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Thermal Hazards of the Vilsmeier−Haack Reaction on *N*,*N*-Dimethylaniline

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Abstract:

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*-dimethylaniline (*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[1−3] is 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 phosphorus oxychloride ($POCl_3$, *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*-dimethylaniline (DMA), as an intermediate for dyes (Scheme 1).

In the European Union the Seveso II directive requires that the hazards of chemical processes are identified 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),[6] depending on the relative position of the following parameters: process temperature (T_p), boiling temperature of the reaction mixture (T_b), maxiumum temperature of the synthesis reaction (MTSR), and the temperature with a time to maxiumum rate of 24 h (TMR24 or MaxT_{safe}24[7]).

Process temperature and boiling point can quite easily be obtained, but MTSR should be calculated from calorimetric data, and MaxT_{safe}24 values come from adiabatic thermal stability testing. For the readers not familiar with reaction calorimetry, the heatflow (Q_r) is a measure for the heat generated by the process(es) 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:

(1) MAT: *M*axiumum *A*diabatic *T*emperature is the temperature that can be achieved when all the process enthalpy is converted to temperature rise.

(2) MTSR: *M*axium *T*emperature of the *S*ynthesis *R*eaction 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.

(3) FHR: *F*raction of *H*eat *R*eleased 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.

In this work the “Runaway index 2” and “Runaway index 5” are most relevant. In Runaway index 2 the following scenario can be envisaged: when cooling fails at a certain stage of the process (worst case is at maximum accumulation), the temperature will rise—by definition—to the value of the MTSR, but the MaxT_{safe}24 will not be attained (the MaxT_{safe}24 value should be 20 °C higher than the MTSR), nor will the reaction mixture start to boil because the boiling point is even higher. In “Runaway index 5” the same scenario will have other consequences: loss of cooling will trigger the temperature to rise to the MTSR value, but in the meantime the MaxT_{safe}24 is also attained or surpassed, and the decomposition can be initiated. In general it is recommended to redesign this type of process or build several well-designed independent layers of protection (pressure relief valves or bursting disks, inhibition or quenching, ...).

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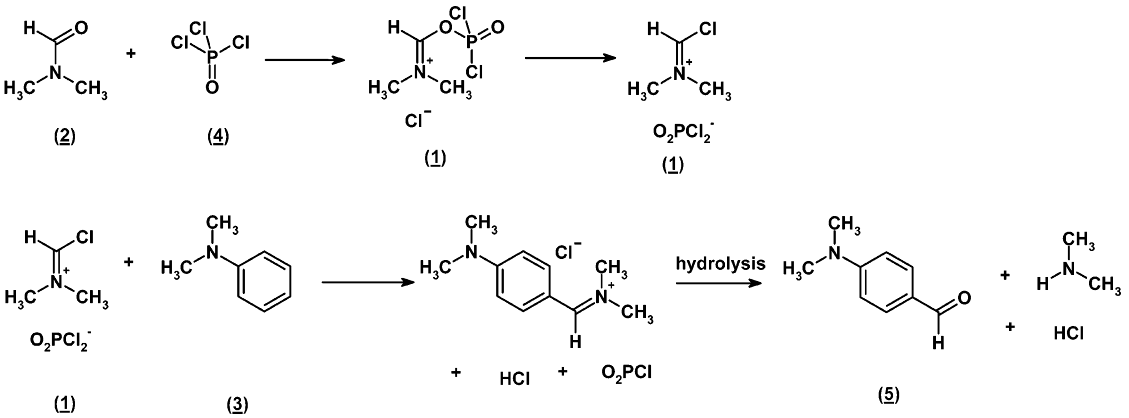
(1) Vilsmeier, A.; Haack, A. *Ber.* **1927**, 119−122.
(2) Hazebroucq, G. *Ann. Pharm Fr.* **1966**, 793−806.
(3) Marson, C. M.; Giles, P. R. *Synthesis Using Vilsmeier Reagents*; CRC Press: Boca Raton, FL, 1994.
(4) Gygax, R. *Chem. Eng. Sci.* **1988,** *43*, 1759−1771.
(5) Stoessel, F. *Chem. Eng. Progress* **1993**, *89*, 1068−1075.
(6) Thematic Network on Hazard Assessment of Highly Reactive Systems, HARSNET; http://www.harsnet.de: HarsBook is a source of background and reference material on the subject of exothermic reaction hazards.
(7) We prefer to use the expression MaxT_{Safe}24 rather than TMR24, because the physical meaning is a temperature, rather than a time.

10.1021/op0580116 CCC: $30.25

Scheme 1. **General reaction scheme of the Vilsmeier−Haack reaction on *N*,*N*-dimethylaniline**



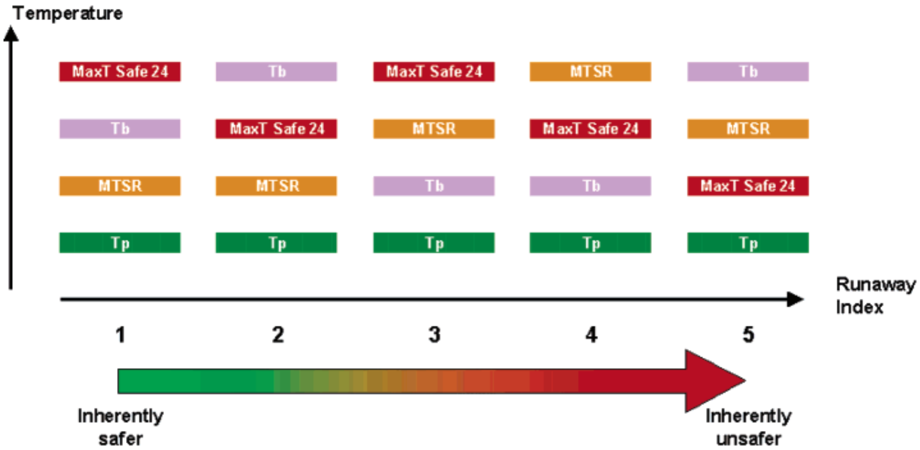


Figure 1. **Runaway indices: classes of thermal runaway scenarios.**

Literature Information

There are only limited literature data on the thermal hazards of the Vilsmeier−Haack reaction.[8,9] These two articles have been examined, and although the information is interesting, these data were 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 min) and high dilution (DMF/$POCl_3$ = 24/1, MFA/$POCl_3$ = 15/1 in mass ratio). Both of these parameters are outside of the range of our process operations. In our opinion it is required that calorimetric data are obtained under conditions as close as possible to plant conditions; the conditions mentioned are quite different from those of 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 $POCl_3$ 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/$POCl_3$ 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 intermediate in the solvent mixture. Calorimetric data were 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 for 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 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

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(8) Miyake, A.; Suzuki, M.; Sumino, M.; Iizuka, Y.; Ogawa, T. *Org. Process Res. Dev.* **2002**, *6*, 922−925.

(9) Dyer, U.; Henderson, D.; Mitchell, M.; Tiffin, P. *Org. Process Res. Dev.* **2002**, *6*, 311−316.

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 $POCl_3$ to excess. Subsequently, this is allowed to react 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. To 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, this was cooled to the process temperature, and $POCl_3$ was added to it, followed by the DMA. As shown, an aging period was used to ensure complete reaction. This yielded results that are listed in Table 1 for the formation of the Vilsmeier intermediate.

The graphical representation of measured and calculated parameters allows more in-depth interpretation of the calorimetry information and results (Figures 2 and 3).

It can be concluded that the rate of 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 min of stirring, all heat production has ceased.

