

A BASIC STRATEGY FOR THE THERMAL STABILITY ASSESSMENT OF PHARMACEUTICAL SYNTHETIC INTERMEDIATES AND PRODUCTS

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A relatively simple strategy is described for the thermal hazard screening of isolated synthetic intermediates and products, as employed within the Research Division of a major pharmaceutical company.

Differential scanning calorimetry under carefully controlled conditions is used as a screening technique to reveal any propensity a material may have towards significant exothermic decomposition. Suspect samples are further investigated via combustion tests, such as train firing studies or flash point determinations, and via accelerating rate calorimetry; data obtained facilitate characterisation with regard to ignition/flammability properties and bulk stability. A real-life case study is presented to illustrate the application of this methodology to an unstable synthetic intermediate for which safe conditions for processing and bulk storage are derived.

1. Introduction

For a number of reasons there is a generally heightened emphasis being placed upon hazard evaluation within the modern chemical industry. Environmental concern and increased legislation, such as the Health and Safety at Work Act (1974) and the recently implemented Control of Substances Hazardous to Health (COSHH) Regulations (1989), place a considerable burden on the manufacturer to ensure that 'his house is in order' with respect to understanding, quantifying and controlling the many hazards which are inherent in an industry consistently utilising more reactive compounds and operating more complex processes.

The pharmaceutical branch of the industry is particularly open to scrutiny in the above respect. Not only do many companies operate relatively large scale, and therefore potentially hazardous, complex organic syn-

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theses, but they also market the end products of such processes for administration as medicines. There is, therefore, considerable pressure in a number of areas to obtain a thorough understanding of potential hazards, firstly to aid in the establishment of safe procedures for the synthesis, processing, formulation and handling of products, and secondly to ensure that the drug substance itself does not pose an unacceptable hazard to the patient.

In essence, within the sphere of activity of the pharmaceutical industry, hazards fall into two main categories:

BIO-HAZARDS, examples of which include the toxic effects arising from the pharmacologically active nature of many of the compounds handled (particularly with low-dose drugs) and the pathogenic nature of micro-organisms encountered in various areas within the industry.

THERMAL HAZARDS, arising from uncontrolled and/or unexpected energy liberation which can, in serious cases, lead to fire, explosion and environmental problems.

This paper describes a basic strategy, as employed within SmithKline Beecham Pharmaceuticals (SB) which can be used to detect and quantify the potential thermal hazards which may arise due to the instability of some isolated synthetic intermediates (and occasionally finished products). The thermal stability of many isolated SB synthetic intermediates has been assessed via this procedure. A real-life case study is presented to illustrate use of the methodology to determine conditions under which a potentially hazardous intermediate can be safely processed/stored.

2. Hazard screening strategy for isolated compounds

As alluded to above, thermal hazards basically arise due to the uncontrolled and/or unexpected liberation of energy. In relatively simplistic terms such hazards can originate from two main sources:

a) Poorly controlled exothermic processes, e.g. a synthetic reaction in which the heat dissipation capacity of the reaction vessel is insufficient to offset the rate of heat generation by the process.

b) The inherent instability of an isolated chemical entity, e.g. a reactive synthetic intermediate.

Although not the domain of this paper, hazard screening of a synthetic reaction is an essential stage in the evolution of a process, and necessitates

the acquisition of characteristic thermodynamic, kinetic and mechanistic data. Techniques such as heat-flow calorimetry (reaction calorimetry) are widely utilised in this sphere, and the data obtained are generally very useful in the closely related area of process optimisation. Novel organic compounds frequently arise as intermediates in the synthesis of original drug molecules and represent the most common sources of hazards falling into category b) above. The hazard screening procedure described below is designed to investigate the thermal stability of such materials. The overall strategy is shown schematically in Fig. 1. Initially a literature search is undertaken to reveal any available data regarding the stability of analogues or molecules which are structurally similar to the material in question. In relevant cases an oxygen balance calculation is performed to classify the substance in terms of its possible explosivity properties. For all samples, practical examination commences with screening by differential scanning calorimetry (DSC), under carefully controlled conditions, in order to reveal any propensity for exothermic degradation. Associated studies utilising thermogravimetry (TG) and visual examination (either heating in a capillary tube using a conventional melting point apparatus, or by hot stage micros-

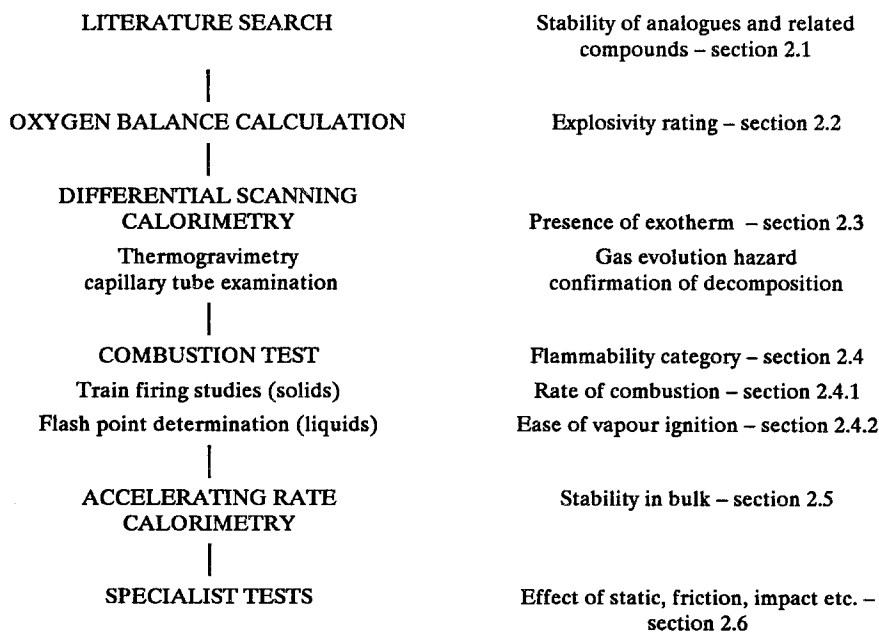


Fig. 1 Thermal stability assessment strategy

copy) are often also performed at this early juncture in order to confirm any apparent decomposition observed in the DSC profile. TG is also valuable in detecting volatile decomposition products.

Materials exhibiting significant evidence of exothermic decomposition below 200–250° are then further characterised to yield more in-depth information with regard to thermal stability. This exercise comprises two discrete, but inter-related aspects. Firstly, flammability properties are investigated (see section 2.4). The vast majority of samples examined are solids in which case the train fire test is applied. Liquid samples are examined via a flash point determination. Data from flammability tests are invaluable in assessing the likely behaviour of a material, should a source of ignition arise during processing or storage. Secondly, in further defining the stability of 'suspect' materials, it is also essential to detect any tendency of the sample to undergo spontaneous exothermic decomposition when subjected to the adiabatic conditions likely to arise during bulk storage, transportation or processing. The technique of accelerating rate calorimetry (ARCTM; see section 2.5) is particularly adept in this respect, and basic data obtained during the adiabatic decomposition of a sample can readily be used to derive parameters such as maximum storage temperatures, safe distillation temperatures etc.

The various facets of the above strategy are discussed in more detail in the following sections.

