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# Safety Aspects of a Cyanamide Reaction: Inherent Safe Design through Kinetic Modelling and Adiabatic Testing

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**Abstract:**

**The synthesis of an active pharmaceutical ingredient involves the use of the highly unstable compound cyanamide. At temperatures above ambient, cyanamide starts to decompose slowly, so that proper safety testing is needed to facilitate safe use in chemical production. To determine the decomposition behaviour of cyanamide, we used the nonparametric kinetic modelling approach as provided in the Advanced Kinetics and Technology Solutions software package. The model was constructed on the basis of five different DSC runs, each with a different heating rate, and its validity was checked through a comparison of the predicted adiabatic runaway profile with the results of actual adiabatic experiments in the Phi-Tec calorimeter. The simulations and the experiments showed that the consequences of a runaway reaction could be very serious. Since very high concentrations of the starting materials were used in the original recipe for this reaction, the severity of a possible runaway reaction could be decreased considerably through diluting the system with extra solvent (in this case water). Thanks to the high heat capacity of water, a relatively small decrease in concentration had a very significant influence on the maximum heat rate of the runaway reaction, resulting in an inherently safer and yet economically viable process. The detailed kinetic model enabled us to evaluate the impact of different thermal conditions on the decomposition behaviour of the reaction mixture.**

## 1. Introduction

In the synthesis of an intermediate for an active pharmaceutical ingredient (API), a 50% (w/w) solution of cyanamide in water is mixed with the starting product, an aniline, and brought to 60 °C. At that point, hydrogen chloride is dosed into the reaction mixture, resulting in the desired coupling reaction. The reaction scheme is given in Figure 1. This reaction proceeds relatively rapidly, with a high yield of high-purity product. The cyanamide used is a very unstable compound, however, which starts to decompose slowly at temperatures above ambient. Because of the high exothermicity of the synthetic reaction, dosing of the hydrogen chloride on a production scale needs to be done slowly, resulting in relatively long reaction times, typically more than 4 h. In this time frame, cyanamide decomposes at a considerable rate, and hence there is a competition between the desired reaction and the decomposition reaction. Because the decomposition of cyanamide is very exothermic as well (the typical enthalpy of decomposition of the 50% solution in water is about 1600 J/g in DSC), this poses a serious safety problem. In the hazard analysis, the most credible runaway scenario was deemed to arise from a cooling failure just before the reaction starts, when the temperature of the reaction mixture is 60 °C and no hydrogen chloride has been added yet. In this scenario, the cyanamide would start to decompose, at first slowly, but then faster as the decomposition proceeded adiabatically. A loss of cooling at this point can be considered as a worst-case scenario, since all cyanamide is still present (coupling reaction has not started yet). The key concern in this scenario is the heat generation at the reflux temperature. If this heat generation is too high, flooding of the vapour lines and subsequent ejection of the reaction mass could occur.[1] Therefore we needed to characterize the decomposition reaction of this process in great detail.

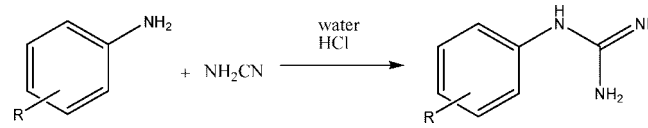


***Figure 1.*** **Coupling reaction of the aniline compound with cyanamide in water.**

## 2. AKTS Modelling Software

For the kinetic modelling we used the Advanced Kinetics and Technology Solutions (AKTS) software.[2] The current kinetic procedure applied in the AKTS Thermokinetics Software is based on the use of the Arrhenius equation in the so-called differential isoconversional method of Friedman, which can be used to elaborate DSC signals.[3] This numerical technique (after baseline optimisation) makes possible an advanced and precise description of the decomposition reactions of most chemicals. The Friedman method is based on the Arrhenius equation:

$$\frac{d\alpha}{dt} = A \exp\left(-\frac{E}{RT(t)}\right) f(\alpha)\, dt \qquad (1)$$

in which $f(\alpha)$ is the model function, $A$ is the pre-exponential factor, $E$ is the activation energy, $T$ is the temperature and $t$ is the time. Friedman's idea was to apply the logarithm of the conversion rate $d\alpha/dt$ as a function of the reciprocal of the temperature at any conversion $\alpha$:

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(2) AKTS-Themokinetics software and AKTS-Thermal Safety Software. http://www.akts.com
(3) Friedman H.L. *J. Polym. Lett.* **1996**, *4*, 323


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$$\frac{d\alpha}{dt} = A(\alpha)\exp\left(-\frac{E(\alpha)}{RT(t)}\right) f(\alpha) \quad (2)$$

$$\ln\left(\frac{d\alpha}{dt}\right) = \ln(A(\alpha)) - \frac{E(\alpha)}{RT(t)} + \ln(f(\alpha)) \quad (3)$$

As $f(\alpha)$ and $A(\alpha)$ are constant at any fixed $\alpha$, the logarithm of the conversion rate $d\alpha/dt$ over $1/T$ gives a straight line with the slope $m = -E/R$ (this implies that the activation energy is not constant but a function of the conversion). By extension, we can also state

$$\frac{d\alpha}{dt} = A'(\alpha)\exp\left(-\frac{E(\alpha)}{RT(t)}\right) dt \quad (4)$$

in which $A'(\alpha) = A(\alpha)\, f(\alpha)$

In this model, a set of different DSC curves is used, each with a different heating rate as input. Since peaks in DSC curves shift towards higher temperatures when higher heating rates are used, this set of data contains the information needed regarding different conversions at different temperatures. This information also enables us to determine the conversion dependence of the activation energy and the pre-exponential factor and hence to construct the appropriate nonparametric kinetic model. With this model we can then predict the thermal behaviour of the system under different conditions (isothermal, linear heating, temperature profiles, adiabatic, etc.).

This equation can also be used to describe the thermal behaviour of a larger amount of substance because the kinetics are the same for 10 mg of substance as for 1 ton. The only requirement for this undertaking is an accurate description of the thermal properties (conductivity, heat transfer properties, etc.) of the system. Once these parameters are known, relatively accurate predictions can be made with regard to the conversion of the product in different thermal conditions.[4]

## 3. Experimental Approach

The synthesis reaction was tested in two different conditions: concentrated and diluted. At room temperature, the reaction mixture is highly heterogeneous. At temperatures around 60 °C, the mixture becomes homogeneous. The specific heat of the mixtures was retrieved from a Mettler RC1 experiment (Quickcal procedure) and was found to be 2.7 J/gK (at 65 °C) for the concentrated process and 3.4 J/gK (at 60 °C) for the diluted process.

All adiabatic experiments were performed in an HEL Phi-Tec calorimeter. Glass cans with magnetic stirring were used. Typically these cans have a $\varphi$-factor of approximately 1.25 for aqueous solutions. A heat-wait-search approach was followed, with a starting point of 60 °C and subsequent heat steps of 5 or 10 °C. All experiments were performed in the closed cell heat-wait-search mode. The observed adiabatic runaway profiles were all due to the decomposition of the cyanamide, since no HCl was added to the solution. This was also analytically checked: a sample was taken from the reaction mixture after a Phi-Tec experiment (experiment was aborted after the first part of the exotherm at approximately 170 °C in the concentrated process) and all aniline was still present, signifying that no coupling reaction had taken place. This confirms that without the addition of the acid no coupling reaction takes place and all heat generated arises solely from the decomposition of the cyanamide.

All DSC runs were performed on a Mettler 822e DSC, and gold-plated 20 $\mu$L high-pressure crucibles from the Swiss Institute of Safety and Security were used. Since the reaction mixture is strongly heterogeneous, the products were brought together in the crucibles and not mixed beforehand. To achieve this, the starting product (the aniline, a solid) was put into the crucible and its weight was recorded. From this weight, the exact amount of required cyanamide 50% solution in water was calculated. This amount was then added to the crucible with a microlitre pipette. For the diluted process, the cyanamide solution was first diluted with extra water, and a similar procedure was then followed. The crucibles were hermetically sealed using a standard press. DSC runs with scanning rates of 8, 4, 2, 1 and 0.5 °C/min were recorded, and the resulting data were used as input for the AKTS Thermokinetics software. The sample mass was in the range of 10–20 mg. The DSC curves used as input for the AKTS software were all normalized to sample size, and no baseline subtraction was performed.

