. To adress this issue, the calorimetric study was extended and the one-pot process was investigated. The initial conditions chosen were close to the existing process in that the temperature was set at 15°C, then the reaction at which the DMA reaction is run in the two-stage process. The reactant feed time was extended to the sum of the two feed periods because more heat generation is expected. In the following experiments an analytical grade of DMF with low water content was used to confirm that the initial heatflow peak comes from the interaction with water, as it is not present. The results of the first experiment are summarized in Table 5 and the profiles are represented in Figures 12 and 13.

| *Table 5.* Calorimetry results Vilsmeier intermediate + DMA at 15°C		
Parameter	Value	Comments
Qr	13 W/mol	Initial plateau first 60 minutes
	21 W/mol	Peak value, probably due to crystallisation
	4 W/mol	Final plateau from 150 to 240 minutes
ΔH	- 142 kJ/mol	This corresponds to the sum of the 'two-stage' process
MAT	165°C	High value due to high reaction enthalpy and low Cp value
		Not relevant for a controlled semi-batch process
MTSR	23°C	8°C potential temperature rise near end of feed period
FHR	95 %	Only small amount of accumulation
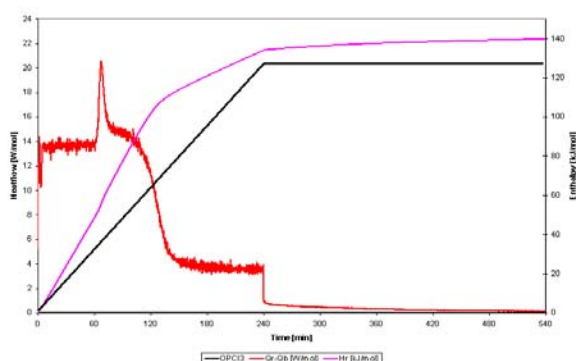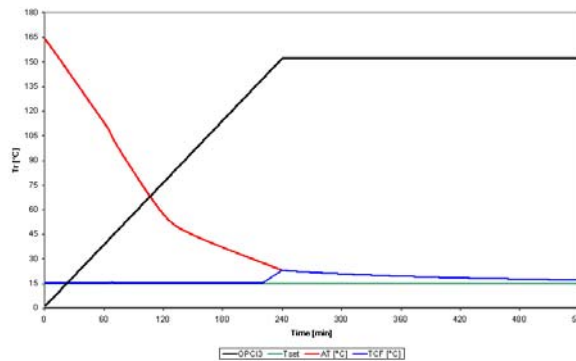
Figure 12.   *Figure 13.*

The heat flow and hence the reaction enthalpy show an unexpected profile : after an initial plateau at about 14 W/mol a peak of nearly 21 W/mol is followed by a decay and ends in a second plateau at about 4 W/mol. After the end of the dosing for more than 5 hours there is still thermal activity detected. The data indicate that 73 % of the total heat is generated with only 50 % of the $OPCl_3$ added and during the remainder 50 % only 23 % of the reaction enthalpy is released.

Since there are indications that the reaction between the Vilsmeier intermediate and DMA requires a higher temperature additional experiments were run. The results from the test at 25°C are contained in Table 6.

| *Table 6.* Calorimetry results Vilsmeier intermediate + DMA at 25°C		
Parameter	Value	Comments
Qr	13 W/mol	Initial plateau first 70 minutes
	21 W/mol	Peak value, probably due to crystallisation
	4 W/mol	Final plateau from 150 to 240 minutes
ΔH	- 146 kJ/mol	This corresponds to the sum of the 'two-stage' process
MAT	166°C	High value due to high reaction enthalpy and low Cp value
		Not relevant for a controlled semi-batch process
MTSR	35°C	10°C potential temperature rise near end of feed period
FHR	93 %	Only small amount of accumulation
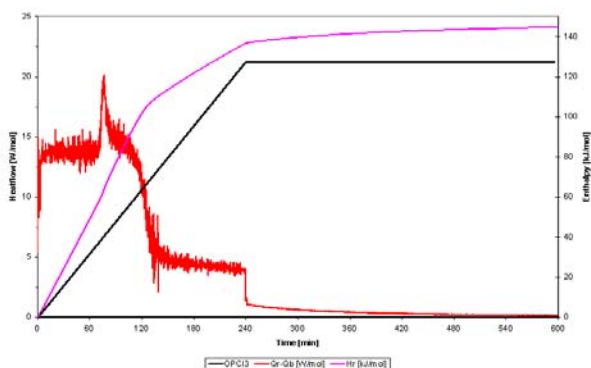
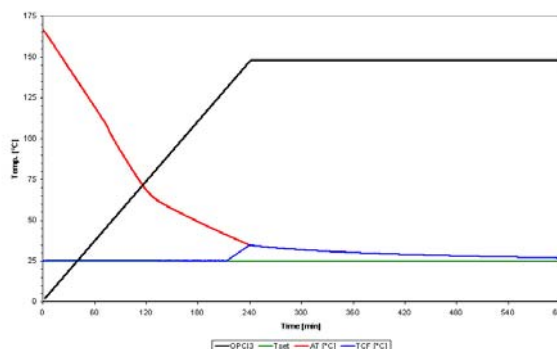**Figure 14.**   **Figure 15.**

The result of this experiment is nearly a copy of the previous one at 15°C with only a minor change in profile due the higher temperature.

Another experiment was run at 40°C, the final temperature of the original process.

| Table 7. Calorimetry results Vilsmeier intermediate + DMA at 40°C		
Parameter	Value	Comments
Qr	13 W/mol	Initial plateau first 80 minutes
	23 W/mol	Peak value, probably due to crystallisation
	4 W/mol	Final plateau from 150 to 240 minutes
ΔH	- 151 kJ/mol	This corresponds to the sum of the 'two-stage' process
MAT	170°C	High value due to high reaction enthalpy and low Cp value
		Not relevant for a controlled semi-batch process
MTSR	47°C	7°C potential temperature rise near end of feed period
FHR	95 %	Only small amount of accumulation
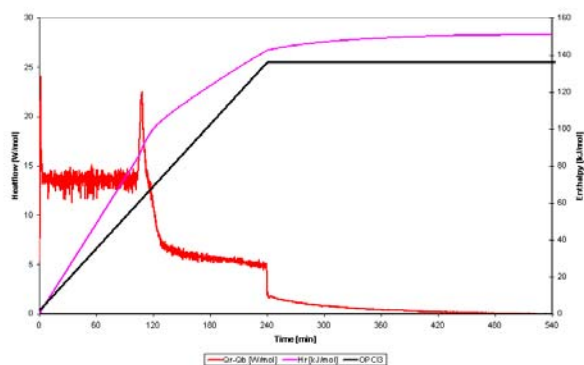
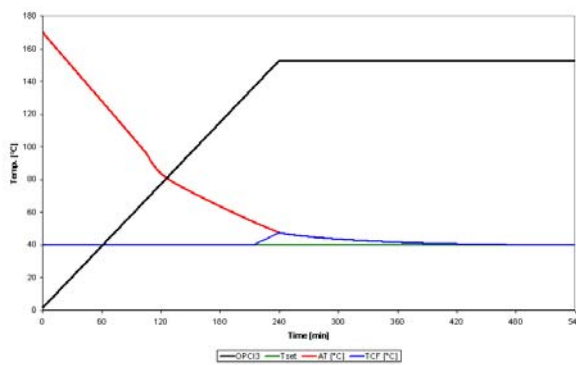**Figure 16.**   **Figure 17.**

The results of this experiment are again close to the previous ones. The heatflow profile shows the same general form, but there are apparent differences : the first plateau lasts longer and is more constant and the peak appears at a later point in time. Surprisingly the accumulation is nearly the same as in the experiments at lower temperatures.