2.1 Literature Search

Within the pharmaceutical industry many of the compounds examined for thermal hazard potential are novel since they typically represent intermediate stages in the synthesis of new drug substances. Despite this fact, it is important not to overlook the value of information which may be available in the chemical literature. Although this may not relate to the exact compound in question, highly pertinent data can often be obtained regarding the stability of materials which are analogues of or are structurally related to the compound under examination (in house safety data are often very useful in this connection). Such information can provide a valuable pointer to any potential instability. Consequently it is commonplace to scrutinise relevant literature for information including:-

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- Explosion Potential
- Flammability Data
- Bulk Stability
- Handling Precautions
- Physical Data
- Toxicity Data

Some of the more important literature sources utilised in this connection include the following:

- Chemical Abstracts (Computer-searched data base)
- Pharmaceutical Abstracts (Computer-searched data base)
- Handbook of Reactive Chemical Hazards [2]
- Hazards in the Chemical Laboratory, 2nd Edition [1]
- Sigma-Aldrich Library of Chemical Safety Data
- 'In House' Safety Data
- General Chemistry Texts

2.2 Oxygen Balance [1, 2]

Within any thermal stability screening strategy it is essential to establish, at an early stage, whether a particular sample has any obvious potential for explosive decomposition. In relevant cases (see below) calculation of the oxygen balance for the material can provide such information.

For a given compound the oxygen balance is essentially the difference between the oxygen content of the molecule and that required to oxidise fully the carbon, hydrogen and other oxidisable elements to carbon dioxide, water and other oxidation products. Any nitrogen atoms present are not considered as oxidisable since they are usually liberated as the gaseous element in explosive decompositions. For a compound of molecular weight M , containing X carbon atoms, Y hydrogen atoms and Z oxygen atoms, the oxygen balance is given by Eq. 1.

$$\text{Oxygen Balance} = \frac{[-1600(2X + Y/2 - Z)]}{M} \quad (1)$$

The concept is only applicable when at least one oxidising functional group is present, examples of which include:

R-ONO ₂	Alkyl Nitrates	N-NO	N-Nitroso Compounds
R-NO ₂	Nitro Compounds	-C-N ⁺ =N ⁻ =N ⁻	Azides
R-O-O-R	Peroxides	R-N=N-R	Azo Compounds
RCH=N·OH	Oximes	R-C≡C-R	Acetylenes

The presence of these functional groups within a molecule reduces the requirement for external oxygen to provide complete combustion. Such materials are therefore often capable of releasing large amounts of energy, in addition to producing large volumes of gas rapidly, leading to explosive behaviour. A negative balance indicates an oxygen deficiency whilst a positive balance indicates an excess (such compounds can act as oxidants). Highly explosive compounds tend to exhibit oxygen balances close to zero, but the tendency towards instability and high energy release becomes apparent well below the balance point. Table 1 indicates how materials are classified in terms of explosivity hazard on the basis of oxygen balance.

Table 1 Explosivity Hazard Classification According to Oxygen Balance

Oxygen Balance Limits	Explosivity Hazard Rating
Greater than +240 or less than -160	LOW
+240 to +120	
-160 to -80	MEDIUM
-80 to 120	HIGH

An oxygen balance calculation is, therefore, performed on all samples containing oxidising functional groups prior to commencing the experimental studies discussed in the following sections. Within the sphere of operation of the author's laboratory, compounds falling into the HIGH risk category are exceptionally rare. No experimental work would be performed on such a compound prior to commissioning specialist explosivity testing (see Section 2.6 below). Compounds falling into the MEDIUM category are treated with great care, but can be safely analysed by DSC in order to obtain an indication of the magnitude and rate of energy release. It is advisable to utilise very low sample weights (~1 mg) in such studies in order to guard against possible damage to the calorimeter in the event of violent decomposition. The data obtained are then used in deciding whether further in-house testing can be performed without recourse to specialist facilities of the type referred to above.

2.3 Differential Scanning Calorimetry (DSC)

The technique of differential scanning calorimetry (DSC) is well known in numerous areas of chemistry and its applications are as diverse as polymer science, mineralogy and freeze-drying technology. Within the pharmaceutical world the applications DSC are multifarious, including such important areas as polymorphism studies, compatibility investigations and

purity determinations. Hazard screening represents a vital, additional, area of application for the technique.

In the current strategy, DSC is used as an initial screening technique on all samples (other than those excluded under the criteria discussed in Section 2.2). Using a Perkin Elmer DSC system, operating on the power compensation principle [3], the material is examined under a number of different sets of conditions routinely including all or some of the following:

Temperature Range:	25–300°
Heating Rate:	Various (often 10 deg·min ⁻¹)
Sample Encapsulation:	(i) Crimped Al Pans (ii) Hermetically Sealed Al Pans (iii) High Pressure, Screw-Topped Stainless Steel Pans (iv) As (iii) above but using inert Pt insert to contain sample
Atmosphere:	(i) Flowing Nitrogen (50 ml·min ⁻¹) (ii) Flowing Air (50 ml·min ⁻¹)
Sample Size:	~1–3 mg

By utilising a combination of the above experimental conditions it is usually possible to determine whether a compound is capable of undergoing exothermic degradation (very slow decomposition occurring over a wide temperature range may prove hard to detect). A material exhibiting a large decomposition exotherm (energy > ~300 J·g⁻¹) at low temperatures (below ~150°) is an immediate cause for concern, particularly if the event is very sharp, indicating that energy release occurs rapidly. Such decompositions may quickly generate large volumes of gaseous breakdown products with the consequent risk of explosion. Thermogravimetry (TG), using a Perkin-Elmer TGA, is often employed in conjunction with DSC to detect and, in some cases to quantify such phenomena. Figure 2 shows the DSC and TG profiles of an unstable penicillin-related compound examined under an atmosphere of flowing nitrogen. The DSC profile comprises a single, sharp decomposition exotherm of considerable energy (-540 J·g⁻¹) in the range 160–200°. The possible explosion hazard of the material is emphasised by the TG profile which exhibits a characteristic rapid weight loss over a corresponding temperature range. This results in 36% (by weight) of the sample being lost by the production of gaseous decomposition products.

In some cases materials exhibiting large exotherms at only moderately high temperatures (150–200°) are stabilised to a certain degree by preceding endotherms e.g. melting or desolvation events. Such phenomena are il-

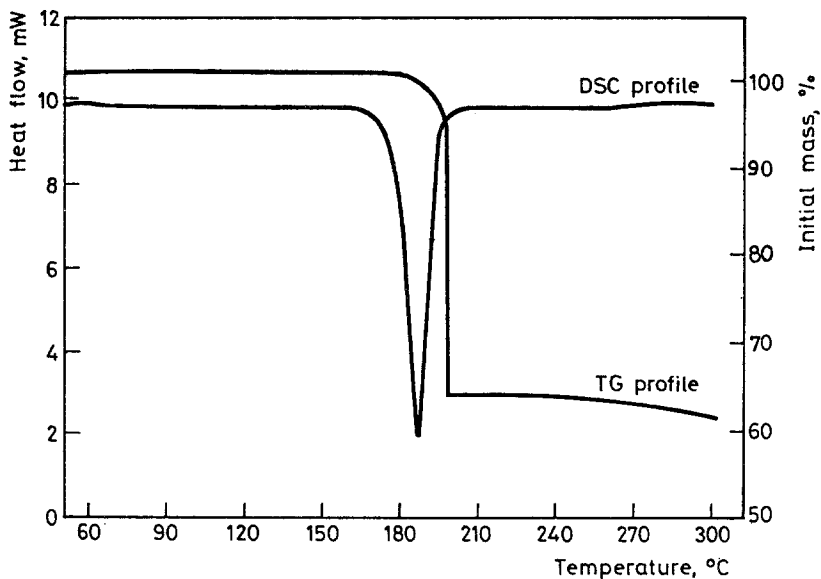


Fig. 2 DSC and TG profiles of a potentially hazardous penicillin-related compound. Note the rapid production of volatiles associated with exothermic decomposition