## 4. Adiabatic Testing

The original (i.e., concentrated) process was tested in the Phi-Tec adiabatic calorimeter. In this experiment, exothermicity was observed from 73 °C. A final temperature of 165 °C was reached after 160 min (see Figure 4). Note that this experiment was conducted in a glass test cell with a $\varphi$-factor of 1.26. What is most important about this run however, is the maximum self-heat rate (SHR), which was found to be 3.5 °C/min. Since the influence of the $\varphi$-factor on the maximum SHR is dramatic,[5] it can be expected that in a real runaway scenario on a plant scale (i.e., at $\varphi = 1$), a rate of at least 10 °C/min would be observed. Under operating conditions, the heat output at the reflux temperature is important: if it is sufficiently low at this temperature, the boiling of the reaction mixture will temper the reaction, the temperature can no longer rise, and the boiling point can be considered as an efficient safety barrier. If, however, the heat output at the reflux temperature is high, flooding of the vapour lines can occur, with subsequent ejection of (part of) the reaction mass from the reactor. In this particular closed cell adiabatic experiment, the SHR at the boiling temperature (100 °C) is 1 °C/min, and it is hard to predict what this value would be at $\varphi = 1$. This process is also extremely concentrated (only 25% (w/w) of the reaction mass is solvent), so that the evaporative loss of a limited amount of solvent would be expected to substantially affect both the reaction kinetics and the boiling temperature. This in turn could greatly increase the observed heat output at the reflux temperature and hence the risk of flooding. We therefore considered this process as not inherently safe and consequently not acceptable for introduction into production.

Given the preceding, an approach was needed to change the process in such a manner that it would become inherently safer,

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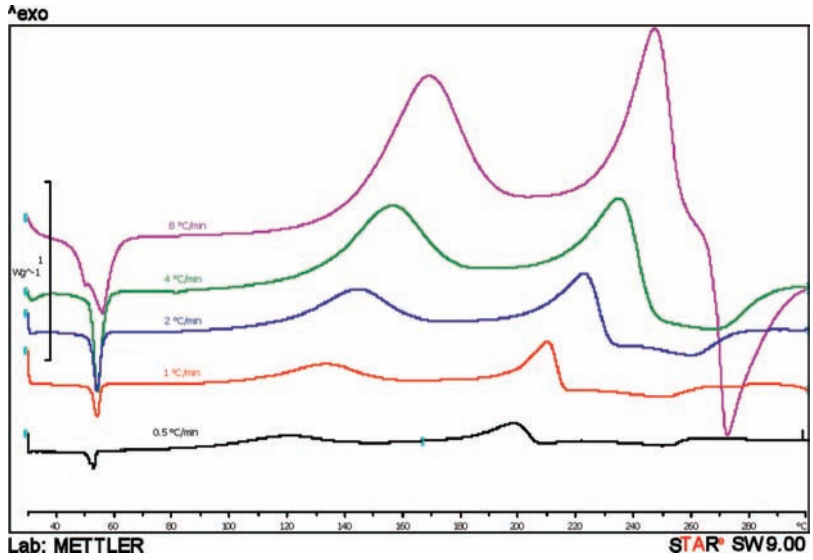


***Figure 2.*** **DSC runs of the process at different heating rates. These curves were generated from the diluted process condition. The appearance of the runs from the concentrated process condition is very similar.**