Table 1. **Calorimetry results: DMF + $POCl_3$ at 5 °C**

parameter	value	comments
Q_r	22 W/mol	at the start there is an interaction with the water present in the technical grade DMF (0.3%)
	5 W/mol	heatflow of the expected reaction
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

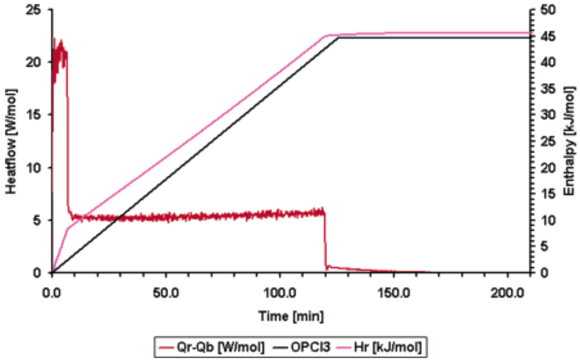

Figure 2. **DMF + $POCl_3$ ⇒ Vilsmeier: profile.**

Adiabatic Calorimetry. A sample taken from a reaction mixture after the dosing of $POCl_3$ to DMF was transferred to the ARC (ARC = *A*ccelerating *R*ate *C*alorimetry) test cell (usually called ARC bomb), and the "heat−wait−seek" profile was applied. The measured data are summarised in Table 2 and illustrated in Figures 4 and 5.

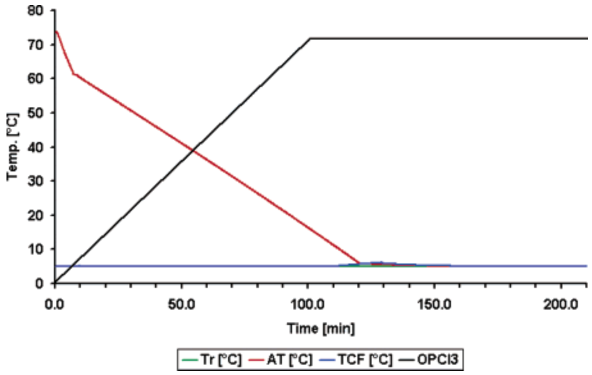

Figure 3. **DMF + $POCl_3$ ⇒ Vilsmeier: safety parameters.**

Table 2. **ARC results: DMF + $POCl_3$ at 5 °C**

parameter	value	comments
onset *T*	67 °C	temperature at which the first heat production above the sensitivity threshold is detected
T @ 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 a high rate
max *P* rate	48 bar/min	the maxiumum pressure rate; this value can be considered a high rate
MaxT_{safe}24	49 °C	this rather low value is the result of low onset temperature and the short time to thermal explosion.

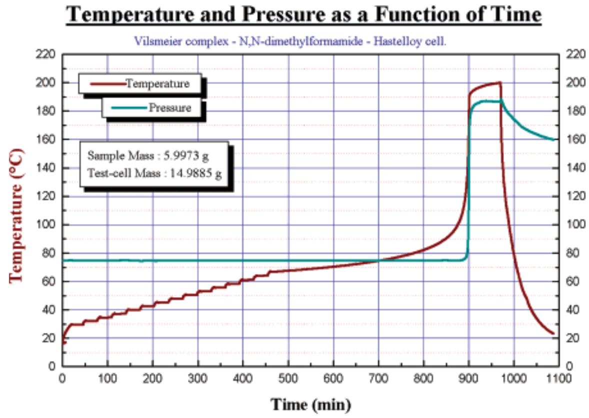

Figure 4. **ARC: *T,P* graph.**

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 by a sharp pressure rise, comparable to an explosion. A MaxT_{Safe}24 value of 49 °C is obtained after extrapolation to 1440 min and correction for the ϕ-factor (the ϕ-factor is the ratio of the total mass (bomb + sample) over the mass of the sample; the lower the value, the better).

The Runaway index for the Vilsmeier intermediate formation is illustrated in Figure 6. Although the MaxT_{Safe}24 value is quite low, this is still a Runaway index 2 process because of the slow dosing, the strong feed control, and the low temperature rise in case of cooling failure.

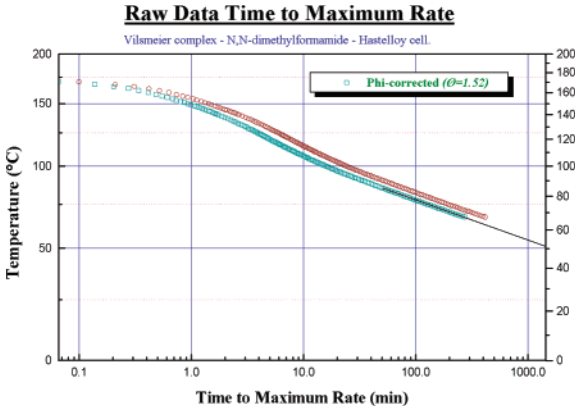

Figure 5. **MaxT_{Safe}24 graph.**

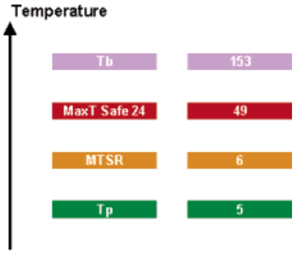

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Figure 6. **Runaway index for the formation of the Vilsmeier intermediate in DMF.**

For the reaction calorimetry of the Vilsmeier intermediate with DMA, Table 3 and Figures 7 and 8 show the results recorded by the RC1. 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 min and during the temperature rise from 15 to 40 °C there is still heatflow. Further reaction is observed, including a sharp peak possibly due to crystallisation. At the final temperature an aging time of 180 min 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 indicated by both 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.

Table 3. **Calorimetry results: Vilsmeier intermediate + DMA at 15 ⟹ 40 °C**

parameter	value	comments
Q_r	±12 W/mol	the heatflow starts at 4 W/mol and increases to ±12 W/mol after 20 min.
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 high reaction enthalpy and 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

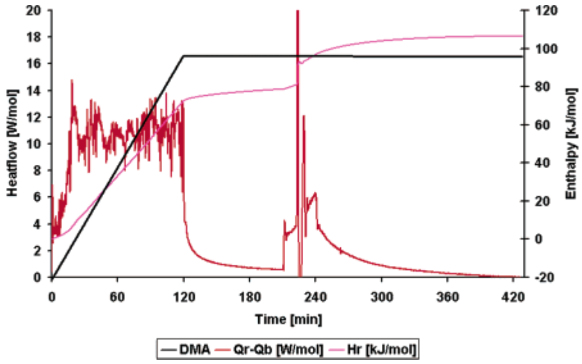

Figure 7. **Vilsmeier + DMA profile.**

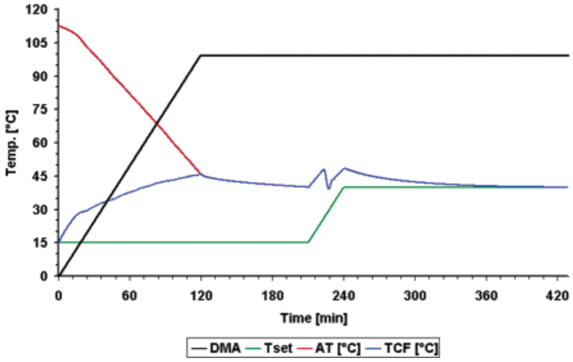

Figure 8. **Vilsmeier + DMA safety parameters.**

A sample of the final reaction mixture was subjected to the same ARC test procedure as the intermediate and yielded the data shown in Table 4 and graphed in Figures 9 and 10. 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).