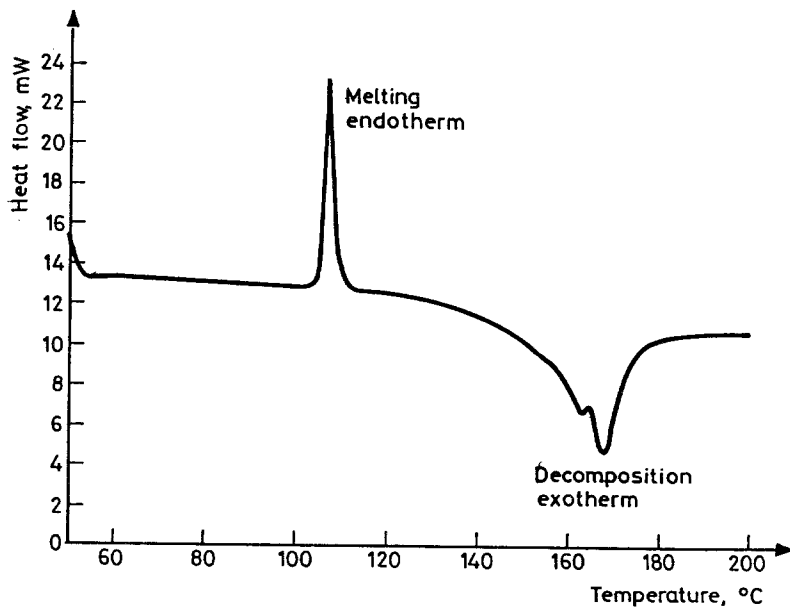


Fig. 3 DSC profile of a synthetic precursor to an antibiotic in which a sharp melting endotherm affords a degree of protection against higher temperature decomposition

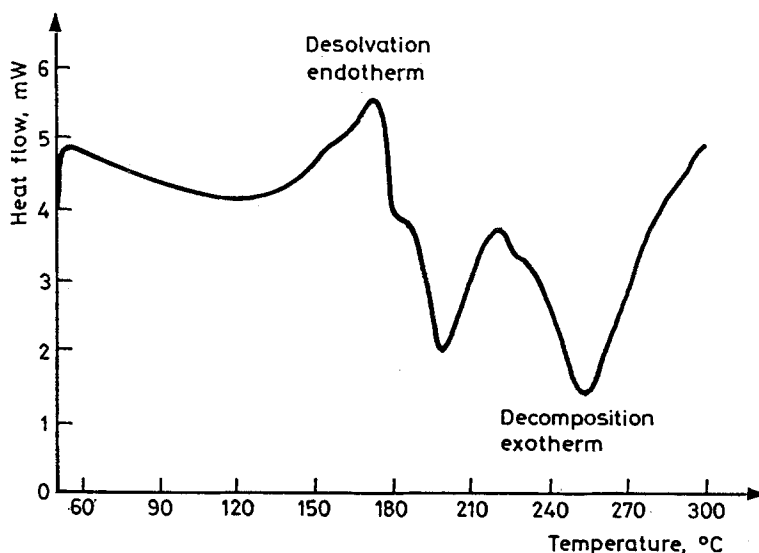


Fig. 4 DSC profile of an isoxazole-type penicillin dihydrate. The large desolvation endotherm at 120–180° affords a degree of protection against higher temperature decomposition

illustrated in Figs 3 and 4 respectively. The endotherms effectively present an 'energy barrier' against exothermic decomposition. However, it is important to consider factors such as the relative energies of the endotherm and the decomposition event (relatively small endotherms providing poorer protection), and also the possibility of the sample dissolving in its own decomposition products, thereby removing the protective influence of the latent heat of fusion. In compounds where a melting endotherm protects an exothermic decomposition, samples spanning a wide range of purity are examined; a relatively small reduction in this parameter can have a markedly deleterious effect on thermal stability. This arises from the profound influence of purity on the temperature range of fusion, and is graphically illustrated in Fig. 5, which shows the DSC profiles obtained from three different batches of a β -lactam synthetic precursor of decreasing purity. Profile A, obtained from material of 98% w/w purity, shows a sharp, symmetrical melting endotherm at 85–95° with an extrapolated onset temperature (T_e) of 90.0° and an energy (ΔE) of 77 J·min⁻¹. This precedes a large, sharp high temperature decomposition exotherm at 180–200° ($T_e = 188.8^\circ$, $\Delta E = -390$ J·min⁻¹). In this case the endotherm acts as an efficient barrier against exothermic decomposition. However, a relatively small reduction in purity (to 94% w/w, Profile B) results in (i) a marked broadening and reduction in energy of the melting endotherm ($T_e = 80.4^\circ$, $\Delta E = 58$ J·min⁻¹) which is also shifted to a consider-

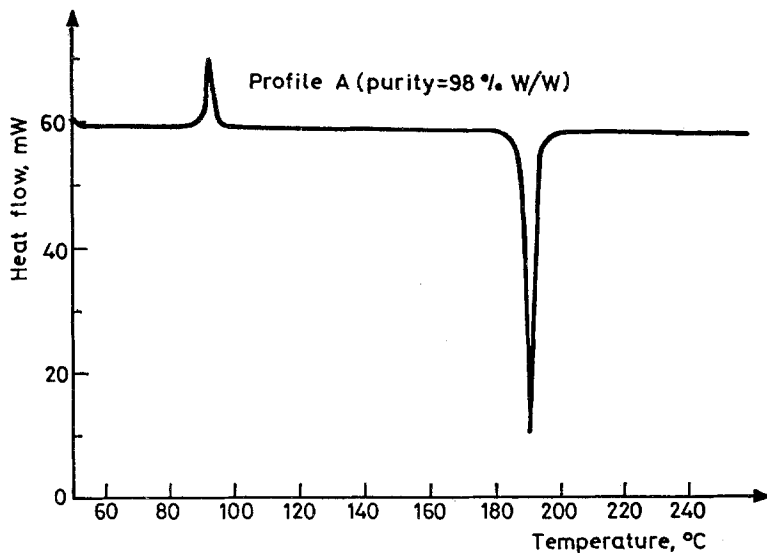


Fig. 5a DSC profiles obtained from samples of a β -lactam synthetic precursor of decreasing purity

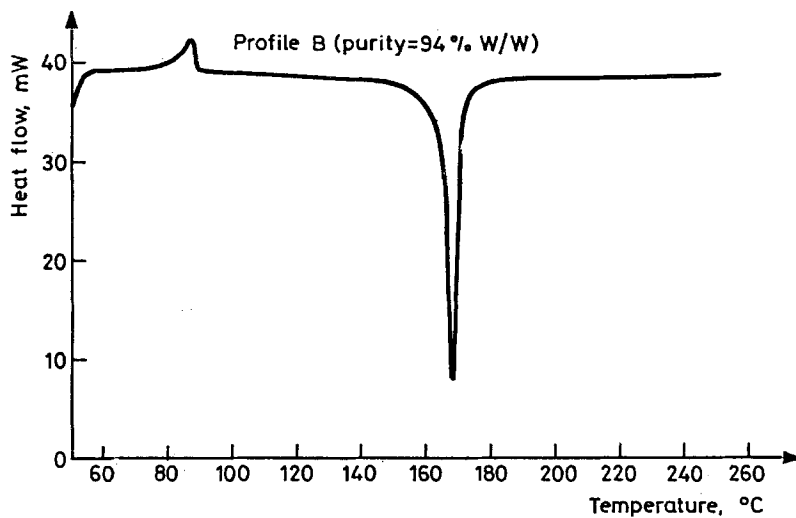


Fig. 5b

ably lower temperature range and (ii) a displacement of the decomposition exotherm to a much lower temperature range (140–185°, $T_e = 165.7^\circ$). Effects such as (ii) may arise, for example, due to the catalytic influence of im-