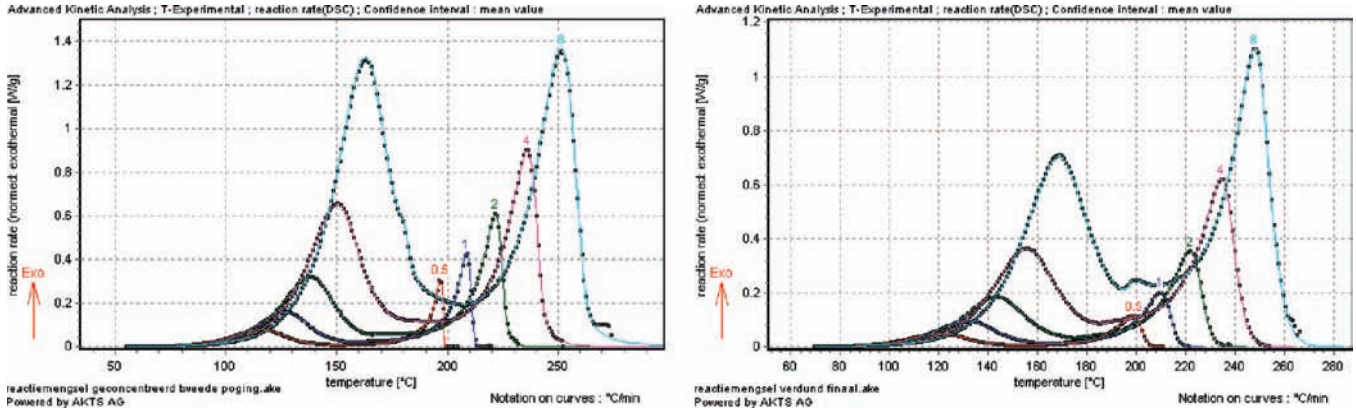


***Figure 3.*** **AKTS model of the concentrated process (left) and the diluted process (right). The solid markers represent the experimental (DSC) points, and the line represents the curve generated by the model.**

without interference with the high yield and quality of the product obtained. This requirement was satisfied through diluting the process with extra solvent, in this case water. The process conditions were not changed, but the amount of solvent was increased from 25 to 53% (w/w) of the starting volume. The effect of this dilution is two-fold: on the one hand, the extra amount of solvent acts as an extra heat sink for the heat generated (thereby decreasing the adiabatic temperature rise), and on the other hand, the dilution results in a lower overall concentration of the reagents, resulting in slower reaction kinetics (hence decreasing the reaction rate). These reaction conditions were tested in the Phi-Tec as well, and the expected decrease in severity of the runaway reaction was confirmed experimentally. For these new process conditions, the exotherm started at 86 °C, the total adiabatic temperature rise was lowered from 143 to 60 °C (first part of the exotherm, calculation corrected for $\varphi = 1$), and the maximum SHR (experimental at $\varphi = 1.25$) from 3.5 to 0.45 °C/min.

It should be noted that in all Phi-Tec experiments, the run was aborted at about 170 °C, so that only the first part of the decomposition reaction was considered, as will be discussed below.

## 5. AKTS: Construction of Model

The two process conditions (concentrated and diluted) were studied by means of AKTS modelling on the basis of DSC runs with different heating rates. The samples were prepared as described in Section 3 above. As can be seen in Figure 2, the decomposition reaction comprises two distinct reaction steps. In the adiabatic tests in the Phi-Tec, the decomposition reaction studied was limited to the first step. Other tests (with pressure measurement) had shown that the first part of the decomposition reaction is not accompanied by any gas generation, but that the second one is. The adiabatic experiments were therefore aborted after the first part of the reaction so that the second decomposition reaction would not be triggered, which could rupture the test cell.

In the AKTS software, it is recommended that the baseline construction be performed in such a way that the standard deviation of the integrated reaction enthalpies of the different DSC runs is less than 10%. For the concentrated process, no major problems were encountered with the construction of the baseline. For the diluted process, however, a clear baseline shift in the DSC signal was observed at around 80 °C. This shift might have been due to the dissolution of the starting material