The combination of the high accumulation during the feed and the low onset temperature for the reaction mixture results 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] it was clear that an alternative method of running the same process should be possible. As indicated earlier, $POCl_3$ could be added to a mixture of DMF and DMA at the required process temperature. Since the reaction between DMF and $POCl_3$ is fast, it can be assumed that the Vilsmeier intermediate is generated in situ and could immediately 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 those of the existing process in that the temperature was set at 15 °C, the temperature 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

Table 4. **ARC results on the reaction mixture Vilsmeier + DMA**

parameter	value	comments
onset *T*	48°C	the start of the exothermic activity in the sample
T @ max rate	238°C	
max *T* rate	4.6°C/min	
max *P* rate	4.2bar/min	
MaxT_{safe}24	30°C	this rather low value comes from the low onset temperature and the high velocity of the decomposition.

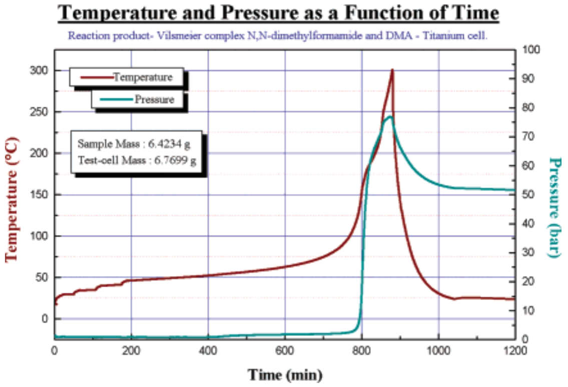

Figure 9. **ARC: *T*,*P* graph.**

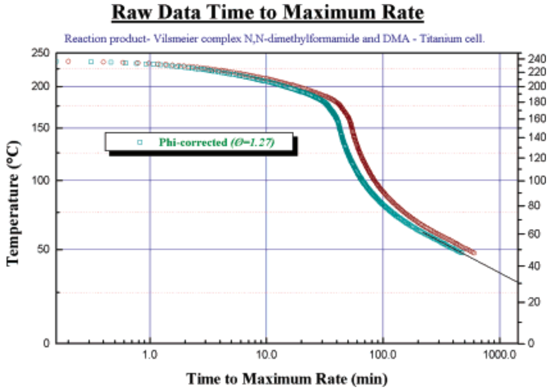

Figure 10. **MaxT_{Safe}24 graph.**

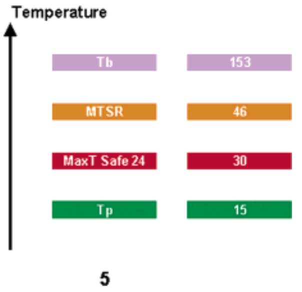

Figure 11. **Runaway index.**

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.

The heatflow 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 h there is still thermal activity detected. The data indicate that 73% of the total heat is generated with only 50% of the $POCl_3$ added, and during the addition of the remaining 50% only 27% of the reaction enthalpy is released.

Table 5. **Calorimetry results: Vilsmeier intermediate + DMA at 15°C**

parameter	value	comments
Q_r	13 W/mol	initial plateau first 60 min
	21 W/mol	peak value, probably due to crystallization
	4 W/mol	final plateau from 150 to 240 min
Δ*H*	−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 C_p 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

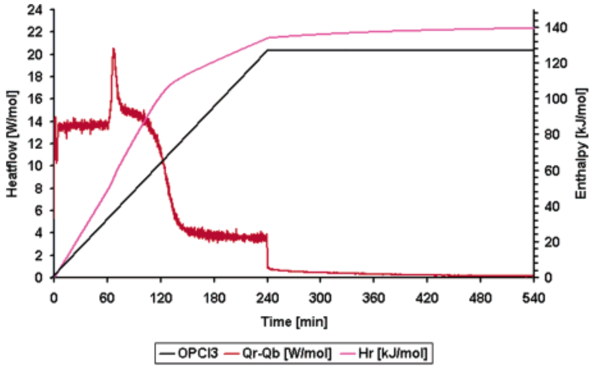

Figure 12. **DMF, DMA + $POCl_3$ ⇒ Iminium salt: profile.**

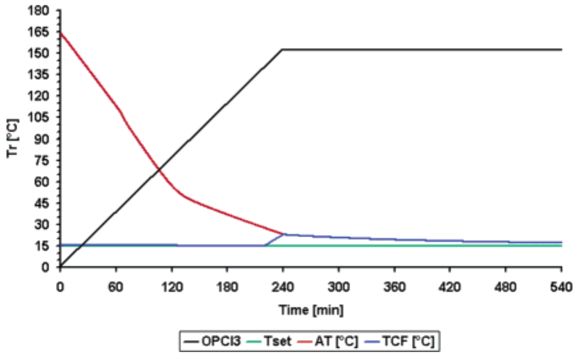

Figure 13. **DMF, DMA + $POCl_3$ ⇒ Iminium salt: safety parameters.**

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 and Figures 14 and 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. The results of this experiment are again close to the previous ones (see Table 7 and Figures 16 and 17). 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

Table 6. **Calorimetry results: Vilsmeier intermediate + DMA at 25 °C**

parameter	value	comments
Q_r	13 W/mol	initial plateau first 70 min
	21 W/mol	peak value, probably due to crystallization
	4 W/mol	final plateau from 150 to 240 min
Δ*H*	−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 C_p 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

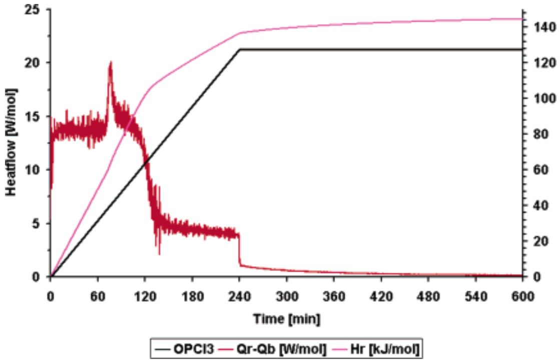

Figure 14. **DMF, DMA + $POCl_3$ ⟹ Iminium salt: profile.**

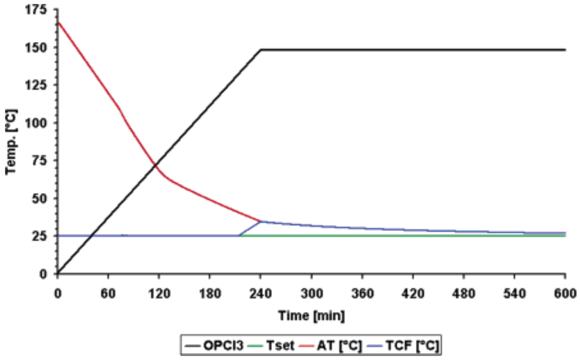

Figure 15. **DMF, DMA + $POCl_3$ ⟹ Iminium salt: safety parameters.**

point in time. Surprisingly the accumulation is nearly the same as those in the experiments at lower temperatures.

On the basis of only the thermal information, it is difficult to draw conclusions on the progress of the reaction. 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 online analytical data to elucidate the course of the chemical conversions. This would help to understand the thermal profile. These 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.