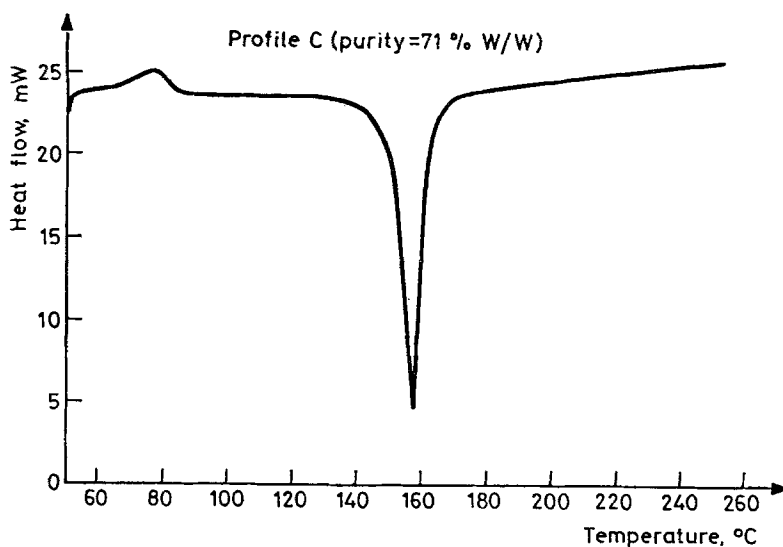


Fig. 5c

purities within the sample (synthetic by-products, reagent residues etc.) or because of autocatalytic influence arising from degradation products of the parent compound. In cases of autocatalysis the 'thermal history' of the material can profoundly influence stability. Isothermal ageing techniques are of great value in assessing this phenomenon as alluded to in section 2.5 below. The effects noted in Profile B are further accentuated in Profile C, obtained from material of 71% w/w purity. The melting range (55–85°, $T_c = 65.2^\circ$) and energy of fusion ($\Delta E = 36\text{J} \cdot \text{min}^{-1}$) are both further depressed, as is the position of the decomposition exotherm which, even using a non-equilibrium technique such as DSC, is detectable from $\sim 135^\circ$ upwards (cf. $\sim 180^\circ$ in material of 98% purity). Clearly as purity drops, the thermal hazard potential of this material is significantly increased, firstly due to the poorer energy barrier presented by the ill-defined and less energetic melting endotherm, and secondly due to the sizeable depression in the onset temperature of decomposition.

The identity and integrity of the headspace atmosphere above a sample within the DSC sample pan can also, in some cases, dramatically affect the thermal profile obtained, due to their influence on the course of decomposition of the material. Failure to retain within the sample pan volatiles generated in the early stages of a DSC run may result in a totally different decomposition mechanism relative to that which would be observed in a

sealed system. In the worst case this may prevent the detection of potentially hazardous exotherms [4]. Examination of samples in high pressure stainless steel pans (capable of operating up to 2000 psi) usually overcomes this problem although care must be taken in cases where the presence of iron may, misleadingly, catalyse a decomposition; hence suspect samples are examined in high pressure pans, contained within inert platinum inserts. Such effects may also be investigated by deliberately 'spiking' a sample with a suspected catalyst and monitoring any effect on the thermal profile.

Deliberate variation in the composition of the headspace atmosphere in a DSC experiment can often yield valuable information regarding the origin of exothermic events, particularly with respect to detecting oxidative decomposition. A sample which exhibits a large exotherm when examined under an atmosphere of air, but a markedly reduced or completely absent event on heating under nitrogen clearly liberates energy on decomposition, primarily due to atmospheric oxidation. This information is of obvious use in, for example, defining safe distillation conditions (operation under vacuum/inert atmosphere, exclusion of air from hot still residues etc.). One major criticism of DSC is that it utilises a very small and therefore potentially unrepresentative sample. This is exemplified by Fig. 6 which shows two distinctly different thermal profiles obtained from the same batch of a

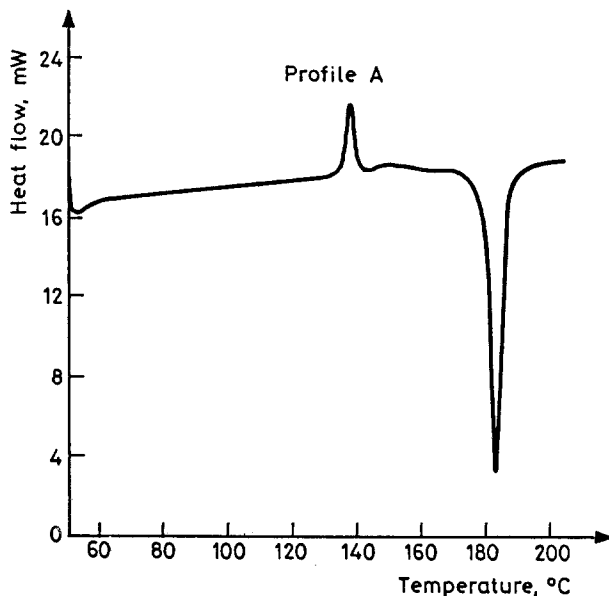


Fig. 6a The effect of inhomogeneous contamination on the DSC profile of a bromosulphoxide synthetic intermediate

bromosulphoxide intermediate to a penicillin-related compound. On average three out of every four DSC examinations of the material gave profile A, comprising a high temperature exothermic decomposition preceded by a lower temperature melt. The remaining run yielded profile B, consisting of a large, sharp decomposition exotherm at alarmingly low temperatures. On subsequent microscopic examination of the sample, this behaviour was attributed to an inhomogeneous contamination with rust particles which appeared to exert a catalytic effect upon the decomposition. When using DSC as a screening tool in hazard evaluation studies, it is, therefore, wise to perform replicate examinations of samples obtained from a number of different locations within, for example, a storage vessel, in addition to examining a range of representative batches.

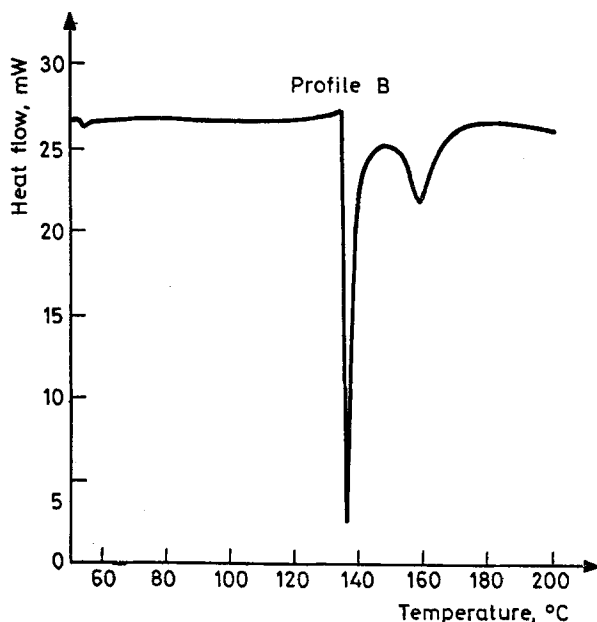


Fig. 6b

Any material showing significant exothermic activity below 200–250° is automatically subjected to further thermal stability evaluation as outlined in sections 2.4 and 2.5 below.

2.4 Flammability Tests

Knowledge of the flammability properties of bulk materials of suspect thermal stability is essential if safe procedures are to be established for

processing and/or storage. In cases where materials are to be exposed to obvious potential sources of ignition (grinding, milling etc.) it is commonplace to perform flammability testing, even when DSC fails to reveal any well-defined exothermic events. This is because, in the author's experience, some materials exhibiting no exotherms can show significant flammability. The relatively basic tests outlined below provide information, such as the ease of ignition of a sample and its behaviour during any subsequent combustion. The parameters obtained allow materials to be classified in terms of their flammability which, in turn, has a direct bearing upon permitted transportation, storage and processing conditions.

2.4.1 Train Fire Testing [5]

The flammability of solid samples is assessed by means of the train fire test which determines a) whether ignition will occur on exposure to a heat source and b) the extent and rate of any resultant propagation of combustion.