It is difficult to draw conclusions on the progress of the reaction based on only the thermal information. As far as we know there is no mechanistic information on the progress of the reaction in case the substrate is present when the Vilsmeier intermediate is generated[3]. It would be interesting to have on-line analytical data to elucidate the course of the chemical conversions. This would help to understand the thermal profile. This data could then be used in reaction modelling software to build a reaction model and kinetic expressions. The model could then be used to design a safe and controllable process[10], also taking into account the decomposition under thermal stress.

Adiabatic calorimetry

A sample of the reaction mixture with dosing at 15°C, after the required stirring time, was transferred to the ARC cell and the heat-wait-seek temperature profile was applied.

| Table 8. ARC results of the one-pot synthesis reaction mixture		
Parameter	Value	Comments
Onset temp.	35°C	The onset recorded is even lower than in the two-stage process !
Temp @ max rate	150°C	This value is lower than for the separate stages
Max. T. rate	8°C/min	
Max. P.rate	18 bar/min	
MaxTsafe 24	31°C	This result indicates that the one-pot process is not better that the original one
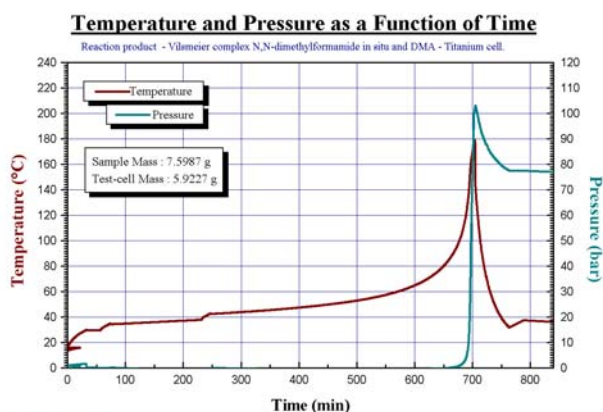
Figure 18. ARC – T,P-graph
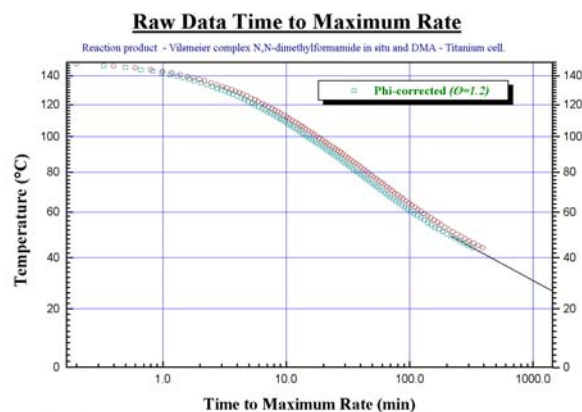
Figure 19. Max T Safe 24 graph

It was decided to start the test at room temperature and the results indicate that there was thermal activity at the start of the test. This could be due to some residual conversion. After the first heat stage further thermal activity was detected but this stopped around 40°C. From 42°C on the exotherm leading to total decomposition of the sample started and this resulted in a temperature rise to 180°C over 450 minutes and a sharp pressure rise. The test was terminated by the instrument to avoid damage. A high residual pressure of 77 bar was observed after cooling. This indicates that non-condensible gases are formed in the decomposition. A MaxTSafe 24 of 31°C was calculated.

Runaway index of the one-pot process at different temperatures.

It can be questioned if the same Max T Safe value would have been obtained from the reaction mixtures at higher temperatures; this was not tested experimentally.
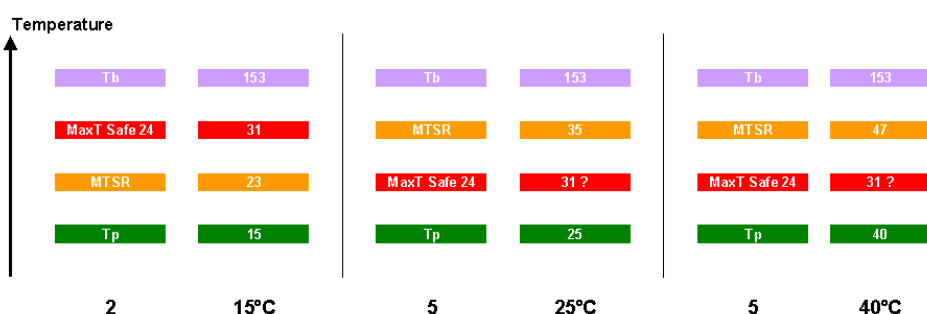
Figure 20. Runaway index

The MaxTSafe 24 values of the two stage and the one-pot process are the same, and hence the problem of instability of the reaction mixture.

The results from the adiabatic calorimetry are not congruent with practical observations. In production the reaction mixture is heated to 80°C to produce a solution, which is then transferred by, gravity, to the hydrolysis reaction vessel 3 m lower. Over more than 500 batches there were no reported incidents of unexpected temperature or pressure rises, foaming or gas formation.

This prompted us to further investigate the adiabatic calorimetry. In fact this was done later in time, when we studied the other formamides (see below), but since the data belong together with the inital study, the results are discussed in this section.

A sample from the one-pot DMF process was prepared and transferred to an Hastelloy ARC bomb and heated. It can be expected that Hastelloy is more resistant to HCl attack and therefore it was also used to study the Vilsmeier intermediates. The Hastelloy ARC bombs have a higher weight compared to the Titanium cells, which results in a higher phi-factor and therefore is further from the adiabatic ideal when phi = 1. To test the hypothesis that there was chemical interaction between the reaction mixture and the test cell material we also decided to use – for the first time – glass cells. These have an even higher phi-factor and a lower pressure resistance, but can be considered as chemically inert to an acidic reaction mixture (except when HF is present). We set the pressure limit to a lower value than for the metal bombs to avoid bursting these vessels.

The results of the test in Hastelloy are shown in Table 9 and Figures 21 and 22.

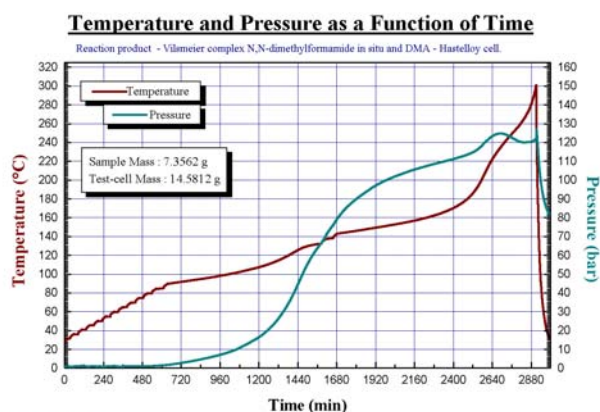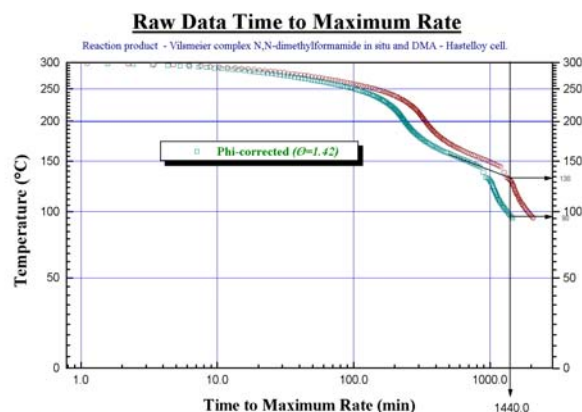| *Table 9.* **Hastelloy ARC cell**		
Parameter	Value	Comments
Onset temp.	85°C	Compared to 35°C in Ti cell
Temp @ max rate	121°C	Compared to 150°C in Ti cell
Max. T. rate	0.1°C/min	Compared to 8°C/min in Ti cell
Max. P.rate	0.2 bar/min	Compared to 18 bar/min in Ti cell
MaxTsafe 24	90°C	Compared to 31°C in Ti cell

Figure 21.

