CHEMICAL REACTION HAZARDS – AN EVOLVING APPROACH

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Process Safety within Pfizer has evolved over a 25 year period and this paper briefly discusses why and how this has happened and what an assessment program should look like. This growth has led to an investment in equipment, people and facilities but in today's competitive environment it is critical we examine how we can maintain a safe working environment whilst using our resource in the most efficient way. This can be achieved by ensuring a safety assessment is not an "add on", but an integral part of chemical development. The use of newer and more efficient calorimetry techniques will be discussed along with the use of non specialist lab resource and equipment, to help provide appropriate safety information for the intended scale of operation.

The development of a modern day strategy for the use of theoretical calculations for reaction heats also forms a major component of this evolving approach.

INTRODUCTION

2009 has several notable anniversaries – It is 35 years since the Flixborough incident in which 28 people were killed in the UK (June 1974), 25 years since the worlds worst chemical incident occurred in Bhopal (December 1984) and lastly 30 years since I started my career at Pfizer (1979).

The reason I mention the above is this paper examines some of the changes that have occurred in the field of reaction hazard evaluation during this time and shows how today's competitive environment is continually challenging the way we ensure the safety of chemical processes. To do this I am going to discuss how reaction hazard assessment has evolved over this time period within Pfizer, what a good assessment program looks like and how we are addressing the challenges to develop processes safely and quickly in today's competitive environment with a particular focus on new approaches in reaction heat calculations.

IN THE BEGINNING...

I started at Pfizer in 1979 as a development chemist and we (in common with a lot of other major companies) had no in house reaction hazard group at this time. For us, like many other industries an incident was a trigger to examine how we went about evaluating chemical reaction hazards and the article clipping[1] below (Fig. 1) highlights the incident we had during which fortunately no person suffered any physical injuries.

After this incident we set up an in-house chemical reaction hazard group and using the then recently published ABPI guidance document as a reference[2] we set up procedures that involved:

- **Desk screening** – Identification of hazardous function groups known to give reaction hazard/stability issues allowing materials to be substituted, minimised or other control measures put in place.
- **Desk calculations** – Bond Energies used to give reaction heats using CHETAH[3] or manual Benson group calculations for example.
- **Basic equipment** – Thermal screening data was obtained using an analytical GC oven and test tubes/thermocouples which gave useful thermal information in a simple and rapid test.

This basic approach gave us an entry into the world of reaction hazard information and enabled us to make informed decisions and assess the safety of our operations at this time. However the appearance of several practical and reliable new instruments brought on a new era of experimental measurement, and as these instruments became more popular, the use of heat estimation and other desk top methods were largely abandoned within our company (and others) However I will return to this point again later in the paper.

Typical equipment we used was differential scanning calorimetry (dsc), reaction calorimetry, variations on carius tube testing such as Thermal Screening Unit (HEL), Rapid Screening Device (THT) and adiabatic calorimeters such as ARC, and variations of, such as Phi Tec (HEL), VSP (Fauske) etc. These sophisticated pieces of equipment entered us into a new era of high quality safety data and risk reduction that enabled us to address the three major reaction chemical hazards:

1. The thermal instability of reactants, reaction mixtures, and products (including intermediates and by-products).
2. Exothermic reactions which raise the reaction temperature to cause uncontrolled boiling or decomposition reactions.
3. Gas evolution – both volumes and generation rates.

The assessment program we introduced had to cover work from small scale discovery chemistry up to commercial manufacturing operations and typically the assessment work flow followed the lines of the schematic shown in Fig. 2.

The reaction heat and thermal stability data was then used to build a picture of the process hazards and this can be illustrated in a simplified Stoessel diagram (Fig. 3) which pictorially relates thermal stability, normal process

letters to the Editor

Explosive azides

Sir – I am writing to inform you of a hazard in the preparation of 2-azidoethanol from 2-bromoethanol and sodium azide. During the preparation an explosion occurred. This letter describes the circumstances of the incident.