The experimental procedure is relatively simple. The solid in question is loosely filled into a triangular cross-section mould 25 cm long and 10 mm high. This is located onto a base plate via two vertical pins projecting 2 cm above the top level of the mould (Fig. 7). In order to achieve a reproducible

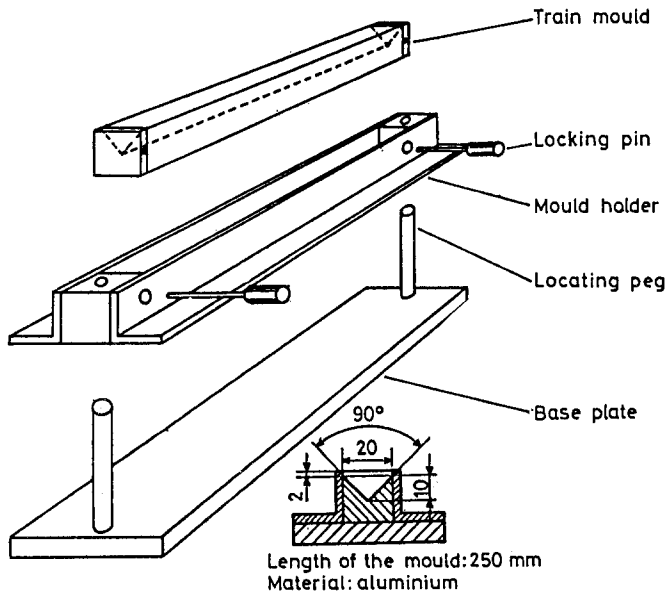


Fig. 7 Exploded view of the train fire test sample mould (all dimensions in millimetres)

degree of compaction, the mould is then dropped onto the base plate three times from the top of the locating pins. If necessary, the mould is then topped up with sample. A strip of refractory alumina matting is placed on top of the mould and the apparatus inverted to release the 'train' of material. An electrically heated redhot nichrome wire element (at $\sim 1000^\circ$) is plunged into one end of the train and the current switched off after a few seconds. If the sample ignites and combustion propagates, the time elapsing during the burning of the central 10 cm of the train is measured to the nearest second. During the test, observations are made with regard to the ease of ignition of the sample, the amount of flame/smoke produced, the intensity of heat evolved and the nature of the residue produced. The test is often repeated several times to ensure that representative results are obtained.

Table 2 Flammability Classification According to Combustion Rate in the Train Fire Test (SB 'In House' System)

Combustion time (10 cm)/seconds	Flammability classification
<45	HIGHLY FLAMMABLE
45-180	FLAMMABLE
181-600	SLIGHTLY FLAMMABLE
>600*	VERY SLIGHTLY FLAMMABLE
Fails to ignite	NON-FLAMMABLE

* This category includes materials exhibiting partial propagation of combustion

Materials burning 10 cm in less than 45 seconds are classified as highly flammable and are subject to a number of restrictions e.g. a ban on air transportation. Classification of materials exhibiting combustion rates corresponding to a lower degree of flammability is open to interpretation. The system utilised within SB is shown in Table 2. For materials falling into the highly flammable and flammable categories, it is commonplace to scrutinise the isolation procedure utilised in the production of the compound and any subsequent processing operations for potential sources of ignition. These may arise in numerous different ways including, from static discharges, mechanical stressing (milling, micronising or grinding), friction (for example metal-to-metal contact of impellor blades with vessel walls) and from heat generated via interaction of desiccants with moisture. With highly sensitive materials it is essential that all such ignition sources are eliminated (as far as is practically feasible). For compounds of this nature a relatively crude test may be performed to determine the minimum ignition temperature of

the material. This is typically achieved using a calibrated soldering iron (with a thermocouple attached to the tip) as the ignition source for the sample train. A rheostat is used to control the voltage applied to the iron, thus allowing its temperature to be slowly increased and monitored to the point where ignition occurs.

Within the author's laboratory, the basic train fire test procedure has been modified in numerous different ways in order to further characterise the flammability properties of potentially troublesome materials. Some examples of these studies include:

(i) Performing the test on a micro scale (50–100 mg of sample loosely packed to give a 'mini train') to obtain an early indication of problematical flammability properties. This modification is invoked if a compound is either in very short supply or, following DSC screening, is thought to have potential for violent decomposition.

(ii) Performing the test under an inert atmosphere, usually nitrogen, in order to determine whether atmospheric oxygen is necessary for pyrolysis to occur.

(iii) Chilling the sample 'train' to subambient temperatures in an attempt to retard the rate of propagation.

(iv) Investigating the influence of residual volatile flammable solvent on the rate of combustion (including 'spiking' experiments).

(v) Examining blends of highly flammable compounds with inert diluents in order to determine ratios which exhibit less hazardous flammability properties.

2.4.2 Flash Point Determination [6]

The flammability of liquid samples is assessed by means of a flash point determination. The flash point is defined as the lowest temperature at which the test liquid (in a closed cup) generates a flammable vapour/air mixture in the headspace above the sample.

In fact, in this hazard screening strategy, the initial procedure employed does not determine the exact flash point of the liquid under test but merely its behaviour at a number of selected equilibrium temperatures. These temperatures relate to the limits of the various categories of flammability (the 'flash/no flash test').

The initial requirement is simply to determine whether or not flashing occurs at these particular temperatures. This, in conjunction with rapid equilibration at each temperature (facilitated by the small sample size employed, usually 2 ml) means that a material can quickly be categorised in terms of flammability. Samples are usually classified using the limits defined in the

Classification, Packaging and Labelling of Dangerous Substances Regulations (1984, EEC), as shown in Table 3.

Table 3 Flammability Classification According to Flash Point Limits

Temperature range/°C	Flammability classification
Below 21	HIGHLY FLAMMABLE
21–55	FLAMMABLE
Above 55	NON-FLAMMABLE

In many cases, as part of the characterisation of the material under examination, a further procedure is subsequently employed to determine the exact flash point of the sample (see below).

All studies are performed in a Setaflash closed cup flash point apparatus (Model 13740-2, Stanhope-Seta Ltd, UK), the main components of which comprise:

- a) A corrosion resistant aluminium alloy test cup (10 mm deep x 50 mm diameter).
- b) A cover bearing an opening slide mechanism, allowing a test flame to be introduced into the headspace above the sample in a highly reproducible manner, and an injection port to allow sample introduction via a syringe.
- c) A thermometer of accuracy better than $\pm 0.5^\circ$ embedded in the base of the test cup.
- d) A heating device/temperature controller to allow the temperature of the test cup to be maintained within $\pm 0.2^\circ$ of the required temperature anywhere in the range ambient to 110° .
- e) A gas supply regulated to supply a 3 mm diameter test flame.
- f) An in-built 1 minute timing device.

For the flash/no flash test method the empty closed cup is heated to exactly 21° (the entire apparatus is typically pre-cooled to $5\text{--}10^\circ$) and 2.0 ml of sample injected. The timing device is simultaneously activated. After one minute the test is performed by opening the slide, inserting and removing the test flame and closing the slide again over a period of ~ 3 seconds. If a flash fails to occur, then the apparatus is thoroughly cleaned out and the test procedure repeated at exactly 55° . The material can then be classified according to the limits outlined in Table 3. If required, the exact flash point of the material can be determined as follows: (assuming it falls within the range $0\text{--}110^\circ$). Initially, a rough figure is obtained by ramping up the test cup temperature in 2° steps and inserting the test flame after each incre-

ment. The temperature at which this strategy is commenced depends upon the behaviour of the sample in the flash/no flash test. For materials showing a flash at the 21° test point the examination is initiated at 0°. Samples flashing at 55° (but not 21°) are examined from 21° upwards, whilst those failing to flash at 55° are examined from this temperature (up to a maximum of 110°). Once a rough value has thus been obtained, the material is tested at 1° intervals beginning at 3° below the approximate figure, a fresh aliquot of sample being used at each test point.

Cleanliness is essential in order to achieve reliable results and the test cup, slide assembly and sample syringe are routinely washed with a suitable solvent (often acetone) between determinations. However, great care should be taken to remove all traces of residual solvents prior to subsequent examinations. Other sources of erroneous results include operation of the system in a draughty environment and incorrect storage of samples prior to testing e.g. in plastic bottles which may be permeable to volatile components of a material.