Table 7. **Calorimetry results: Vilsmeier intermediate + DMA at 40 °C**

parameter	value	comments
Q_r	13 W/mol	initial plateau first 80 min
	23 W/mol	peak value, probably due to crystallization
	4 W/mol	final plateau from 150 to 240 min
Δ*H*	−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 C_p 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

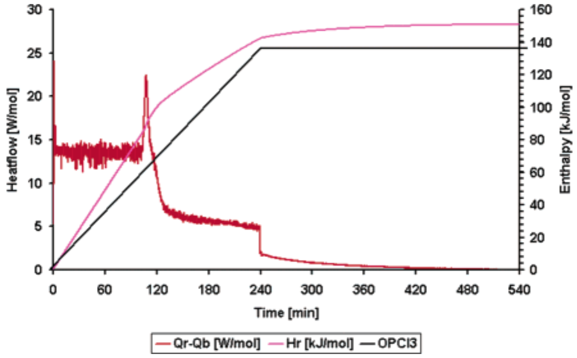

Figure 16. **DMF, DMA + $POCl_3$ ⟹ Iminium salt: profile.**

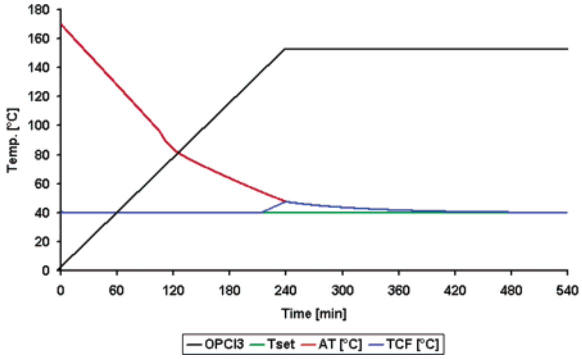

Figure 17. **DMF, DMA + $POCl_3$ ⟹ Iminium salt: safety parameters.**

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 and Figures 18, and 19).

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 min 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 noncondensable gases are formed in the decomposition. A MaxT_{Safe}24 of 31 °C was calculated.

Figure 20 illustrates the runaway index of the one-pot process at different temperatures. It can be questioned if the

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(10) Bollyn, M.; Van den Bergh, A.; Wright, A. *Chem.-Anlagen Verfahren* **1996**, *29*, 95−100.

Table 8. **ARC results of the one-pot synthesis reaction mixture**

parameter	value	comments
onset T	35 °C	the onset recorded is even lower than in the two-stage process !
T @ 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	
max $T_{safe}24$	31 °C	this result indicates that the one-pot process is not better than the original one

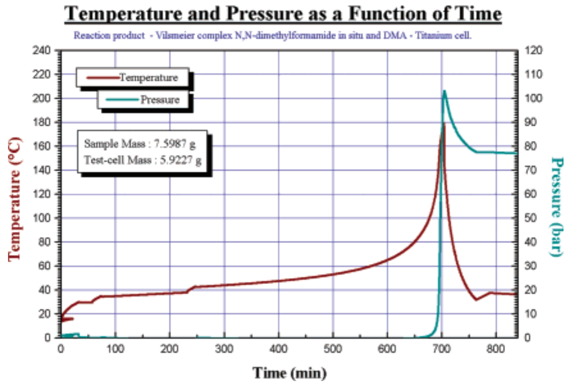


Figure 18. **ARC: *T*,*P* graph.**

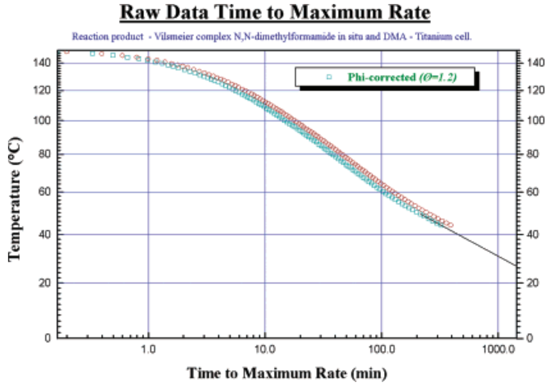


Figure 19. **MaxT_{Safe}24 graph.**

same MaxT_{Safe}24 value would have been obtained from the reaction mixtures at higher temperatures; this was not tested experimentally.

The MaxT_{Safe}24 values of the two-stage and the one-pot process are the same; hence, there is a 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. For 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. A sample from the one-pot DMF process was prepared and transferred to a Hastelloy ARC bomb and heated. It can be expected that Hastelloy is more resistant to HCl attack; therefore, it was also used to study the Vilsmeier intermediates. The Hastelloy ARC bombs have a higher weight compared to that of the titanium cells, which results in a higher ϕ-factor, and therefore is further from the adiabatic ideal when $\phi = 1$. To test the hypothesis that there is 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 ϕ-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 that for the metal bombs to avoid bursting these vessels.

The results of the test in Hastelloy bombs are shown in Table 9 and Figures 21 and 22. On heating, the sample shows a different decompostion profile: exothermic activity is not observed until 90 °C (at 600 min test time), and this takes the temperature to about 130 °C and the pressure to 66 bar after 1500 min, where further heating induces the second exotherm which is terminated by the safety setting at 300 °C and 120 bar pressure. The test took about 2900 min. 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 MaxT_{Safe}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. These results are comparable to and confirm the findings of the tests in Hastelloy bombs. In the temperature range of 40−60 °C some exothermicity can be observed, probably due to further chemical conversion. From about 90 °C and 940 min of test time on, self-heating is observed, and this takes the temperature to about 125 °C and 35 bar pressure over a period of about 900 min.

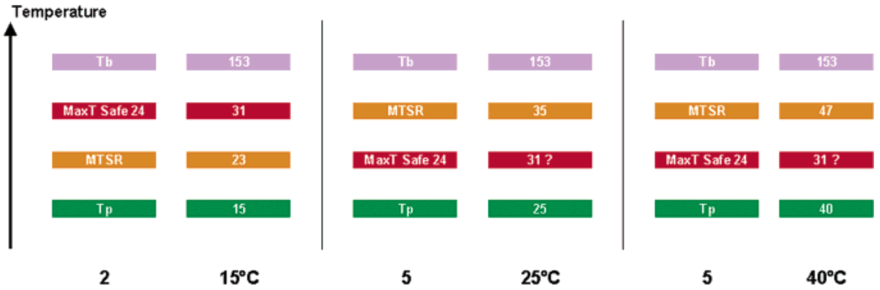


Figure 20. **Runaway index of one-pot process at different temperatures.**

Table 9. **Hastelloy ARC cell**

parameter	value	comments
onset T	85 °C	compared to 35 °C in Ti cell
T @ 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
max $T_{safe}24$	90 °C	compared to 31 °C in Ti cell

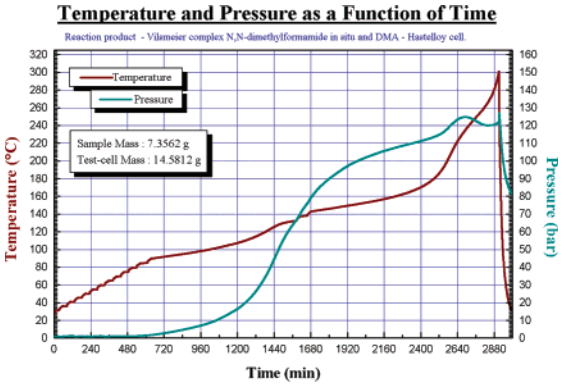


Figure 21. **ARC: *T,P* graph.**

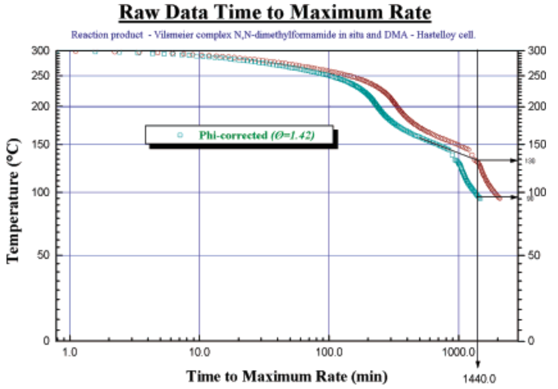


Figure 22. **MaxT_{Safe}24 graph.**

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 MaxT_{Safe}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 (MaxT_{Safe}24 of 80 °C).