A five litre three-necked round-bottomed flask was equipped with an air driven glass stirrer through a PTFE guide, an air condenser, and a glass stopper. 2-Bromoethanol (1.83/kg – 14.65 moles) was charged to the reactor followed by sodium azide (1.0kg – 13.4 moles) over 5-6 minutes with stirring. Heat was applied from a steam bath, and the resultant hot heterogeneous mass maintained at steam bath temperature with continual stirring. After 1 hour 40 minutes, during which time the reaction required no attention, the whole exploded, with no resultant fire. The explosion, estimated at a force equivalent to 100-200g of TNT,[1] caused extensive damage; but fortunately no personal injury.

The preparation of 2-azidoethanol has been conducted numerous times in our department; indeed a 64 per cent larger preparation had been carried out similarly without mishap.

The literature on 2-azidoethanol highlights three relevant papers which refer to hazards. Forster & Fierz[2] prepared 2-azidoethanol from 2-chloroethanol (0.8 mole) and sodium azide (1.23 moles) without solvent on a steam bath. They mention a very mild detonation of a sample on a hot plate, but that the preparation of this material presents no difficulties. The extract of an article by Urbanski[3] mentions that 'triazoethanol itself is an explosive owing to the presence of the N_3 group'. A further paper[4] describes the preparation which proceeded normally, but refers to the violence of an explosive combustion when the material was ignited. Other papers refer to the preparation, but none mention a problem of the kind we have experienced.

Organic azides in general do display instability and this effect is greater the lower the molecular weight. The closest analogue for which firm data are available, ethyl azide, is a hazardous compound and has recently caused laboratory explosions.[5,6]

An alternative reason for the explosion may be the inadvertent formation of hydrazoic acid by intrusion of water but there is no evidence of this in our case. The literature is replete with data on the explosive nature of this material.[7]

I urge those who work with low molecular weight organic azides in general and 2-azidoethanol in particular to be aware of the hazards associated with these materials, and apply the same caution to 2-azidoethanol as other low molecular weight organic azides.

Yours faithfully
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Figure 1. 1986 Azide incident communication

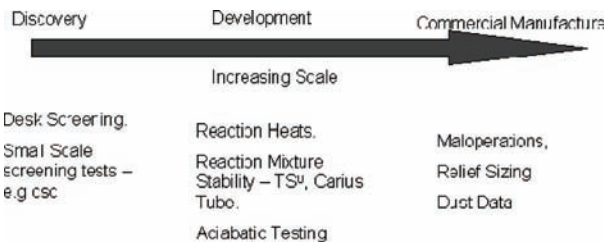

Figure 2. Safety assessment across the development timeline

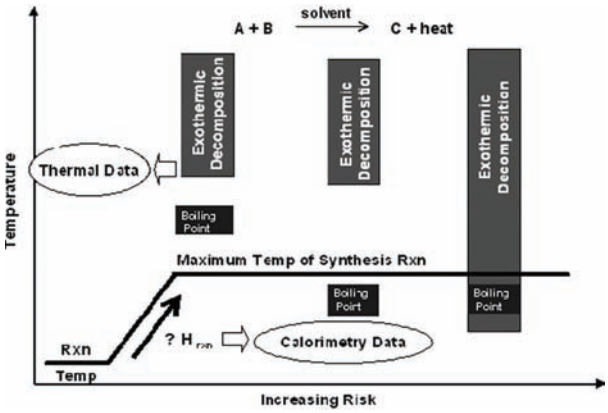

Figure 3. Simplified stoessel hazard scenario diagram

temperatures, boiling points and exothermic decompositions together to highlight the hazards of a particular process.

Over the years this approach has been used very successfully within our company as we grew experience and knowledge in the area of reaction hazard evaluation. We invested heavily in people and equipment to understand risk and make informed decisions. However what tended to happen was process safety became an "add on" to chemical development reducing the chance of influencing safe design at an early stage of the chemical development lifecycle and causing delays if safety concerns were identified on critical development timelines.

EVOLUTION

One of the main reasons for the above workflow was the desire to assess the process as it will be operated on plant facilities. Chemists (in general) like to keep improving the process right up until the last minute and hence safety work became squeezed in between the fixed process being ready and the planned scale up date, and this would often be a period of only a few days.

So how do we overcome this and make process safety an integral part of chemical development?

Several initiatives are summarised below.