Virtually all liquid samples examined within the author's laboratory represent reagents for use in synthetic reactions. Operations involving the handling, storage or processing of liquids falling within the highly flammable and flammable categories are closely controlled in order to avoid potential sources of ignition in a similar manner to that described in Section 2.4.1 above.

Flash point determinations are also performed on solvent-laden solids which can, in many cases, generate flammable vapour/air mixtures. This is particularly important if ignition of the residual solvent can initiate combustion of the solid (for example due to the inadvertent production of a spark during processing).

2.5 Accelerating Rate Calorimetry [7, 8]

Accelerating rate calorimetry (ARC) is a relatively novel method. Its origins, from the early 1970's, lie within the Dow Chemical Company (USA), prior to subsequent commercialisation by Columbia Scientific Industries, Texas. The technique is essentially dedicated to the detection and quantification of exothermic processes and probably for this reason, is not as well-known or widespread as other more versatile thermal analysis methods. Nevertheless, ARC is an extremely valuable tool within a thermal hazard assessment strategy, and the technique is currently employed in well over 200 establishments worldwide.

Within the author's laboratory ARC is routinely used in the characterisation of suspect materials in terms of bulk stability. Safe conditions for the storage/transportation of such compounds can then readily be defined via simple processing of raw data obtained during an ARC run. Other applications of the technique within SB include defining safe conditions for distillations, assessment of pressure hazards arising from gas evolution and investigation of the energetics of simple synthetic reactions.

The construction and operating principle of the ARC have been thoroughly reviewed [7] so only a brief overview is necessary. As alluded to above, seemingly stable materials can often pose a hazard when stored in bulk due principally to the adiabatic conditions pertaining in such a situation. The ARC is essentially a highly efficient, computer-controlled calorimeter which is capable of recreating such an environment in a small (1–10 g), and therefore more manageable sample. The instrument can search for evidence of exothermic activity and, if detected, can subsequently maintain the sample in a near perfect adiabatic environment whilst monitoring and collecting data from any self-accelerating reaction which may ensue.

The hub of the ARC system is a highly efficient calorimeter, the basic components of which are shown in Fig. 8. The calorimeter jacket is constructed of nickel-plated copper and has a demountable lid. Heaters are dis-

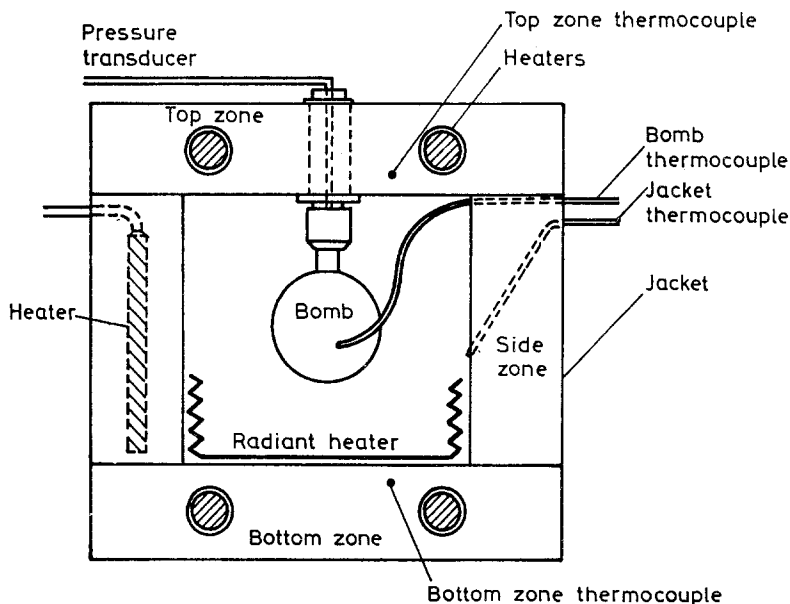


Fig. 8 The ARC calorimeter assembly

tributed within three distinct zones of the jacket, each of which has a control thermocouple. The sample is contained within a 'bomb', which is usually a 1" diameter sphere constructed of titanium, owing to its high corrosion resistance and low density. Bombs may be formed of numerous other materials for specialist applications e.g. hastelloy, tantalum, stainless steel, glass, aluminium foil etc. The sample bomb is mounted on the underside of the lid and occupies a central position within the well of the calorimeter. A fourth thermocouple is attached to the outside of the bomb for sample temperature measurement. A radiant heating element is provided within the calorimeter well for heating the sample where necessary. High specification nisol-nicrosil thermocouples are employed. These show minimal thermal hysteresis effects and allow sample self-heat rates as low as $0.005^{\circ} \text{ min}^{-1}$ to be detected. The sample bomb is connected to a transducer via a sidearm assembly, thus facilitating the acquisition of pressure data during a run. The standard operating ranges of the instrument are $25\text{--}500^{\circ}$ and $0\text{--}2500$ psia.

The complete ARC system is shown schematically in Fig. 9. Central to all operations is the microprocessor control unit into which run-parameters are initially entered. On commencing a run, the test will proceed under fully automatic control utilising the logic outlined below. The calorimeter support module and power management module control the power supply to the jacket heaters, radiant heater and pressure monitoring system. Self-heating rates up to at least $15^{\circ} \text{ min}^{-1}$ can be accurately tracked. The various ther-

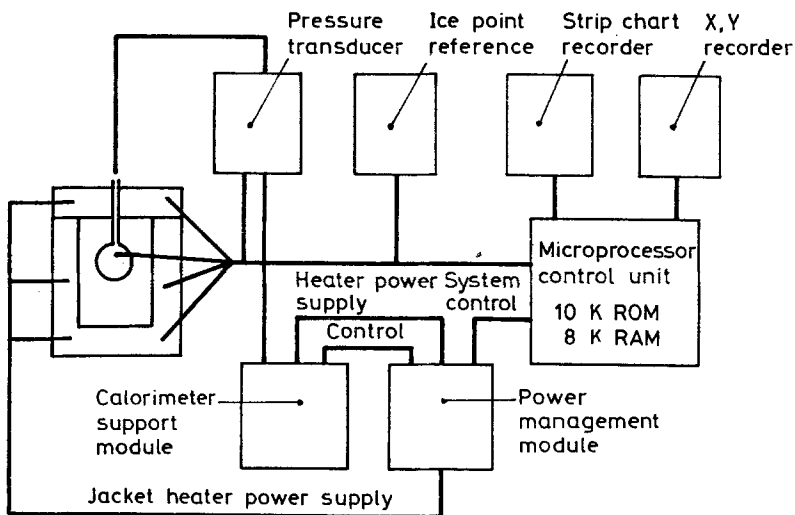


Fig. 9 Schematic representation of the complete ARC system

mocouples in the system are referenced to an icepoint unit containing water held at exactly 0° by a small refrigeration unit. X-Y and strip chart recorders provide both real time data plots and also graphical representations of raw and processed data post run. Data handling is now typically PC mediated, often using custom written software.