Figure 22.

On heating the sample shows a different decompostion profile : exothermic activity is not observed until 90°C (at 600 minutes test time) and this takes the temperature to about 130°C and 66 bar after 1500 minutes, where further heating induces the second exotherm which is terminated by the safety setting at 300°C and a pressure of 120 bar. The test took about 2900 minutes. This indicates that the decomposition is much slower and also less violent than in the Titanium test cell. For this sample, and taking the first exotherm into account, a MaxTsafe 24 value of 90°C is calculated – this value is not obtained by extrapolation, but fits within the experimental measured data.

There is a remarkable difference between the results in the Titanium and Hastelloy bombs. It appears that there is some catalytic interaction of the Titanium with the reaction mixture which starts the decomposition at lower temperature and makes it more violent (higher pressure). The report in the literature[8] was based on Titanium bombs and thus should be considered with care.

The results of the test in a glass bomb are presented in Table 10 and Figures 23 and 24.

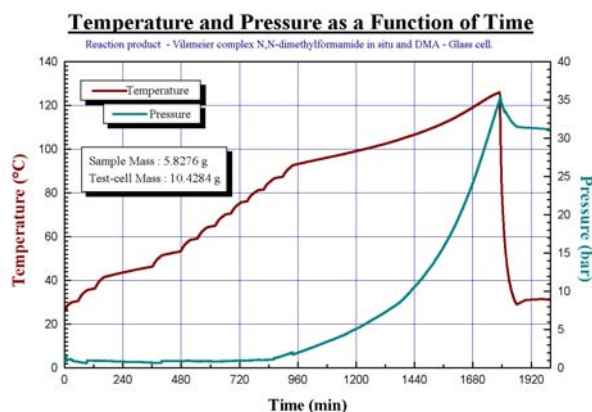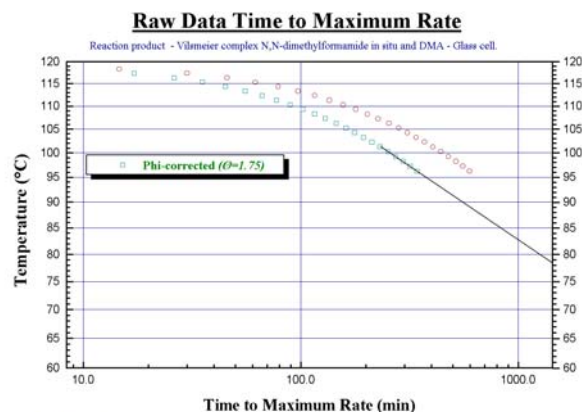| Table 10. Glass ARC bomb		
Parameter	Value	Comments
Onset temp.	93°C	Comparable to the test in Hastelloy
Temp @ max rate	94°C	The decomposition slows down immediatly after the start
Max. T. rate	0.08°C/min	
Max. P.rate	0.29 bar/min	
MaxTsafe 24	77°C	Only a limited number of datapoints are available, becaust the test was terminated to protect the test cell

Figure 23.

Figure 24.

The results in the glass bombs are comparable to and confirm the results of the Hastelloy ones. In the temperature range of 40 to 60°C some exothermicity can be observed, probably due to further chemical conversion. From about 90°C and 940 minutes test time on, self-heating is observed and this takes the temperature to about 125°C and 35 bar over a period of about 900 minutes. At this stage the test was terminated because the pressure limit set for the glass bombs was reached. There is a high residual pressure in the bomb after cooling to room temperature. From this – incomplete experiment – a MaxTsafe 24 value of 77°C is obtained by extrapolation. The test in the glass ARC bomb was also run for the reaction mixture made at 25°C and this provided the same values as for the previous reaction mixture (MaxTSafe 24 of 80°C).

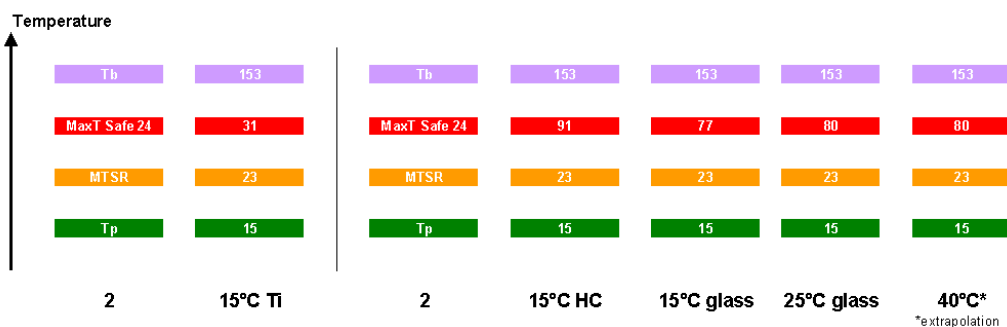Based on these results the runaway index can be calculated.

Figure 25.

3. Screening study of formamides

Since the alternative process method – before the ARC tests in Hastelloy and glass bombs - did not yield the desired result, a more thermally stable reaction mixture, it was decided to investigate the role of DMF in the decomposition process. A.Miyake *et al*[8] indicated that the Vilsmeier intermediate of *N*-methylformamide (6) shows a decomposition behaviour comparable to that of DMF, but no other information is available from the literature. A set of potentially interesting formamides was selected for further testing : *N*-methylformamide (MFA, 6), *N,N*-diethylformamide (DEF, 7), *N,N*-dibutylformamide (DBF, 8), *N*-formylpiperidine (PIF, 9) and *N*-formylmorfoline (MOF, 10).
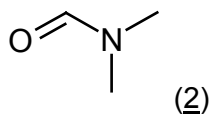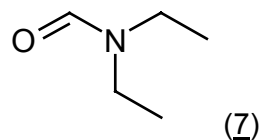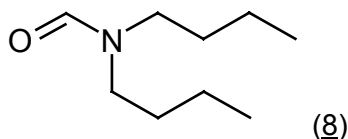
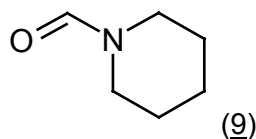*N,N*-dimethylformamide (DMF)   *N*-methylformamide (MFA)   *N,N*-diethylformamide (DEF)
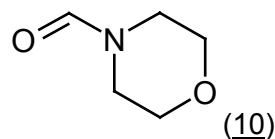

(2)

(6)

(7)
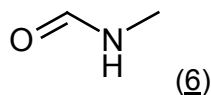
N,N-dibutylformamide (DBF)   *N*-formylpiperidine (PIF)   *N*-formylmorfoline (MOF)

(8)

(9)

(10)

Before running the calorimetric tests in the RC1, the Argonaut AS3400 parallel synthesizer was used to test the interaction of $OPCl_3$ with the formamides in two series of 4 experiments. All formamides show an exothermic reaction on adding $OPCl_3$ (molar ratio of 3.88 to 1), but the reaction mixture of MFA became unstirrable and 100 % more MFA was required to get the solids in solution to get a viscous liquid. Samples of the final reaction were screened for thermal activity on heating in the Radex instrument, using Hastelloy vials. In this case we were especially interested in the pressure profile, as shown in Figure 26.