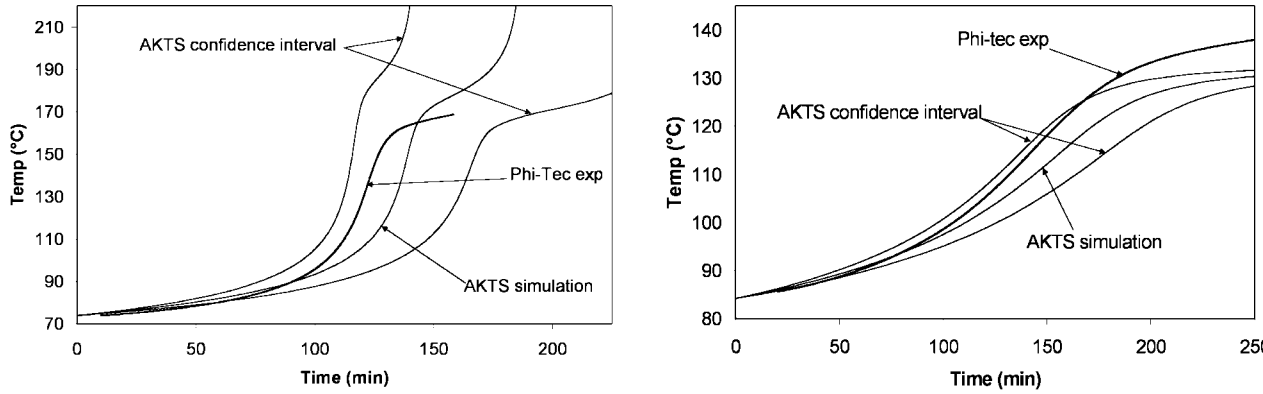


***Figure 4.*** **Comparison of the experimental adiabatic runs (thick curves) with the AKTS simulations (thin curves), including the AKTS confidence interval. Concentrated process in the left-hand graph, diluted process in the right-hand graph.**

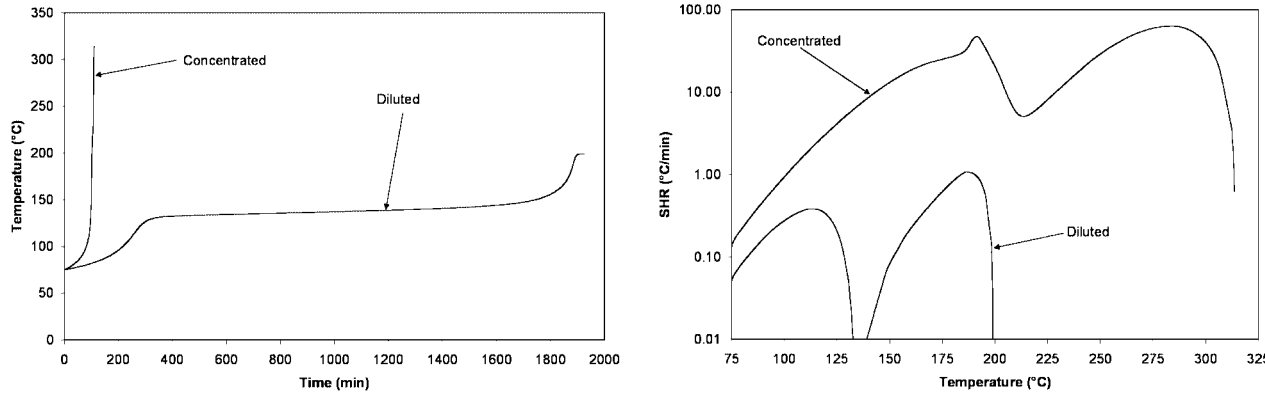


***Figure 5.*** **AKTS simulations of runaway profiles for the concentrated and the diluted process (starting temperature 75 °C, $\varphi = 1$). Temperature profiles are in the left-hand graph, heat-rate curves are in the right-hand graph. (NB: the scale in the latter is *logarithmic*.)**

in the reaction mixture or to some other change in physical properties and should therefore not be taken into account for the determination of the reaction enthalpy. Hence the tangent used for the baseline construction at the beginning of the reaction was the one constructed right after this baseline shift. This approach resulted in a small confidence interval for the reaction enthalpy (422 ± 3.5 J/g) and a good fit with the experimental Phi-Tec data, confirming the validity of the kinetic model. Figure 3 shows the fit of the experimental DSC data with the model for both processes.