1. **Increased use of small scale calorimeters** – Small scale micro calorimeters (~5–10 ml volume) enable us to obtain simple heats of reaction quickly with low sample usage. There is no need for detailed reaction studies in many cases if we just need a quick/simple reaction heat. This reduced the desire to perform material hungry tests and enabled us to do safety studies earlier in development when materials are generally in short supply.
2. **Integration of development laboratory equipment** – newer lab equipment is capable of obtaining heat flow profile data (Tr-Tj) in many computer controlled jacketed reactors. Often this can be all the heat information that is required and if UA values for vessels are determined a more quantitative heat can also be

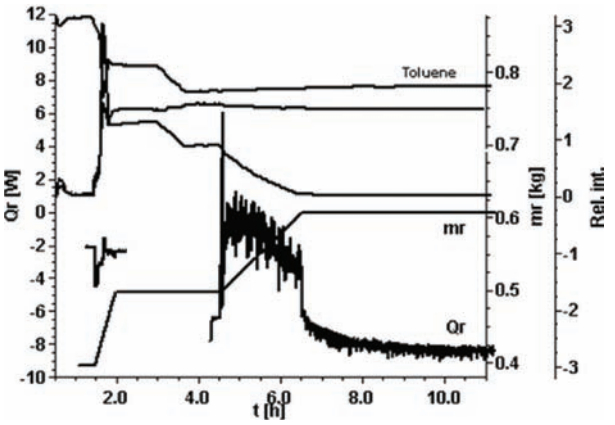

Figure 4. Heat flow and IR data gathered in a single experiment

obtained. The heat flow profile can also be used by the chemistry teams to help reaction understanding by indicating, for example, reaction start/end points, accumulation, intermediate formation etc.

3. **Process understanding** – The overlap between process safety groups and other technology specialists such as reaction engineers has increased greatly. This enables us to get more information per experiment by combining a number of experimental techniques such as IR and heat flow (Fig. 4) to aid the project teams in their reaction understanding and allow us to get safety information at the same time.
4. **Specialist reaction hazard lab equipment used to supply development material requirements** – Specialist reaction calorimeters should not just be used for safety data. They should be used to prepare material and obtain safety information at the same time – this saves both time and materials and increases the interaction between the project teams and the technical safety specialist.
5. **Reaction heat calculations** – This was mentioned earlier as an approach to obtaining heat of reaction data that had been used in the past. The appearance of several practical and reliable calorimeters brought on a new era of experimental measurement, and as these instruments became more popular, the use of heat estimation decreased. This is unfortunate because experimental testing and estimation techniques are complimentary, and experimental measurement is not always practical, accurate, or necessary. This technique has been the subject of some re-investigation within Pfizer and this area is discussed in more detail below. Further details are also available.[23]

REACTION HEAT ESTIMATION RE-VISITED

The heat of reaction is an important parameter in the safe, successful scale up of chemical processes. Reaction heat data is used to calculate the potential adiabatic temperature rise of the desired reaction, providing a worst-case scenario for rapid reaction of the entire batch with no heat loss to the surroundings. The data is used in parallel with information regarding the thermal stability of reaction mixtures/components, and an intimate knowledge of the process to analyze the risk associated with running it on-scale. If the level of risk is judged to be unacceptable, the analysis can be used to make rational process changes in order to reduce the risk to an acceptable level.

The Pfizer global process safety network provides a heat of reaction for all processes run in our kilo labs, pilot plant, and manufacturing facilities. In general, there are two methods used to determine reaction heats: (1) experimental measurement using some form of calorimetry, or (2) estimation techniques. Since experimental measurement is not always practical, accurate, or necessary, we set out to show that estimation techniques could be used reliably and efficiently to provide heat of reaction data for a wide range of chemistry.

To gain confidence in our ability to accurately predict reaction heats, we carried out a comparative study of measured vs. estimated values. The results of this study are discussed below. We have also created a heat estimation database that allows for (1) rapid archival/retrieval of model compounds, (2) calculation of reaction heat and adiabatic temperature rise, and (3) reporting/documentation of the results.