On the basis of these results the runaway index can be calculated (Figure 25).

Table 10. **Glass ARC bomb**

parameter	value	comments
onset T	93 °C	comparable to the test in Hastelloy
T @ max rate	94 °C	the decomposition slows down immediately after the start
max T rate	0.08 °C/min	
max P rate	0.29 bar/min	
max $T_{safe}24$	77 °C	only a limited number of datapoints are available, because the test was terminated to protect the bomb

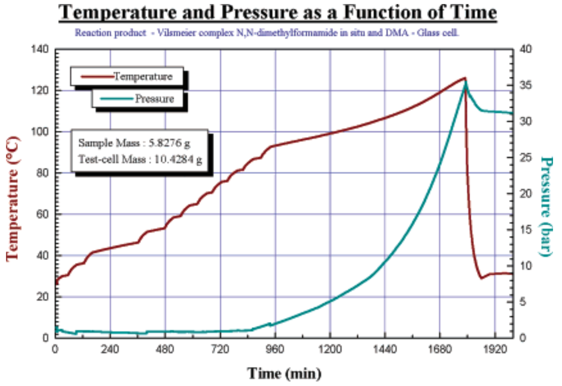


Figure 23. **ARC: *T,P* graph.**

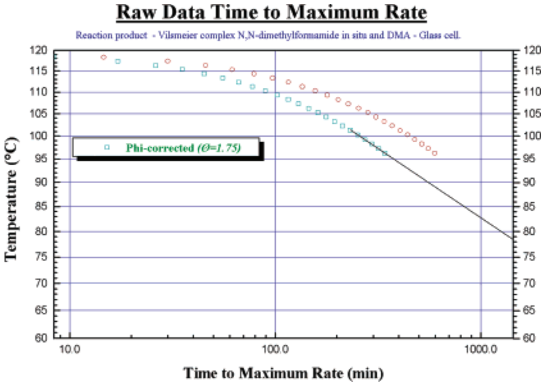


Figure 24. **MaxT_{Safe}24 graph.**

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

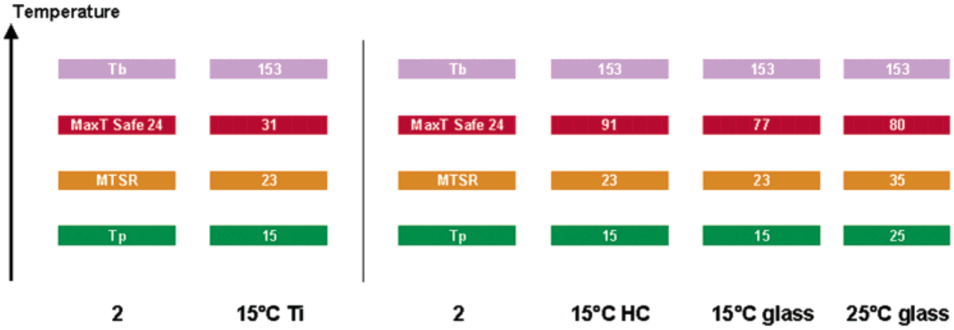
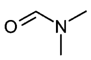


Figure 25. **Runaway index.**

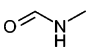
the literature. A set of potentially interesting formamides was selected for further testing: *N*-methylformamide (MFA, *6*), *N*,*N*-diethylformamide (DEF, *7*), *N*,*N*-dibutylformamide (DBF, *8*), *N*-formylpiperidine (PIF, *9*), and *N*-formylmorfoline (MOF, *10*).

N,*N*-dimethylformamide (DMF)



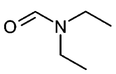
(2)

N-methylformamide (MFA)



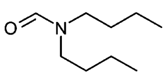
(6)

N,*N*-diethylformamide (DEF)



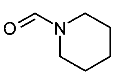
(7)

N,*N*-dibutylformamide (DBF)



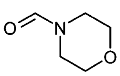
(8)

N-formylpiperidine (PIF)



(9)

N-formylmorfoline (MOF)



(10)

Before running the calorimetric tests in the RC1, the Argonaut AS3400 parallel synthesizer was used to test the interaction of $POCl_3$ with the formamides in two series of four experiments. All formamides show an exothermic reaction on adding $POCl_3$ (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 and get a viscous liquid.

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. 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.

The results from this thermal screening led 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 that for the other formamides. From these results it was decided to limit 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 results shown in Table 11 and Figures 27 and 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 and with addition 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 and Figures 29 and 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 were used to calculate the MaxT_{Safe}24, and this yielded a value of 47 °C, which is close to the DMF value. It appears that the thermal stabilities of the Vilsmeier intermediates of DMF and DEF are comparable.

On the basis of these results the runaway index can be calculated (Figure 31). 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.

5. The One-Pot DEF Process. As part of the systematic study of the different combinations of process modes and

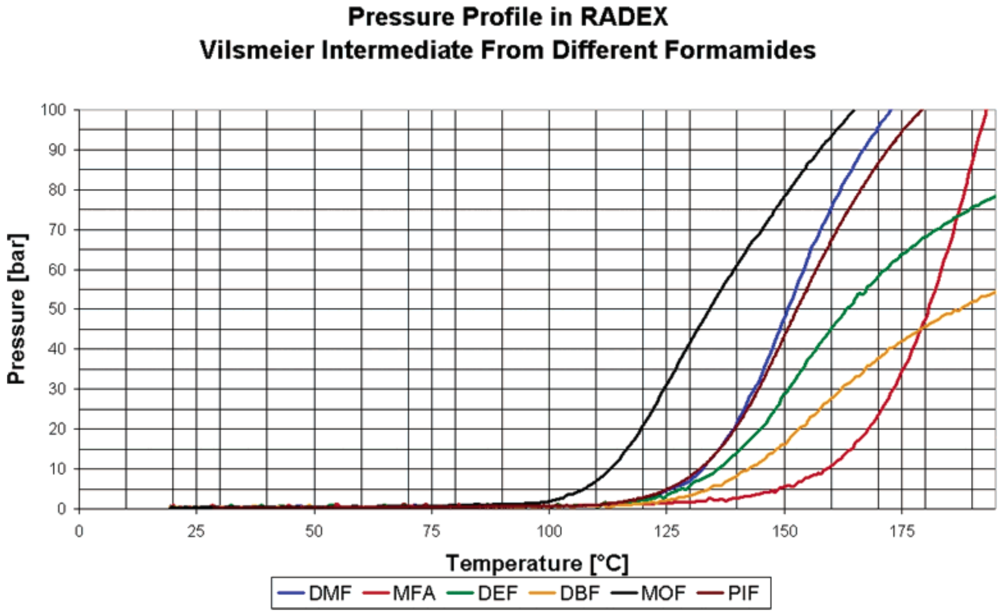


Figure 26. **Pressure versus temperature of reaction mixture with different formamides.**

Table 11. **Calorimetry results: DEF Vilsmeier intermediate at 25 °C**

parameter	value	comments
Q_r	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 $POCl_3$, once the water has reacted
Δ*H*	−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