Pressure Profile in RADEX
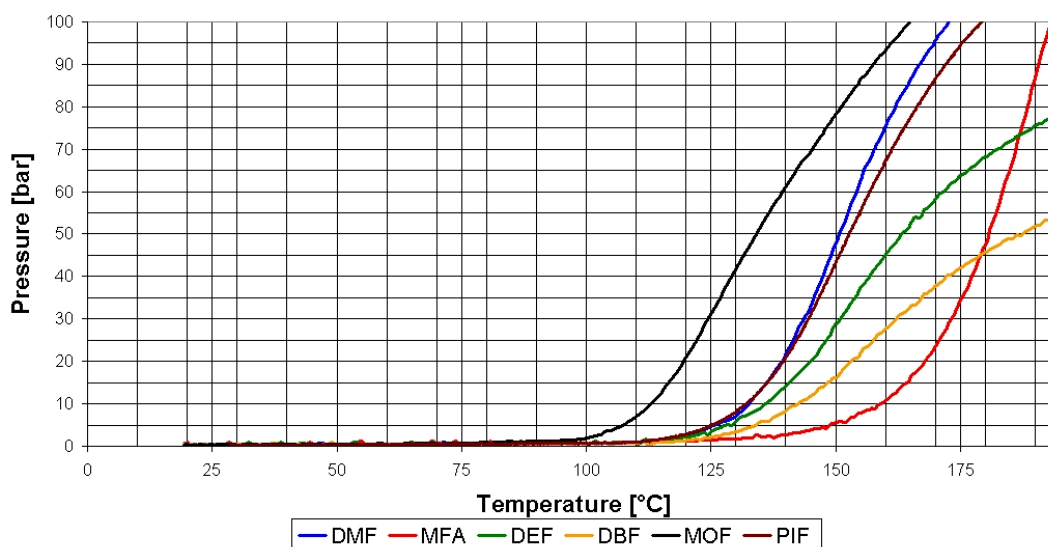**Vilsmeier Intermediate From Different Formamides**

Figure 26. Pressure versus temperature of reaction mixture with different formamides.

The reaction mixtures were subjected to the standard hydrolysis process and although the mixture could not be worked-up in all cases, we were able to confirm with TLC that DMAB had been formed in each reaction using the standard methodology.

The results from this thermal screening lead to the following conclusions : all reaction mixtures show decomposition with pressure build up from around 100°C in the following series sequence : MOF, DMF, PIF, DEF, DBF and MFA. Only DEF and DBF do not generate pressures > 100 bar at 190°C and the pressure rise is clearly slower than the other formamides. From these results it was decided to limit the further study to DEF and DBF. MFA was eliminated because of the practical problems encountered with the high viscosity.

4.   The two-stage DEF process

The Argonaut AS3400 tests indicated that DEF could be used to run the Vilsmeier-Haack reaction on DMA and therefore a calorimetry study was initiated.

Reaction calorimetry

The standard conditions for the Vilsmeier reaction with DMF were also applied to DEF and this yielded the following results.

| Table 11. Calorimetry results DEF Vilsmeier intermediate at 25 °C		
Parameter	Value	Comments
Qr	38 W/mol 20 W/mol ± 5 W/mol	These peak comes from the interaction with the water in DEF (0.3 %) This is the average value of the reaction between DEF and $OPCl_3$, once the water has reacted
ΔH	- 52 kJ/mol	This value includes the interaction with water
MAT	83 °C	
MTSR	26 °C	Limited accumulation near end of the feed
FHR	99 %	Nearly complete conversion at the end of the dosing
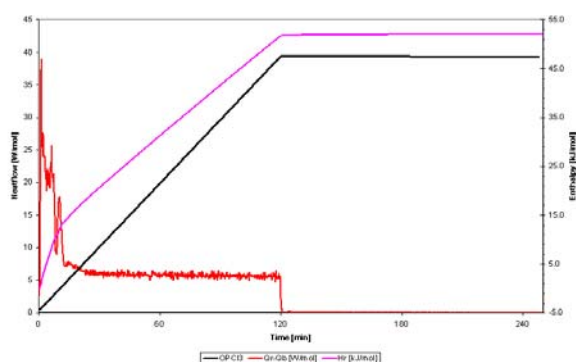
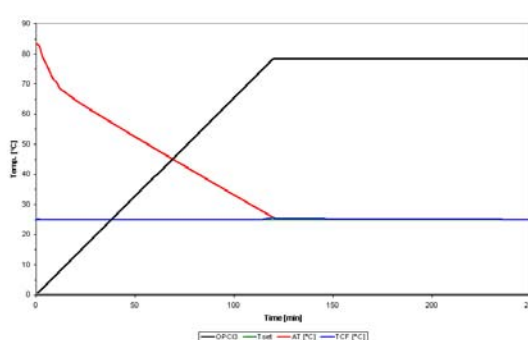*Figure 27.*   *Figure 28.*

The heatflow shows a profile comparable to that of DMF : here also there is an additional peak due to the interaction of the water present in the technical DEF (0.3 %). It would have been possible to use analytical grade of DEF to avoid this, but the technical grade provides a more realistic simulation of the final "plant" process. The reaction is fast with additional control within the parameters of this experiment.

Adiabatic calorimetry

A sample of the previous reaction mixture was transferred to an ARC Hastelloy bomb and subjected to the heat-wait-seek temperature profile.

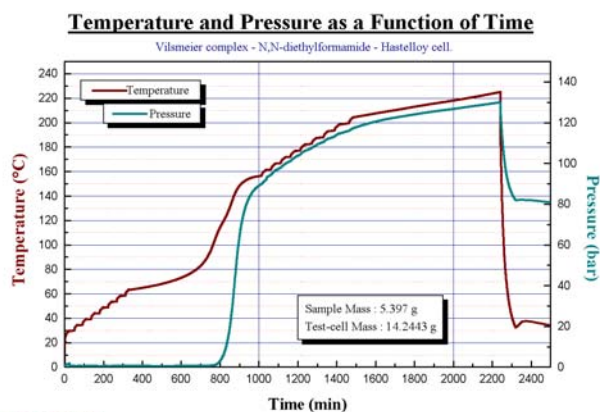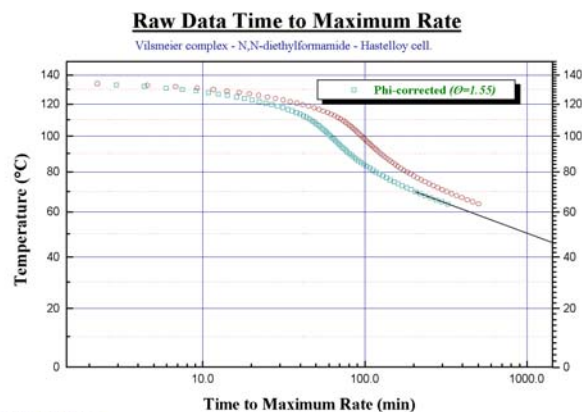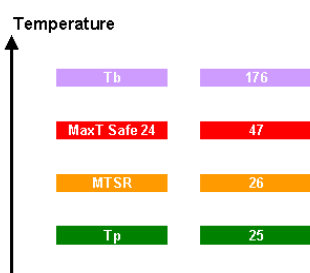| Table 12.		
Parameter	Value	Comments
Onset temp.	63°C	This is for the first exotherm, a second exotherm is detected at > 200°C
Temp @ max rate	135°C	This exotherm stalls at 155°C
Max. T. rate	0.46°C/min	
Max. P.rate	1.05 bar/min	
MaxTsafe 24	47°C	Value obtained for the first exotherm

Figure 29.