## 6. Comparison Kinetic Model with Experimental Phi-Tec Data

Once the kinetic model is constructed, predictions can be made about the thermal behaviour of the system in different thermal conditions. One of the possible thermal scenarios is fully adiabatic behaviour. Model predictions were therefore calculated for the two processes under the conditions used in the Phi-Tec (same starting temperature and same $\varphi$-factor). For the model prediction, an upper and lower confidence interval was calculated as well. The results are shown in Figure 4. From the two graphs, it can be concluded that the model predicts the experimental curves very well. Part of the difference between the experimental curves and the predicted ones may arise from the difficulty of accurately determining the $\varphi$-factor of the glass test cells used or from the fact that the heat capacity and the $\varphi$-factor are kept constant throughout the temperature range in the AKTS model (whereas in reality they are a function of the temperature). The differences are small however, which makes it likely that the other AKTS predictions are reliable as well.

## 7. Simulation of Runaway Behaviour at $\varphi = 1$ and Recommendations

In practice, it is very difficult to perform accurate adiabatic measurements at a $\varphi$-factor close to unity. However, the AKTS model enables us to perform simulations of virtually any adiabatic runaway scenario imaginable, at any $\varphi$-factor. Because the process is run at 60 °C, the following scenario was thought to represent a worst-case situation: the reaction mixture is heated to 60 °C, and an overshoot of 15 °C occurs, after which there is a loss of cooling power. This would result in an adiabatic runaway from 75 °C. This scenario was simulated at $\varphi = 1$, and the results are given in Figure 5. Already at first glance, it is obvious that the severity of a possible runaway scenario is far worse for the concentrated process than for the diluted process. First of all, the maximum SHR of the first part of the decomposition reaction is several orders of magnitude higher in the concentrated process (47 versus 0.3 °C/min for the diluted process). Second, in the concentrated process, the first and the second part of the decomposition are hardly distinguishable from one another. This results in a higher maximum SHR, but the pressure profile is influenced as well. The first part of the decomposition is not accompanied by any pressure buildup (apart from the increase in vapour pressure with increasing

temperature), whereas the second part of the decomposition is accompanied by substantial gas generation and hence pressure buildup. It would therefore be unacceptable from a safety perspective to run any risk of triggering the second part of the decomposition reaction. In the diluted process, the two steps of the decomposition are sufficiently separated that the risk of triggering the second part of the decomposition is virtually nonexistent.

Another reason for which the diluted reaction is preferable to the concentrated one is related to the heat output at the reflux temperature. As already mentioned, the reflux barrier of the reaction mixture can be used safely to prevent the temperature from rising any further during a runaway reaction, providing that the heat generation at the boiling point is sufficiently low. The heat rates at the boiling point (100 °C) predicted by the AKTS model are relatively low in both scenarios: 0.3 °C/min for the diluted process and 1 °C/min for the concentrated process, which corresponds to 14 and 57 W/kg. Normally, the reflux barrier would be sufficient in both cases, and the process could be deemed safe enough for introduction into the production plant. There are some concerns, however, regarding the heat profile of the concentrated process. First, very little solvent is used, and the possibility of part of the solvent being lost when the boiling point is reached cannot be ruled out. A small loss of solvent could result in both a significant increase in the boiling point and an increase in concentration, which would lead to a substantially higher heat rate at the actual boiling point. It can be seen from the heat rate curves that the sensitivity of the heat rate to the reaction temperature at around 100 °C is much higher for the concentrated than for the diluted process. A small increase in the boiling temperature would therefore have a considerable effect on the heat generation in the concentrated process. All of these factors are of no concern for the diluted process, since in that case the overall maximum heat rate is only 0.3 °C/min, which would pose no problem whatsoever at the boiling point. Moreover, the energy potential that is left at the boiling point in case of a runaway would only be sufficient for the evaporation of maximum 10% of the total amount of solvent present in the diluted process. The evaporation of such a small amount of solvent will have very little effect on the further behaviour of the system. All factors considered, we conclude that the diluted process is preferable for production since it would result in inherently safer reaction conditions, whereas the concentrated process does not.

## 8. Conclusions

A synthetic reaction in which cyanamide in water was used was kinetically modelled with the aid of AKTS software. The results of adiabatic Phi-Tec testing agreed well with the model predictions. Simulations established that the concentrated process is not appropriately safe. The process was therefore redesigned on the basis of a diluted reaction, and appropriate testing showed that this process is inherently safer, so that it can be introduced into the chemical production facility.

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