Theoretical prediction of reaction heats using equation (1) has a long history in process safety analysis.[4–13]

For the hypothetical reaction: $aA + bB \rightarrow cC + dD$, then

$$\Delta_r H = c\Delta_f H^\circ(C) + d\Delta_f H^\circ(D) - a\Delta_f H^\circ(A) - b\Delta_f H^\circ(B) \quad (1)$$

The reaction enthalpy, $\Delta_r H$, is calculated from the standard heats of formation, $\Delta_f H^\circ$, of the reactants and products. The standard heat of formation is the enthalpy change upon formation of the material from the elements in their standard states at the temperature T. Frurip and coworkers have reported a seven step process to successfully estimate the heat of reaction using equation 1.[13]

1. **Define and balance the chemical equation**. It is critical to have the reaction written down correctly with the states of all species defined.
2. **Reduce complex chemical structures to model compounds**. The "Analog Reaction Hypothesis" states that the heats of reaction for structurally similar reactions are identical.[14] Chemical groups that do not change throughout the reaction cancel across equation (1) and, therefore, do not significantly affect the thermodynamics. This step is performed because the $\Delta_f H^\circ$ data is available for thousands of small molecules, but not for larger ones.
3. **Make simplifying assumptions**. There are three basic assumptions that are used for most estimations: (a) the heat of dissolution of most organic liquids in organic

solvent is small, therefore $\Delta_f H^\circ$ for the liquid instead of the solution is used, (b) most reaction heats are weakly dependent on temperature, so temperature effects can be ignored, and (c) most reaction heats are weakly dependent on pressure, so pressure effects can be ignored.

4. **Obtain the literature $\Delta_f H^\circ$ data for the compounds or model compounds if available**. There are a few key sources for $\Delta_f H^\circ$ data.[14–17]
5. **Estimate $\Delta_f H^\circ$ data for compounds and model compounds for which literature data does not exist**. If literature data does not exist, then the $\Delta_f H^\circ$ can be estimated. Benson's method is preferred over bond energy approaches.[18–21]
6. **Perform the calculation based on equation (1)**.
7. **Perform a reality check**. Is an endothermic prediction reasonable based on reaction temperature or favorable entropy change? Is the estimation conservative compared to observations made in the laboratory? How does the estimation compare with similar chemistry that has been measured?

RESULTS AND DISCUSSION

Comparison of the measured and estimated heat of reaction for 50 reactions[23] was carried out. Inspection of the reactions reveals a broad range of reaction types including a variety of substitution, reduction, oxidation, addition-elimination, electrocyclic, and salt forming reactions.

There are three general trends that appear: (1) Estimation tends to be more conservative than measurement. (2) The transition metal catalyzed hydrogenations tend to show excellent agreement between the measurement and the estimation. The percent difference is less than 6% in all but one example, entry 6, which has a −13% difference on a small $\Delta_r H$, −57.3 kJ/mol. This close correlation is likely due to reaction heats that tend to be fairly large, reliable measurement due to straightforward processing, and reliable estimation due to simple models that have accurate, thoroughly studied $\Delta_f H$ data. (3) The estimated alkali metal and amine salt formations tend to be very conservative since these equilibrium reactions are assumed to go to 100% conversion in the estimation.

In order to rapidly assess the overall correlation, the estimated value was plotted against the measured value, as shown in Figure 5. Perfect correlation is indicated by the solid line running through the data points. The points that fall below the line indicate those instances where the estimated reaction heat is greater (more negative) than the measured reaction heat. Conversely, the points that fall above the solid line indicate those instances where the measured reaction heat is greater than the estimated reaction heat. Twenty-two of the comparisons have a percent difference of 10% or less, and we will assume that those are identical within experimental error. Estimation is more conservative for 26 out of the remaining 28 comparisons, or 93%. From a process safety perspective, the use of conservative values is desirable, assuming the number isn't so overly conservative that unnecessary controls are put in place. In all the examples used in Figure 5, the final safety recommendation was independent of approach.