Figure 30.

Thermal acitivity is recorded from 63°C ending around 155°C with a sharp pressure rise to around 85 bar around 100°C. On further heating a second exotherm starts around 205°C, but this was terminated at 225°C because the set pressure limit (130 bar) was reached. The data from the first exotherm was used to calculate the MaxTsafe 24 and this yield a value of 47°C, which is close to the DMF-value. It appears that the thermal stability of the Vilsmeier intermediate of DMF and DEF are comparable.

Based on these results the runaway index can be calculated.

In a semi-batch process with a long feed time this process has a runaway index of 2. Control of the dosing is essential to ensure safety.

Figure 31.

5. The one-pot DEF process

As part of the systematic study of the different combinations of process modes and formamides, het one-pot process was subjected to the test procedure.

Reaction calorimetry

The one-pot Vilsmeier reaction with DEF was also run in the RC1 calorimeter. In order to obtain additional information on the accumulation during the dosing two 'stop-start' sequences were incorporated. A 'stop-start' sequences means that the dosing is halted during a certain time and hence the reaction of the reagent stops. In case there is a fast reaction - dosing control – the heatflow will drop sharply and should attain the baseline shortly after the interruption of the dosing. Once the dosing is restarted it is expected that the reaction simply continues and the heatflow signal should come back to the value before the stop. If the heatflow signal diminishes only slowly and/or does fall to 0, then dosing control is limited and accumulation is observed. This could of course be due to parallel slower reactions.

The results of this experiment are presented in Table 13.

| *Table 13.* Calorimetry results DEF Vilsmeier intermediate + DMA at 25 °C		
Parameter	Value	Comments
Qr	23 W/mol	Peak value due to the interaction with water
	13 W/mol	Average heatlfow during first part of the dosing
	20 W/mol	Peak heatlfow, due to crystallisation ?
	4 W/mol	Average heatflow during second part of the dosing
ΔH	126 kJ/mol	Total reaction enthalpy lower than in DMF process
MAT	139°C	
MTSR	32°C	Some accumulation near the end of the dosing (low heatflow)
FHR	90 %	This confirms the accumulation
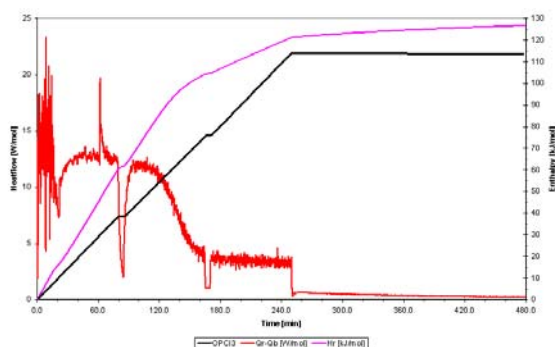
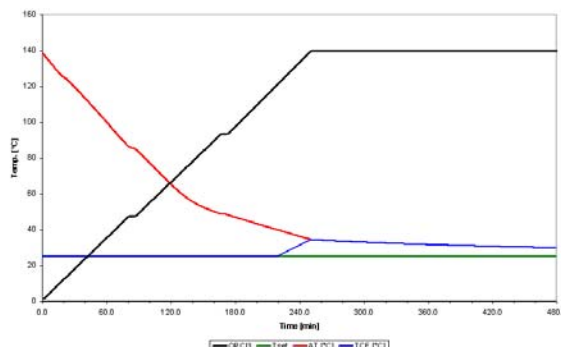*Figure 32.*   *Figure 33.*

At the start there is additional heat production from the interaction of $OPCl_3$ and water, but overall the reaction profile is comparable to that of DMF. In this case the peak in the heatlfow is smaller. The response of the system to the stop of the feed indicates that there is no full feed control on the heat production. Although there is a substantial drop in the heatflow signal it never reaches 0 within the "stalled" period.

Adiabatic Calorimetry

A sample of the reaction mixture was transferred to the ARC bomb and the heat-wait-seek temperature profile was imposed.

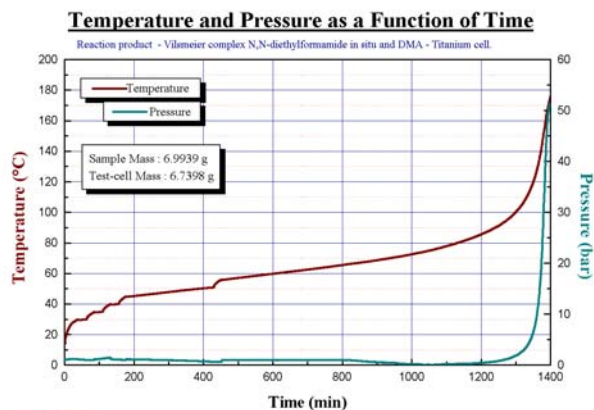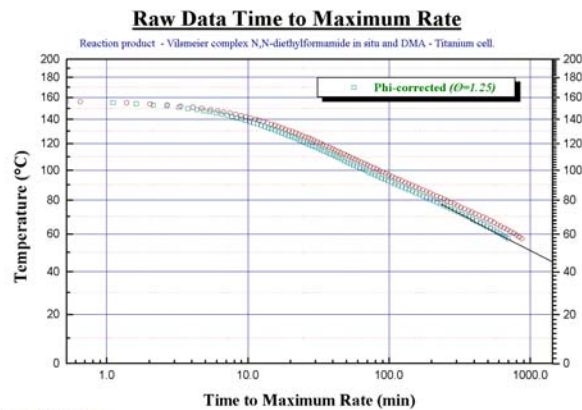| *Table 14.*		
Parameter	Value	Comments
Onset temp.	45°C	Temperature at which the first exotherm starts
Temp @ max rate	157°C	
Max. T. rate	1.6°C/min	
Max. P.rate	1.9 bar/min	
MaxTsafe 24	44°C	This indicates that there is thermal instability for the DEF reaction mixture

Figure 34.

Figure 35

The sample showed thermal activity from 45°C and heated over a period of 220 minutes to 50°C. At 50°C one heat step was applied and a second exotherm initiated leading to a slow decomposition with a pressure peak of > 50 bar at 150°C, which terminated the test. The adiabatic temperature profile yields a MaxTSafe value of 44°C for the DEF reaction mixture.

Based on these results the runaway index can be calculated.
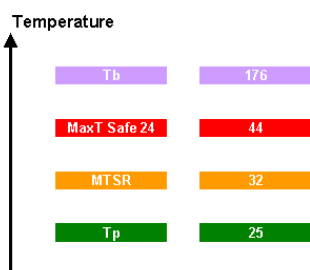
The MaxTSafe 24 value is close to the MTSR and this is a borderline case between index 2 and 5.