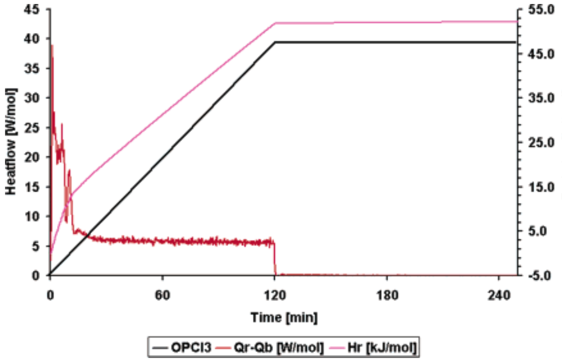


Figure 27. **DEF + $POCl_3$ ⟹ Vilsmeier profile.**

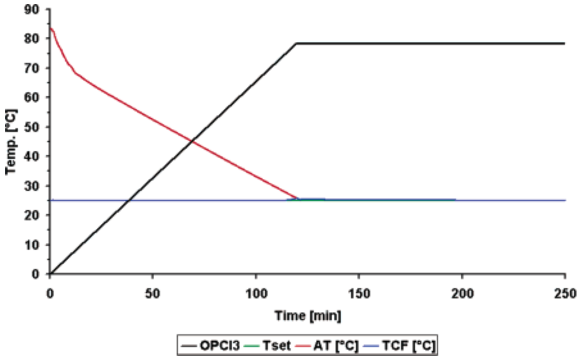


Figure 28. **DEF + $POCl_3$ ⟹ Vilsmeier: safety parameters.**

formamides, the 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. To obtain additional information on the accumulation during the dosing, two “stop−start” sequences were incorporated. A stop−start sequence 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 not fall to 0, then dosing control is limited and accumulation is observed. This could, of course, be due to parallel slower reactions.

Table 12. **ARC results: DEF Vilsmeier intermediate**

parameter	value	comments
onset *T*	63 °C	this is for the first exotherm, a second exotherm is detected at >200 °C
T @ max rate	135 °C	this exotherm stalls at 155 °C
max *T* rate	0.46 °C/min	
max *P* rate	1.05 bar/min	
max $T_{safe}24$	47 °C	value obtained for the first exotherm

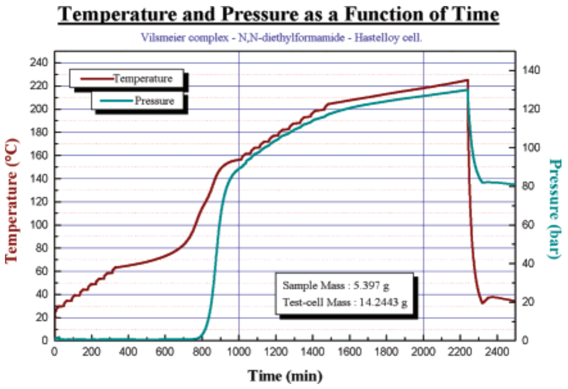


Figure 29. **ARC: *T*,*P* graph.**

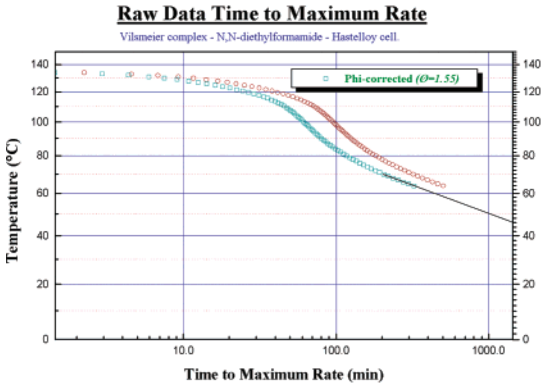


Figure 30. **MaxT_{Safe}24 graph.**

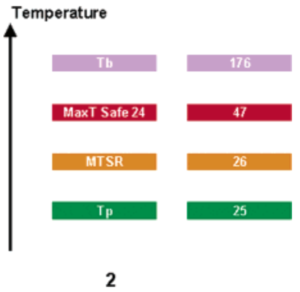


Figure 31. **Runaway index.**

The results of this experiment are presented in Table 13 and Figures 32 and 33. At the start there is additional heat production from the interaction of $POCl_3$ and water, but overall the reaction profile is comparable to that of DMF. In this case the peak in the heatflow 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). The sample showed thermal activity from 45 °C and heated over a period

Table 13. **Calorimetry results: DEF Vilsmeier intermediate + DMA at 25 °C**

parameter	value	comments
Q_r	23 W/mol	peak value due to the interaction with water
	13 W/mol	average heatflow during first part of the dosing
	20 W/mol	peak heatflow, due to crystallization
	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

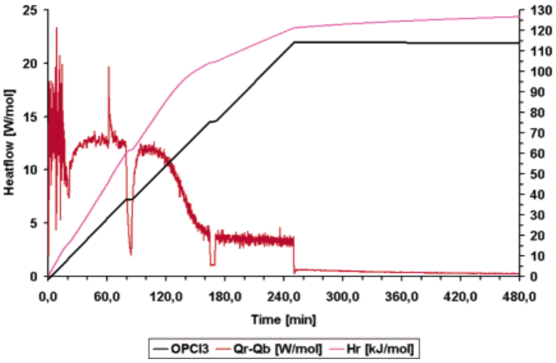


Figure 32. **DEF, DMA + $POCl_3$ ⟹ iminium salt: profile.**

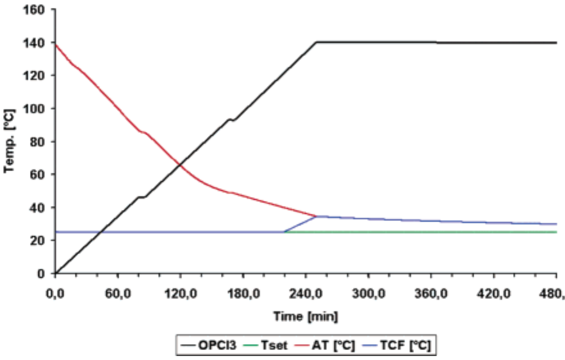


Figure 33. **DEF, DMA + $POCl_3$ ⟹ iminium salt: safety parameters.**

Table 14. **ARC results: DEF Vilsmeier intermediate in Ti bomb**

parameter	value	comments
onset T	45 °C	temperature at which the first exotherm starts
T @ max rate	157 °C	
max T rate	1.6 °C/min	
max P rate	1.9 bar/min	
max $T_{safe}24$	44 °C	this indicates that there is thermal instability for the DEF reaction mixture

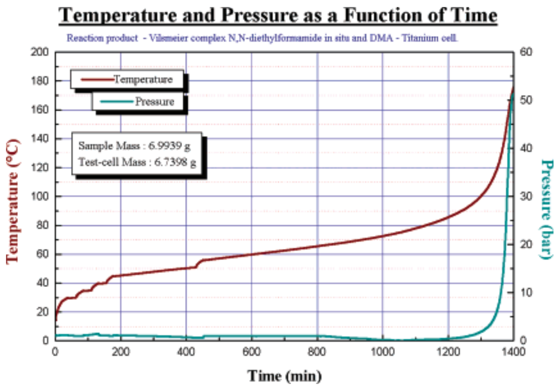


Figure 34. **ARC: *T,P* graph.**

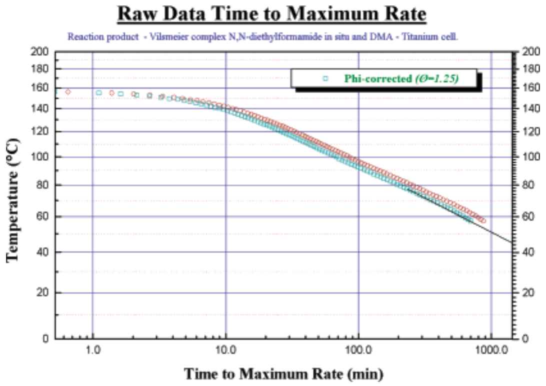


Figure 35. **MaxT_{Safe}24 graph.**

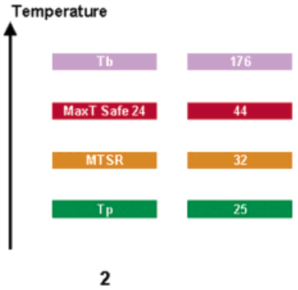


Figure 36. **Runaway index.**

of 220 min 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 MaxT_{Safe} value of 44 °C for the DEF reaction mixture (Figures 34 and 35).