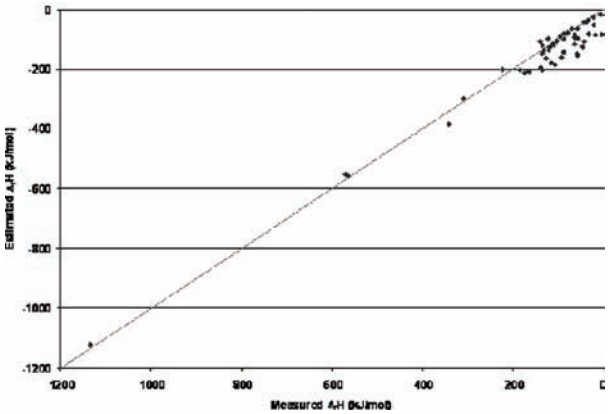

Figure 5. Graph of the estimated ΔrH data vs. the measured ΔrH data. The dots represent the 50 individual comparisons and the line indicates a perfect 1:1 correlation

CHECKLIST OF FACTORS THAT LEAD TO AN ACCURATE HEAT ESTIMATION

We have developed several guidelines that lead to an accurate heat estimation. The following guidelines should be used in parallel with Frurip's 7 step process to successfully estimate a heat of reaction.

a. **Start with an accurate, balanced equation**.
b. **Only estimate reactions that have a high yield or known side reactions that can be estimated**. Exothermic side reactions that are not accounted for in the estimation will result in a predicted reaction heat that is too low.
c. **Know when the reaction heat is released**. For example, if the formation of an unisolated intermediate is highly exothermic and the next step is endothermic, estimation of the overall sequence would result in a prediction that is a combination of the two heats. This prediction would suggest a reaction that is only mildly exothermic even though the formation of the intermediate is highly exothermic.
d. **Identify equilibrium reactions**. Heat estimation assumes 100% conversion to products and, therefore, estimation of an equilibrium reaction gives conservative results. However, if the equilibrium reaction is the first part of a two-step reaction, then the estimation of the second reaction may be erroneously lower than the measured value which includes the heat from driving the first step equilibrium to completion.
e. **Identify potential physical phenomenon that may produce heat**. Exothermic heats of solution/mixing/coordination need to be considered. For example, water formed in the presence of alcohols, H_2SO_4, DMSO, etc. can have relatively large exothermic heats of solution and must be considered in the overall estimation

f. **Be aware of off-gassing**. Estimation may be used for reactions that off-gas if: 1) The estimation is being used as a conservative backup for a measured value, or 2) The total theoretical amount and/or rate of off-gassing are not considered to pose a significant over-pressurization hazard. Off-gassing can affect both measurements and estimations, so care should be taken when working with reactions that have the potential to produce non-condensable gases.

g. **Match calculation to production process operations**. It is important to consider the details of how the process will be run on-scale in order to maximize accuracy. This is closely related to the section above for knowing when the reaction heat is released. For example, if NaOH pellets are added to an aqueous reaction mixture the heat of solution must be added to the estimation, but if dilute caustic will be made in separate tank before addition to the reaction mixture you may be able to use the smaller heat of dilution.

h. **True catalysts should not be entered into the heat of reaction estimation**. Catalysts may need to be taken into account if they are used stoichiometrically (i.e. large amounts of in-situ intermediates generated before desired reaction initiates). Some catalysts are actually precursors and must be activated, releasing a significant amount of heat. These types of heat may be unknown or difficult to estimate.

i. **Preserve estimation technique across the equation**. Here, "estimation" refers to estimation of the heat of formation, not the heat of reaction. There are several different techniques that can be used to estimate heats of formation including Benson groups, bond energies, and quantum mechanics.[18,19] If you use a Benson group approach to estimate $\Delta_f H$ in the gas phase for a starting material, then use a Benson group approach to estimate $\Delta_f H$ in the gas phase for the product. Do not use a Benson group approach for one and a bond energy approach for the other. By not mixing techniques, the inherent assumptions in the estimation technique are potentially carried across the equation and, therefore, potentially cancel. For example, if there is a ring structure in an estimated molecule, the $\Delta_f H$ contribution of the ring may not be the same for different estimation techniques, therefore creating a difference across the equation that is not real.

j. **For thermally neutral reactions, what is the effect of a 40 kJ/mol error?** Be wary of estimations that suggest thermal neutrality, especially for reaction masses that provide a small heat sink, because even a small exothermic heat of reaction could result in a very large adiabatic temperature rise. There can easily be a 20 to 40 kJ/mol error in an estimation, so it's prudent to check the adiabatic temperature rise for a worst-case reaction heat, -40 kJ/mol, rather than 0 kJ/mol. For dilute systems the ATR will likely not be a concern, but for a concentrated one the difference could produce a significant temperature rise.

k. **Choose model compounds carefully**. The vast majority of proprietary compounds will not have known heats of formation. Accuracy can be maintained by using smaller, easier to estimate model compounds.