Figure 36.

The same sample was also tested in an Hastelloy cell and this showed a different decompostion behaviour. Some thermal activity below the detection of the instrument can be observed from 70°C onwards, but a first real exotherm starts at 95°C (after 700 minutes test time) and takes the sample temperature to 102°C. The next heat pulse initiates another exotherm which ends around 122°C. In the meantime there is already a pressure of 50 bar. After 6 heat pulses, around 157°C a third exotherm start and takes the temperature up to 200°C and 120 bar, at which the test is terminated to protect the instrument.

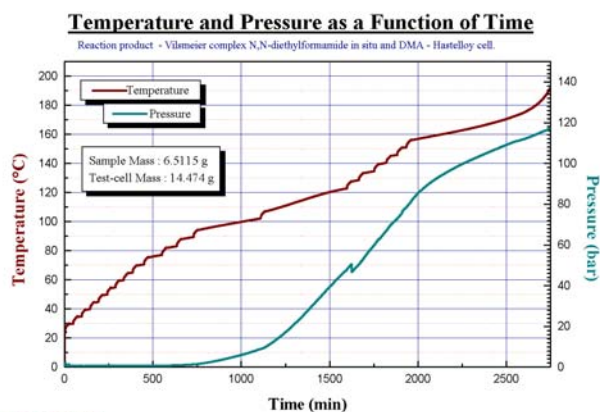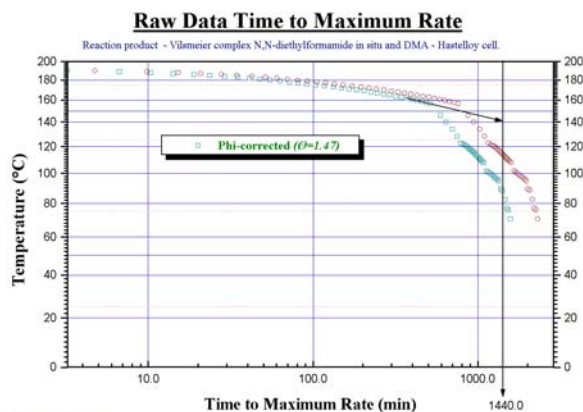| Table 15.		
Parameter	Value	Comments
Onset temp.	70°C	Other exotherms start at 96 and 108°C
Temp @ max rate	95°C	
Max. T. rate	0.04°C/min	
Max. P.rate	0.1 bar/min	
MaxTsafe 24	91°C	This is considerably higher than in the Titanium bomb

Figure 37.

Figure 38.

This was the first time a difference between the results obtained within different materials was observed. This prompted us to extend the study on the DMF samples (see above).

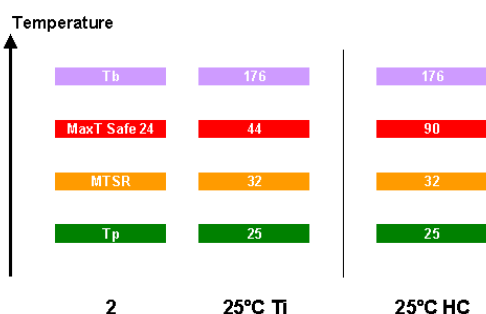Based on these new results the runaway index can be recalculated.

Figure 39.

Now there is a substantial difference between MTSR and MaxTSafe 24 and this is clearly a process with runaway index 2.

6. The two-stage DBF process

DBF was subjected to the same tests as DMF and DEF. It should be noted that we use the same molar ratio of reagents, but with the higher molecular weight of DBF results in a larger mass.

Reaction calorimetry

The standard calorimetry test in the RC1 was applied to DBF and OPCl$_3$ over 2 hours at 25°C. In this case also we used technical DBF and the batch used contained 0.6 % water. This causes some side reactions but unfortunately this - off-spec - was the only material available at that time (our technical grade should have < 0.3 % water).

| Table 16. Calorimetry results DBF Vilsmeier intermediate + DMA at 25°C		
Parameter	Value	Comments
Qr	± 22 W/mol	Peak region due to interaction with water present (Max 29 W/mol)
	± 5 W/mol	Flat region : expected reaction
ΔH	51 kJ/mol	About 10 kJ/mol can be attributed to the reaction with water
MAT	61°C	Including the interaction with water
MTSR	26°C	Dosing controlled reaction
FHR	99 %	Dosing controlled reaction
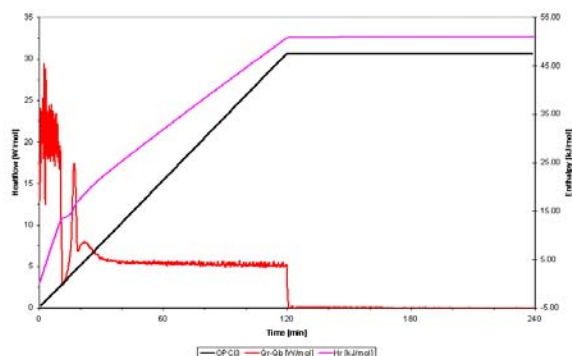
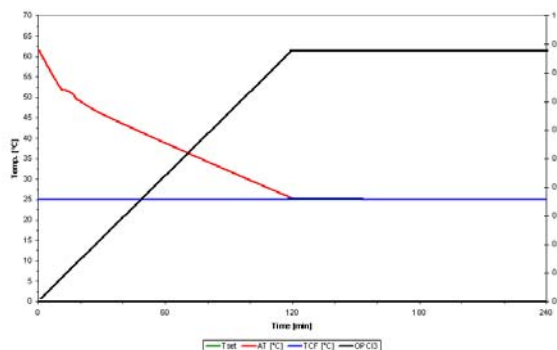**Figure 40.**   **Figure 41.**

It can be seen that this reaction shows the same profile as DMF and DEF : initially the interaction with the water, followed by a constant heatflow of 5 W/mol which stops at the end of the feed period.

Adiabatic calorimetry

A sample of the reaction mixture was tested in the ARC (Hastelloy bomb) and provided the following results.

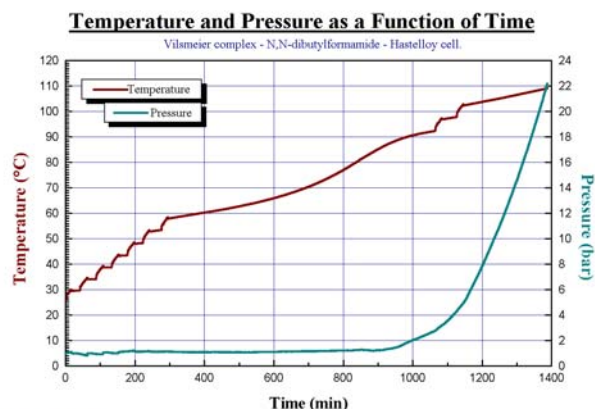| Table 17.		
Parameter	Value	Comments
Onset temp.	58°C	Start of a slow decomposition
Temp @ max rate	59°C	
Max. T. rate	0.1°C/min	This can be considered as a low value
Max. P.rate	0.013 bar/min	
MaxTsafe 24	56°C	In the same range as DMF and DEF
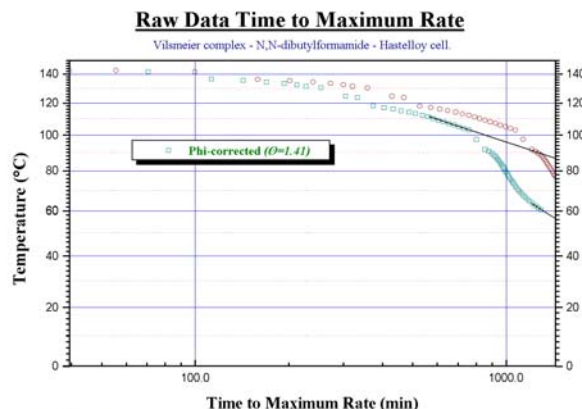
Figure 42.   **Figure 43.**

The sample shows thermal activity on heating to around 58°C and this exotherm takes the temperature to 92°C over 750 minutes with a limited pressure rise of around 3 bar. Two additional heating steps start a further exotherm, which generates substantial pressure, (22 bar at 110°C). The test was terminated at 160°C when the pressure limit of 120 bar was reached (not shown in the graph). From this data a Max T Safe 24 value of 56°C was calculated.