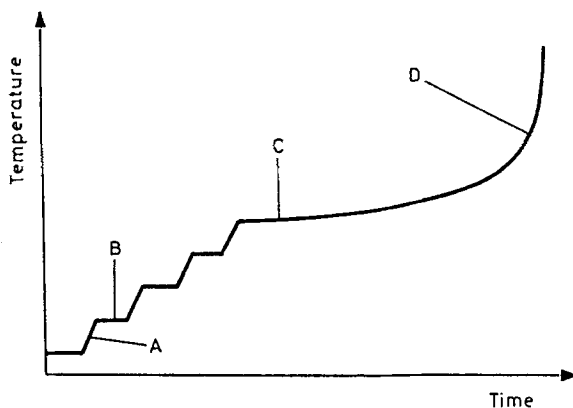


Fig. 10 The ARC heat-wait-search logic. (A) = heat and wait period; (B) = search for sample self-heating; (C) = detection of exotherm; (D) = maintenance of sample in adiabatic environment during runaway reaction

In principle, if an inherently unstable material were placed in the ARC at ambient temperature, a runaway reaction would eventually ensue. Such experiments would be inordinately long, however, and in order to improve sample throughput (typically to one per day), the instrument utilises the so-called heat-wait-search logic as outlined in Fig. 10. This is programmed to permit user selection of run parameters and provides an on-line display of critical variables such as temperature, pressure, time and self heat rate. Searching for reaction exotherm is achieved by elevating the sample temperature by a fixed increment and allowing thermal equilibration to occur (period A), then checking whether the sample self-heat rate exceeds a user-selected threshold (period B). If it does not, this cycle continues until point C, the detection of exotherm, is reached. From this point onwards, no further heat is applied to the sample, which is then maintained in an adiabatic environment by appropriate heating of the calorimeter jacket. Automatic acquisition of time, pressure and temperature data is simultaneously instigated. In unstable compounds the adiabatic conditions will lead to a self-accelerating reaction. This is likely to exhibit an exponential increase in rate leading to a 'thermal runaway' (D), which closely mimics the course of events in an uncontrolled bulk decomposition.

Typical experimental conditions for the initial examination of a sample by ARC are as follows:

Temperature Range:	40–400°
Heat Step Increment:	5 or 10°
Threshold Self-Heat Rate:	0.02° min ⁻¹
Bomb Type:	8.75 g Titanium
Atmosphere:	Sealed under air
Sample Weight:	2–5 g

Further experiments may prove necessary, according to the nature of the data obtained.

The ARC is capable of producing a number of different data plots following the completion of an experiment. Amongst the most important is that of sample self-heat rate (°C min⁻¹, log scale) vs. 1/Temperature (°C, scale = K/T), from which a great deal of information can be derived. For a single reaction, following classical Arrhenius kinetics, the self-heat rate (SHR) plot appears as shown in Fig. 11, Profile A, but such a profile is rarely obtained in practice and the data are generally far more complex. Discussed below are the quantities, derived from the SHR plot, which are of particular relevance to the current hazard screening strategy.

The temperature of detection of exotherm (T_o) and the range of exothermic activity are immediately apparent from the SHR plot as well as a qualitative indication of the rate of liberation of energy. The spontaneous temperature rise occurring during the experiment (ΔT) is given by Eq. 2.

$$\Delta T = T_t - T_o \quad (2)$$

(when T_t = temperature of termination of exotherm).

However, this does not represent the worst case situation, i.e. the temperature rise which would occur in a totally adiabatic environment (a situation often approached during bulk storage of organic compounds). The raw data obtained from an ARC run are subject to the inherent thermal inertia of the system arising principally from the heat capacity of the sample bomb. Correction of ARC data to represent the worst case is achieved via the \emptyset factor which is calculated from Eq. 3.

$$\emptyset = 1 + \left(\frac{M_b \times C_{pb}}{M_s \times C_{ps}} \right) \quad (3)$$

where M_b and M_s and C_{pb} and C_{ps} are the respective masses and heat capacities of the bomb and sample. The true adiabatic temperature rise, ΔT_{AB} , is then given by Eq. 4 which, in turn, gives access to T_{max} , the maximum temperature attainable from the decomposition, via Eq. 5.

$$\Delta T_{AB} = \Delta T \times \emptyset \quad (4)$$

$$T_{max} = \Delta T_{AB} + T_o \quad (5)$$

The SHR plot also allows the calculation of an approximate enthalpy of reaction, ΔH , from the expression shown in Eq. 6.

$$\Delta H = \emptyset \times \Delta T \times C_{ps} \times M/P \quad (6)$$

where M is the molecular weight of the sample ($g \cdot mol^{-1}$) and P is its purity ($mol \cdot mol^{-1}$).

In some cases, the initial portion of the SHR graph is linear, arising from a single reaction, and essentially representing a classical Arrhenius plot. This, therefore, gives ready access to E_a , the activation energy for the decomposition via Eq. 7.

$$E_a = \left(\frac{RT_1T_2}{T_2 - T_1} \right) \cdot \log \frac{M_2}{M_1} \quad (7)$$

where R is the universal gas constant and M_1 and M_2 represent the self-heating rate of the sample ($K \cdot min^{-1}$) at temperatures T_1 and T_2 (K) respectively. The magnitude of E_a gives an indication of the ease with which a decomposition may be initiated; for example, very low values are often associated with easily detonated compounds.

The interpretation of ARC data can be difficult and considerable experience is often required in order to generate reliable safety parameters. This is exemplified by the SHR plot which can vary markedly in form according to the nature of the exothermic process (or processes) occurring [9], as illustrated in Fig. 11. Whilst the SHR plot can be of great diagnostic value in terms of mechanism, it can also result in misinterpretation. The phenomenon of an autocatalytic is a classic example. Autocatalytic decompositions can yield SHR plots which are characterised by very steep onsets (Fig. 11, Profile B). This can result in a misleadingly optimistic stability assessment if viewed in isolation leading, for example, to maximum processing temperatures being set dangerously close to the onset of rapid exothermic decomposition. The onset temperature of an autocatalytic decomposition

tends to be highly sensitive to the 'thermal history' of the sample. Consequently, in cases where this phenomenon is suspected, isothermal ageing techniques are employed in which the sample is held in the ARC at a temperature close to but below that of the observed onset of decomposition in the standard ARC run. Where autocatalysis exists, this treatment can cause a dramatic drop in onset temperature and judicious use of such ageing techniques can yield information regarding the worst case situation i.e. the lowest likely onset temperature.

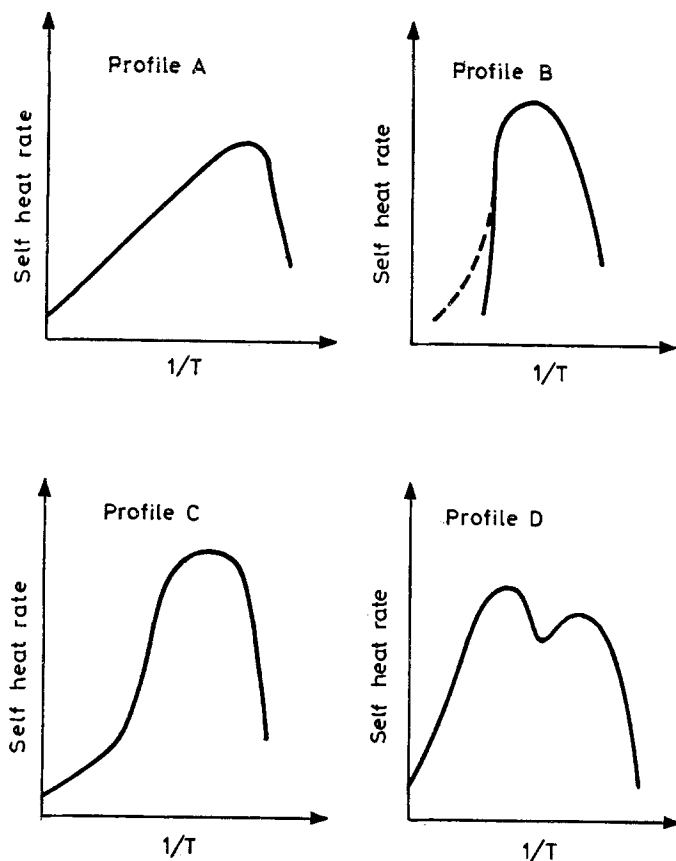


Fig. 11 Variation in the form of the ARC self-heat rate plot as a function of reaction mechanism. Profile A arises from a simple single reaction, Profile B from an autocatalytic process before (—) and after (---) isothermal sample aging, Profile C from two distinct reactions and Profile D from consecutive reactions