MODEL COMPOUNDS

The vast majority of proprietary compounds will not have known heats of formation and must be modeled for use in heat estimation. There will likely be several reasonable model compounds for any given molecule. There are two basic rules to follow for choosing a good model. First, focus on the functional groups that are reacting. The second rule is to avoid the first compound in a series unless the actual species in the reaction is the first member in the series. For example, don't choose methanol, methyl amine, or formic acid as models for an alcohol, amine, or carboxylic acid, respectively, unless the actual compound in the reaction is methanol, methyl amine, or formic acid. This is because the first compound in a series usually has a heat of reaction that is slightly out of line with the rest in the group.

DETERMINATION OF HEATS OF FORMATION

Once you have decided on a model compound you must find a reliable value for the heat of formation. Keep your model compounds as simple as possible and there is a good chance that you will find a literature value for the heat of formation.

The physical phase of the heats of formations should match the components of the planned experimental run. In most cases a heat of formation in the liquid phase is preferred. If the reaction involves solids or gases then you may want to use a heat of formation in the in liquid or solid phase. The phase can have a large effect on the heat of reaction, particularly gas verses condensed, so choose carefully. If the phase is unclear, we typically choose the value that will make the estimation more conservative.

If a literature value cannot be found then the heat of formation can usually be estimated using a Benson group approach.[18,19] CHETAH and the NIST website are the two most common software packages used to estimate $\Delta_f H$.[17,22] The Benson group approach gives the estimated heat of formation in the gas phase. Gas phase heats of formation can be adjusted to the liquid phase by subtracting the enthalpy of vaporization, $\Delta_{vap} H$.

HEAT ESTIMATION DATABASE

In order to maximize the efficiency gain and to ensure accuracy in our estimations, we have created a heat estimation database that allows for (1) rapid archival/retrieval of model compounds, (2) automatic calculation of reaction heat and adiabatic temperature rise, and (3) reporting/documentation of the results. A significant amount of work goes into finding reliable heat of formation data for the more

complex model compounds. Therefore, it makes sense to capture the data in a format that is easy to locate for future use, and our database contains structure, keyword, and reaction searching to meet this need.

To conclude this section on heat estimations predictive techniques have a very important place in the reactive chemicals evaluation process, and the use of estimation techniques based on $\Delta_f H$ for calculation of reaction heats has been shown to be a valid technique for a number of chemistries. The benefit of predictive techniques is that their judicious and knowledgeable use can save valuable time in today's global arena where the timelines to scale-up are compressed. Efficiency, without compromising on safety, can be achieved by allowing process safety professionals to make sound scientific judgment on how and when estimation can be used.

Experimental testing and estimation techniques are complimentary in the sense that agreement between experiment and theory adds to the reliability of, and hence one's confidence in, the hazard assessment prior to scale-up. Any disparity between experiment and prediction should lead to further analysis, testing, or calculations. However, only in a few number of cases are we likely to determine the reaction heat by both estimation and measurement. Therefore, this paper outlines our strategy for the independent use of either technique, when appropriate, to assess process hazards within Pfizer. In fact, in many cases, estimation can have distinct advantages over measurement techniques. In addition, estimation can be used to give heat values for reactions where measurement is not practical or safe. The use of predictive techniques will also help to focus the efforts of the hazard evaluation specialist on the most appropriate reactive chemical testing.

SUMMARY

This paper has shown how a reaction hazard evaluation function in a large pharmaceutical company has grown over a period of years and how we are continuing to constantly challenge how and when we generate information to ensure safe chemical operations. New equipment, greater overlap with development teams and re-invigoration of reaction heat calculations has shown how we are adapting to today's competitive pressures whilst still keeping safety paramount. We must continue to advance the science on reaction hazard evaluation if we are to remain able to develop processes in an efficient and safe manner and avoid further tragedies such as Bhopal being repeated despite the pressures the chemical industries face.

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