Based on these results the runaway index can be calculated.
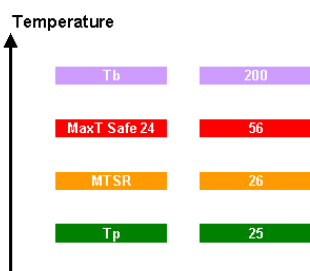
Figure 44.

The difference in MTSR and MaxTSafe is large enough to make sure that the runaway index is indeed 2.

7. The one-pot DBF process

To complete the study a one-pot experiment with DBF was run in the RC1 instrument.

Reaction calorimetry

Since previous experiments indicated that the reaction is run best at higher temperature to increase the reaction rate, this test was run at 40°C and the 'start-stop' procedure was applied to get information on potential accumulation during the feed of $OPCl_3$.

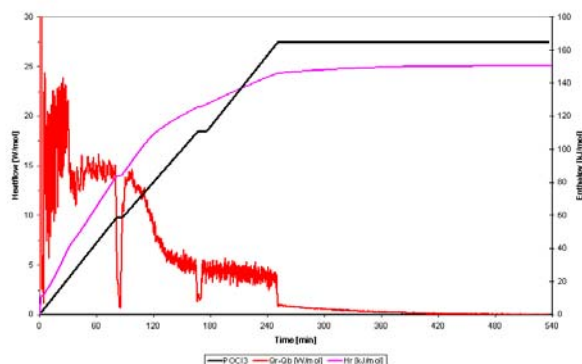| Table 18. Calorimetry results Vilsmeier intermediate + DMA at 40°C		
Parameter	Value	Comments
Qr	17 to 22 W/mol	Additional heatflow due to the interaction with water
	14 W/mol	Average value over the first 80 minutes
	14 ⇨ 5 W/mol	Decline in heat production
	± 5 W/mol	Average value over the last 90 minutes of the dosing
ΔH	- 150 kJ/mol	Including about 10 kJ/mol for the reaction with water
MAT	130°C	Including the effect of the reaction with water
MTSR	43°C	
FHR	97 %	Some slow residual reaction after the end of dosing over a period of 240 minutes.

Figure 45.
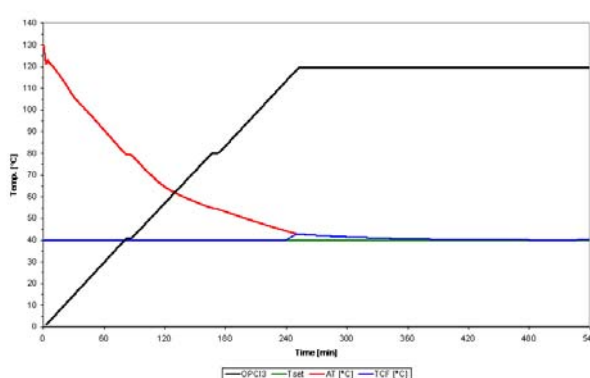
Figure 46.

The on-pot reaction in DBF exhibits the same profile as DMF and DEF : additional heatflow at the start due to the presence of water, then a plateau around 15 W/mol, after 50% of the feed is complete, the second half of the dosing the heatflow gradually drops to a value of ± 5 W/mol. Once the dosing is stopped there is a small heatflow for an additional 240 minutes, even at 40°C. Taking into account the contrubution of the interaction with water, the total reaction enthalpy is lower than in DMF and DEF.

Adiabatic calorimetry

A sample of the reaction mixture was heated in an Hastelloy bomb.

Table 19.

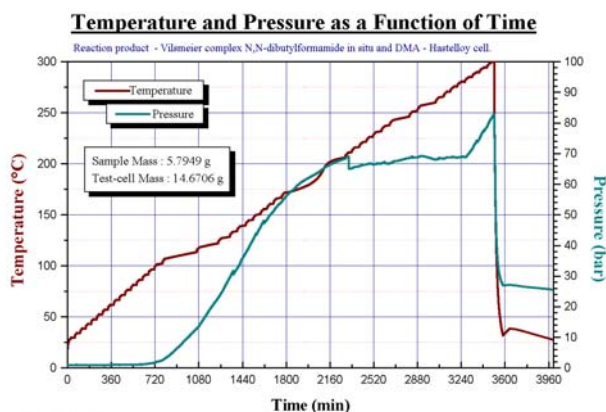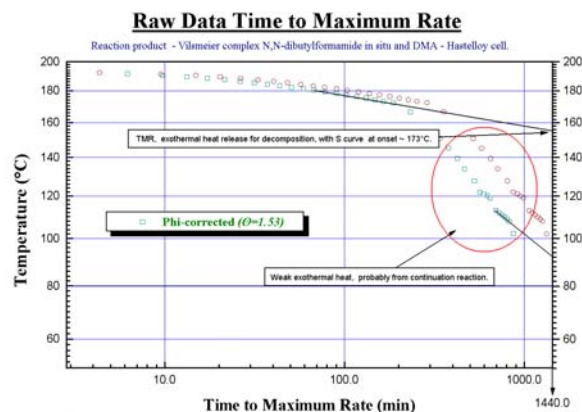| Parameter	Value	Comments
Onset temp.	102°C	Start of a small exotherm; around 170°C another exotherm starts
Temp @ max rate	193°C	
Max. T. rate	0.23°C/min	
Max. P.rate	0.07 bar/min	
MaxTsafe 24	91°C	Calculated from the first – weak - exotherm

Figure 47.

Figure 48.

During the first 720 minutes with a stagewise temperature rise from 25 to 105°C there is no exothermic activity and no pressure generation. Above this temperature several weak exotherms occur to take the temperature to 120°C and 25 bar. On further heating small exotherms are detected in until 300°C is reached. During this period the pressure reaches 84 bar however the profile suggests that this measurement is not reliable, probably due to some material blocking the tubing to the pressure transducer. A Max T Safe 24 value of 91°C is obtained for the first – weak – exotherm.

Based on these results the runaway index can be calculated.
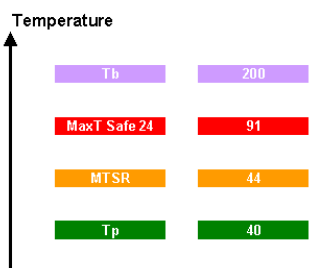
Figure 49.

Conclusions

From this study of the thermal behaviour of the Vilsmeier-Haack reaction the following conclusions can be drawn on the thermal hazards (other process hazards are not within the scope of this discussion).