On the basis of these results the runaway index can be calculated (Figure 36). The MaxT_{Safe}24 value is close to the MTSR, and this is a borderline case between index 2 and 5.

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 min 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 six 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 and Figures 37 and 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).

On the basis of these new results the runaway index can be recalculated (Figure 39).

Table 15. **ARC results: DEF Vilsmeier intermediate in Hastelloy bomb**

parameter	value	comments
onset *T*	70 °C	other exotherms start at 96 and 108 °C
T @ max rate	95 °C	
max *T* rate	0.04 °C/min	
max *P* rate	0.1 bar/min	
max T_{safe}24	91 °C	this is considerably higher than in the titanium bomb

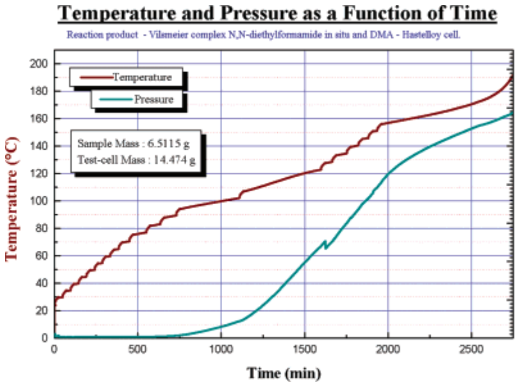


Figure 37. **ARC: *T*,*P* graph.**

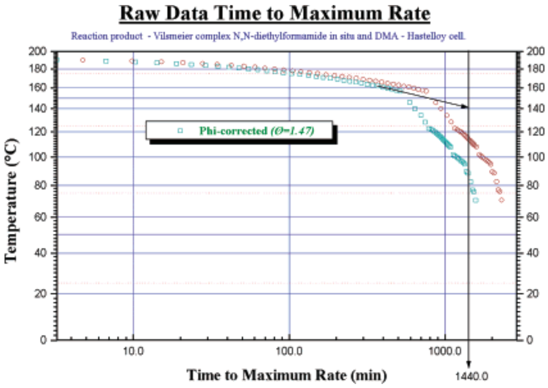


Figure 38. **MaxT_{Safe}24 graph.**

Figure 39. **Runaway index.**

Now there is a substantial difference between MTSR and MaxT_{Safe}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 this results in a larger mass.

Reaction Calorimetry. The standard calorimetry test in the RC1 was applied to DBF and $POCl_3$ over 2 h at 25 °C.

Table 16. **Calorimetry results: DBF Vilsmeier intermediate + DMA at 25 °C**

parameter	value	comments (DVD246)
Q_r	±22 W/mol	peak region due to interaction with water present (max 29 W/mol)
	±5 W/mol	flat region: expected reaction
Δ*H*	−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

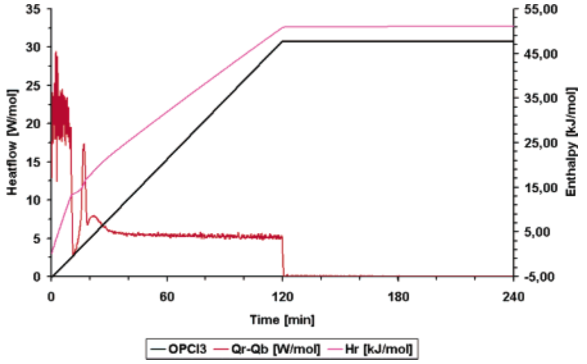


Figure 40. **DBF + $POCl_3$ ⟹ Vilsmeier profile.**

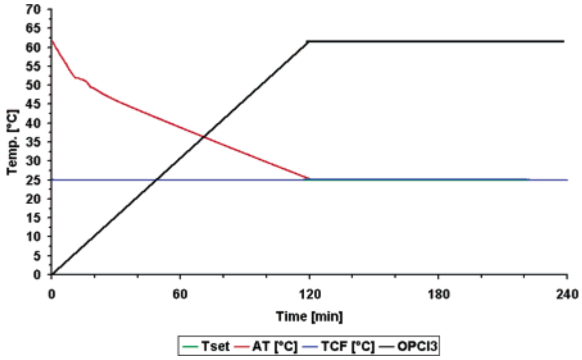


Figure 41. **DBF + $POCl_3$ ⟹ Vilsmeier: safety parameters.**

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).

It can be seen (see Table 16 and Figures 40 and 41) 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 results shown in Table 17 and Figures 42 and 43.

The sample shows thermal activity on heating to around 58 °C, and this exotherm takes the temperature to 92 °C over 750 min 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 these data a MaxT_{Safe}24 value of 56 °C was calculated.

The combination of these experimental results yields a Runaway index 2.

Table 17. **ARC results: DBF Vilsmeier intermediate**

parameter	value	comments
onset *T*	58 °C	start of a slow decomposition
T @ max rate	59 °C	
max *T* rate	0.1 °C/min	this can be considered a low value
max *P* rate	0.013 bar/min	
max T_{safe}24	56 °C	in same range as DMF and DEF

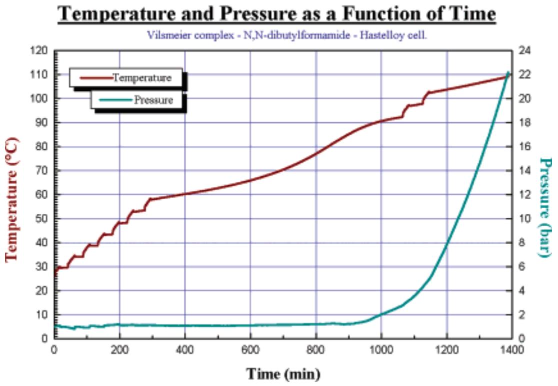


Figure 42. **ARC: *T*,*P* graph.**

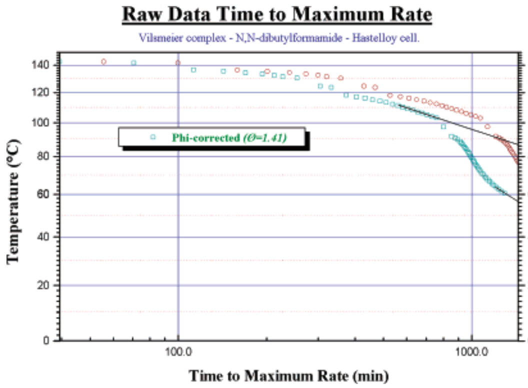


Figure 43. **MaxT_{Safe}24 graph.**

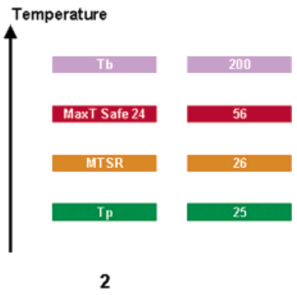


Figure 44. **Runaway index.**

The difference in MTSR and MaxT_{Safe} 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 $POCl_3$ (Table 18 and Figures 45 and 46).