Reaction calorimetry.

The results from the reaction calorimetry experiments indicate clearly that – under the experimental conditions used here – the interaction of $OPCl_3$ with the three studied formamides is fast and exhibits a moderate exothermicity (-45 ± 5 kJ/mol). These reactions can be considered dosing controlled, with almost no accumulation when run in semi-batch mode with sufficient feed time (which should be adapted to the cooling capacity of the reactor used). As a result, the MTSR is close to the process temperature.

The reaction of the Vilsmeier intermediate with DMA is quite exothermic (± 100 kJ/mol,) but relatively slow at 15°C compared to the feed time of 2 hours, which leads to a substantial accumulation of reagent and a substantial difference between process temperature and MTSR.

The reaction profile of the one-pot process, where the substrate DMA is already present when $OPCl_3$ is added to generate the Vilsmeier intermediate, appears to be different from the sum of the individual processes. When DMA is added to the Vilsmeier intermediate the heatlfow is approximately constant until the end of the feed, whereas in the one-pot process there seems to be a changeover in course of the reaction around the time where 50 % of $OPCl_3$ is added (and only 50 % of Vilsmeier intermediate is expected to have been formed). The total reaction enthalpy (± 140 kJ/mol) corresponds to the sum of the reaction enthalpy of the individual transformations and also the isolated yield of the product is comparable in case of DMF. Formally there is only limited accumulation at the end of the dosing (FHR > 90 %, adiabatic temperature rise of < 10°C), but the start-stop procedure indicates that a certain stages during the dosing the process is not completely dosing controlled.

In this type of process DEF and DBF exhibit a reaction profile and enthalpy comparable to DMF.

Further research is required to understand and explain the reaction profile observed and this is outside the scope of this study.

Adiabatic calorimetry.

The first conclusion from this study is that great care should be taken in the selection of the test cell material. It is clear that in this case there is an interaction between the reaction mixture and Titanium which accelerates the decomposition and lowers the onset temperature. The decomposition profile itself doesn't indicate that there is a catalytic effect and the ARC tests reported in the literature were also run in Titanium cells. Only by testing other materials this issue became clear. This was triggered by the discrepancy between the ARC test results and the practical experience. Without this observation we would have come to a wrong runaway index (index 5 instead of index 2).

The results of the tests conducted in inert test cells indicate that the Vilsmeier-Haack reaction can be considered as hazardous because of the high pressures associated with the decomposition. There are clear indications that a permanent gases are formed.

The thermal stability of the Vilsmeier intermediate - as a solution in the corresponding formamide – shows thermal decomposition starting around 60°C, but the profile of decomposition is different. It would be required to run additional tests under carefully controlled conditions (e.g. identical concentration and/or solvent free sample) to be able to compare the results and draw unambiguous conclusions. From a practical point of view, DMF and DEF have the same MaxTSafe 24 value and the stability seems to be a little better for DBF (56°C).

Both the two stage and the one-pot process lead to the same final reaction mixture, which starts to self-heat from ± 90°C. All the formamides used in this process lead to a thermally unstable reaction mixture, which generates gas and hence pressure in a closed cell or vessel – at a temperature ± 100°C. From a pure thermal point of view, DMF is much more reactive than DEF, which is more reactive than DBF. Despite the different rate and the adiabatic temperature rises, for all reaction mixtures a MaxTSafe 24 value of 90°C was calculated.

Based on the combination of reaction and calorimetry a runaway index of 2 is obtained for all combinations tested. At first sight the process can be considered as acceptable. This is only because the runaway index takes only the temperature effects into account and not the pressure generated during the decomposition.

Experimental Section

Equipment.

For the reaction calorimetry a Mettler Toledo RC1 with a standard AP01 reactor with anchor stirrer was used in combination with the WinRC V7.11 (SR6) software. Prominent pumps with PTFE head and PTFE tubing was used for the dosing from a Mettler balance. The quickcal option is used for the calibrations. Data files are exported to Microsoft Excel 97 for further calculations and charting.

Adiabatic calorimetry experiments are run in an EuroARC from Thermal Hazard Technology with EuroARC software V1.1 and ARCCal (based on Origin 3.53) is used for data processsing and charting. The following types of tests cells were used : ARCTC-Ti-LCQ (Titanium), ARCTC-HC-MCQ (Hastelloy) and ARCTC-GL-LMSQa (Glass with metal stem, in which a PTFE tubing was

mounted to isolate the reaction mixture with the metal of the stem). Sensitivity threshold was set to 0.02°C/min).

For the screening of the chemical reactivity the Argonaut AS3400 with 4 reactors of 250 ml was used; one feed unit was used for $OPCl_3$ and the other for DMA.

Thermal stability testing was also done using the Systag RADEX instrument, with 3 ml Hastelloy vials.

Chemicals.

DMF and DBF were obtained from bulk suppliers and used without drying, in some experiments dry DMF was obtained from Acros Fine Chemicals (Belgium), $OPCl_3$, MFA, MOF and PIF were obtained from Acros Fine Chemicals (Belgium) and used without pre-treatement.

Experiments.

1) Two stage process : DMF (564 g, 3.78 mol per mol $OPCl_3$) are charged to the reactor and thermostated at the initial temperature. $OPCl_3$ (312 g) is added from the flask on the balance over the programmed feed period at the set temperature. The reaction mixture was stirred for the required time at the set temperature. DMA (248 g, 1.01 mol per mol $OPCl_3$) was added from a separate flask on a second balance over the programmed feed period at the set temperature and then the mixture was stirred for the required time at the set temperature. Calibations and CP determinations were performed preprogrammed as required to obtain the calorimetry data. The reaction mixture was withdrawn from the reactor and added to a mixture of water and sodium acetate for hydrolysis and further workup. DMAB is isolated by filtration, washed with water and dried. In general a yield of ± 75 % is obtained.

2) One pot process : DMF (564 g, 3.78 mol per mol $OPCl_3$) and DMA (248 g, 1.01 mol per mol $OPCl_3$) are charged to the reactor and thermostated at the initial temperature. $OPCl_3$ (312 g) is added from the flask on the balance over the programmed feed period at the set temperature and then the mixture was stirred for the required time at the set temperature. Calibations and CP determinations are performed preprogrammed as required to obtain the calorimetry data. The reaction mixture is withdrawn from the reactor and added to a mixture of water and sodium acetate for hydrolysis and further workup. DMAB is isolated by filtration, washed with water and dried.

3) Screening experiments : the formamide (1.16 mol) was charged to the reactor and thermostated at the initial temperature (25°C), $OPCl_3$ (0.30 mol) was added to the reaction mixture over the programmed period (1 hour), after a stirring period DMA was added over the programmed period (1 hour) and stirred for 1 hour; after heating to 40°C the mixture was stirred for 3 hours, cooled to room temperature and hydrolysed in a water/sodium acetate mixture. In this experiment a yield of 68 % was recorded.

4) For experiments with DEF and DBF a molar ratio of 3.88 mol per mol $OPCl_3$ was used. The reaction mixsture was hydrolised and then discarded withour further workup.

5) ARC tests : samples of 5 to 6 g of the reaction mixture was transferred wit a pipette to a pre-weighed test cell. This was mounted in the calorimeter and fastened. After closing the instrument the initial data is entered and the heat-wait-seek temperatur program is started. At the end of the test the data are transferred to the ARCCal software package and the sample is collected as chemical waste.

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