Table 18. **Calorimetry results: Vilsmeier intermediate + DMA at 40 °C**

parameter	value	comments
Q_r	17−22 W/mol	additional heatflow due to the interaction with water
	14 W/mol	average value over the first 80 min
	14 ⟹ 5 W/mol	decline in heat production
	±5 W/mol	average value over the last 90 min of the dosing
Δ*H*	−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 min

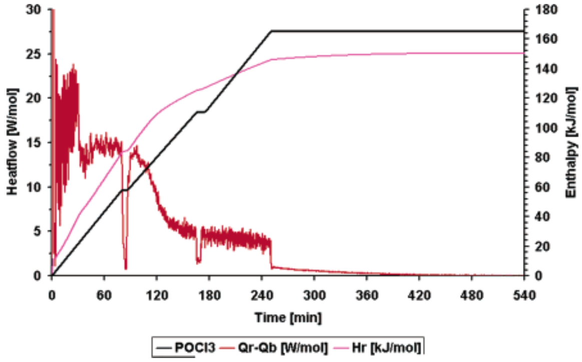


Figure 45. **DBF, DMA + $POCl_3$ ⟹ iminium salt: profile.**

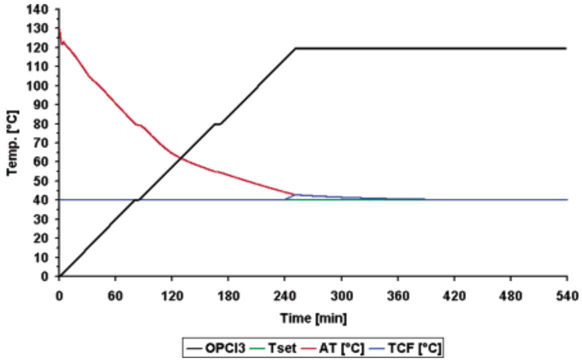


Figure 46. **DBF, DMA + $POCl_3$ ⟹ iminium salt: safety parameters.**

The one-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; in 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 min, even at 40 °C. Taking into account the contrubution of the interaction with water, the total reaction enthalpy is lower than that in DMF and DEF.

Adiabatic Calorimetry. A sample of the reaction mixture was heated in a Hastelloy bomb (Table 19 and Figures 47 and 48). During the first 720 min 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 the pressure to 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 MaxT_{Safe}24 value of 91 °C is obtained for the first weak exotherm.

On the basis of these results the runaway index can be calculated (Figure 49).

Table 19

parameter	value	comments
onset T	102 °C	start of a small exotherm; around 170 °C another exotherm starts
T @ max rate	193 °C	
max T rate	0.23 °C/min	
max P rate	0.07 bar/min	
max T_{safe}24	91 °C	calculated from the first weak exotherm

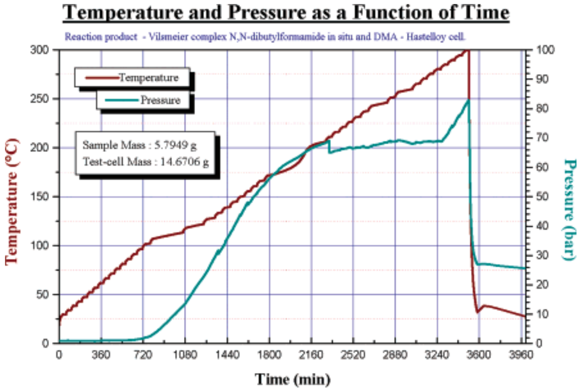


Figure 47. **ARC: *T*,*P* graph.**

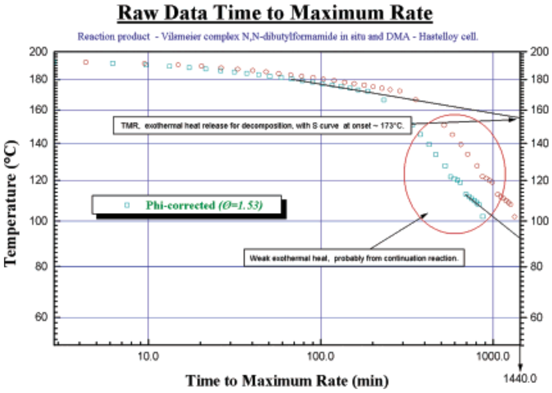


Figure 48. **MaxT_{Safe}24 graph.**

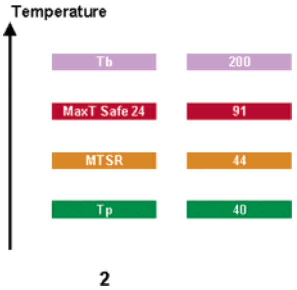


Figure 49. **Runaway index.**

Conclusions

From this study of the thermal behaviour of the Vilsmeier–Haack reaction the following conclusions can be drawn regarding 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 $POCl_3$ 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 h, 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 $POCl_3$ 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 heatflow is approximately constant until the end of the feed, whereas in the one-pot process there seems to be a changeover in the course of the reaction around the time where 50% of $POCl_3$ 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 to that 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 stop–start procedure indicates that at 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, but 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 does not 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 did this issue become clear. This was triggered by the discrepancy between the ARC test results and those of 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 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 MaxT_{Safe}24 value (±48 °C), and the stability seems to be a little better for DBF (56 °C).

Both the two-stage and the one-pot processes 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 of ±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 MaxT_{Safe}24 value of 90 °C was calculated.

On the basis of 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 exclusively 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 was used for the calibrations. Data files were exported to Microsoft Excel 97 for further calculations and charting.

Adiabatic calorimetry experiments were run in an EuroARC from Thermal Hazard Technology with EuroARC software V1.1, and ARCCal (based on Origin 3.53) was used for data processsing and charting. The following types of test 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 four 250-mL reactors was used; one feed unit was used for $POCl_3$ 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), $POCl_3$, MFA, MOF, and PIF were obtained from Acros Fine Chemicals (Belgium) and used without pretreatement.

Experiments. *(1) Two-Stage Process*. DMF (564 g, 3.78 mol per mol $POCl_3$) is charged to the reactor and thermostated at the initial temperature. $POCl_3$ (312 g) is added from the flask on the balance over the programmed feed period at the set temperature. The reaction mixture is stirred for the required time at the set temperature. DMA (248 g, 1.01 mol per mol $POCl_3$) is added from a separate flask on a second balance over the programmed feed period at the set temperature, and then the mixture is stirred for the required time at the set temperature. Calibrations 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 work-up. 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 $POCl_3$) and DMA (248 g, 1.01 mol per mol $POCl_3$) are charged to the reactor and thermostated at the initial temperature. $POCl_3$ (312 g) is added from the flask on the balance over the programmed feed period at the set temperature, and then the mixture is stirred for the required time at the set temperature. Calibrations 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 work-up. DMAB is isolated by filtration, washed with water, and dried.

(3) Screening Experiments. The formamide (1.16 mol) is charged to the reactor and thermostated at the initial temperature (25 °C). $POCl_3$ (0.30 mol) is added to the reaction mixture over the programmed period (1 h). After a stirring period, DMA is added over the programmed period (1 h) and stirred for 1 h; after heating to 40 °C the mixture is stirred for 3 h, 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 $POCl_3$ is used. The reaction mixture is hydrolysed and then discarded without further work-up.

(5) ARC Tests. Samples of 5−6 g of the reaction mixture are transferred with a pipet to a preweighed test cell. This is mounted in the calorimeter and fastened. After closing the instrument the initial data are entered, and the heat−wait−seek temperature 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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