For an inherently unstable material the adiabatic conditions pertaining in bulk can induce a potentially catastrophic self-accelerating decomposition reaction ('thermal runaway'). In order to prevent such an occurrence, it is

essential that the heat dissipation capacity of the sample container (storage keg, reaction vessel etc.) always exceeds that of heat generation within the sample (due to decomposition), thus allowing the system to remain at a safe equilibrium temperature. These competing factors are represented in Fig. 12. Heat loss from a vessel (line CD) varies as a linear function of temperature and drops off rapidly with increasing bulk size, due to decreasing surface area: volume ratio. On the other hand, heat generation due to decomposition (line AB) tends to show an exponential increase with temperature (from the Arrhenius equation). At point X the rate of heat generation exceeds that which can be offset by heat dissipation from the vessel; this corresponds to the temperature of no return, TNR. (This is defined as the maximum temperature at which equilibrium can be maintained under a particular set of conditions.) With unstable materials, such as the example discussed in Section 3, this would eventually lead to thermal runaway and a possible explosion. Knowing the heat dissipation properties of, for example, storage kegs of various sizes, values of TNR can readily be derived from basic ARC data. Heat dissipation rates are expressed as time constant values which can be obtained experimentally. Within SB it is common for materials to be stored in 10, 20 or 36 kg lots in polythene kegs, and these have approximate time constants of 6, 12 and 26 hours respectively.

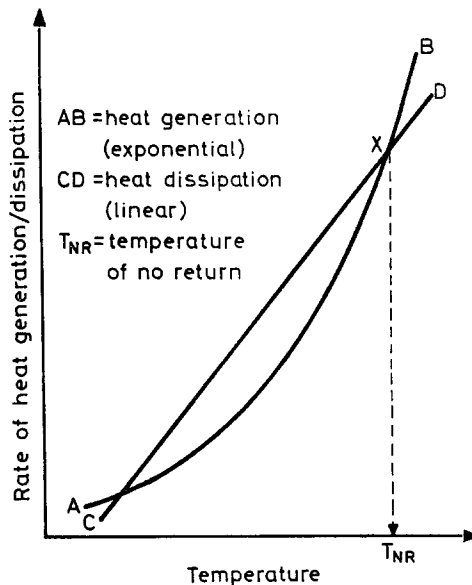


Fig. 12 The origin of the temperature of no return (TNR) within a vessel

TNR values are attainable from a second very important ARC data plot, namely that of time to maximum rate vs. $1/T$ (TMR plot). This graph shows the time available to the maximum rate of reaction on subjecting the sample to a particular temperature. The original TMR plot obtained from an ARC run is subject to the influence of the inherent thermal inertia within the system but this is readily computer-corrected to the worst case situation (i.e. total adiabaticity) utilising the \emptyset factor for the experiment, derived from Eq. 3 above. On knowing the time constant for each keg size, TNR values can be directly read off from the \emptyset corrected TMR plot as shown in Fig. 13, which depicts the data obtained from the decomposition of an unstable synthetic intermediate, the hazard screening of which is presented as a case study in Section 3 below. In defining safe storage conditions, the respective TNR values are used to calculate the maximum ambient air temperature at which the different bulks of material can be stored without a runaway reaction occurring i.e. the self accelerating decomposition temperature (SADT) is determined from Eq. 8.

$$\text{SADT} = \text{TNR} - \left(\frac{R (\text{TNR} + 273)^2}{E_a} \right) \quad (8)$$

Maximum safe storage temperatures are then typically obtained by subtracting 20° from the respective SADT values obtained above.

The TMR plot is also very valuable in indicating appropriate temperatures at which to set process alarms to allow time for corrective action or to instigate evacuation. A particularly pertinent factor with regard to ARC-derived TMR information is that the data are directly obtained from experimentation and are typically accurate to within a few per cent. This is in marked contrast to calculated TMR data indirectly derived from DSC studies. In this case the expression used to calculate time to maximum rate utilises the activation energy (E_a) for the reaction in an exponential term.

Consequently a relatively small error in E_a can result in alarmingly erroneous TMR predictions [10] and data generated in this manner are, therefore, highly suspect. Finally, it is important not to overlook the value of pressure data obtainable from the ARC. In many incidents it is an unexpected rapid pressure generation, rather than a thermal runaway, which causes vessel rupture and consequent hazards. Particularly useful in this connection is the log pressure vs. reciprocal temperature plot. This only appears linear when pressure arises solely from the vapour pressure of liquid within the sample bomb. Deviation from linearity implies that other processes are occurring and a marked positive deviation indicates additional pres-

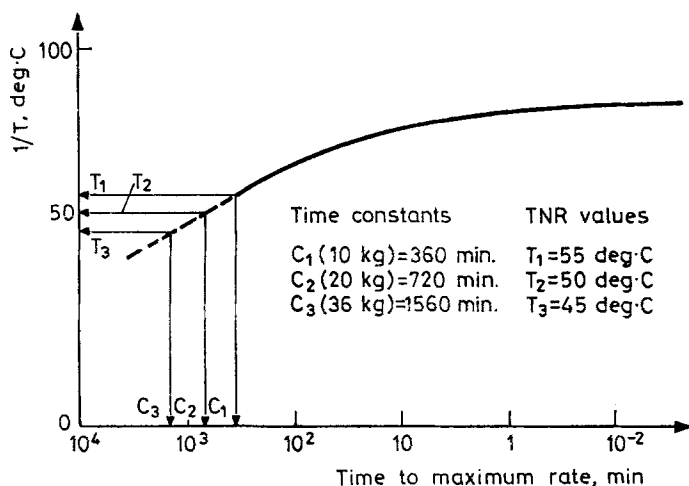


Fig. 13 Silver salt - ARC time to maximum rate plot for decomposition

sure generation due to the liberation of gaseous decomposition products. Since the total residual pressure at the termination of an ARC run is known, after suitable correction for void volume, solubility and vapour pressure, the quantity of gas generated is readily derived from Eq. 9. The maximum possible pressure arising from decomposition of a particular bulk of material within a vessel of known volume can, therefore, be calculated [11].

$$N = \frac{PVM_w}{RTM_s} \quad (9)$$

where N = moles of gas formed per mole of sample, M_s = sample mass, M_w = molecular weight of sample, R = universal gas constant, V = system void volume, P = pressure maximum, T = final temperature.

A plot of pressure rate vs. temperature rate is linear for simple reactions proceeding via a single mechanism. This graph is very useful in determining when a mechanistic change occurs, as this is often not obvious from other data plots. Pressure data from ARC can also be utilised in relief vent sizing, but calculations are complex due to corrections necessary in order to determine the reaction-pressure curve.

2.6 Specialist Tests

In the vast majority of cases the tests described in the preceding sections are sufficient to provide a good indication of the likely thermal stability of a material, and allow conditions to be defined under which it can be safely

stored, transported or processed. However, occasionally additional testing is required to characterise satisfactorily the sample. Examples of such tests, some of which have been commissioned in the past from within the author's laboratory, are briefly discussed below.

2.6.1 Propensity For Violent Decomposition

Assessment of any tendency towards violent decomposition, including explosive behaviour, is probably the most important area of additional compound testing. Due primarily to the facilities required, and the stringent safety precautions necessary, such studies are generally performed by specialist laboratories. Materials tested for explosive behaviour are those which:

- (i) Fall into the HIGH hazard classification according to the oxygen balance calculation (Section 2.2 above).
- (ii) Exhibit very sharp, highly energetic decomposition exotherms in a DSC screen (Section 2.3 above).
- (iii) Are involved in 'in-plant' incidents in which explosive decomposition is implicated.

Numerous techniques exist for the assessment of propensity to violent decomposition, many of which are referred to in a review by Cutler [12]. Typically, the sensitivity of a suspect material to a variety of stimuli is investigated.

Mechanical stimuli often arise via friction, impact, or a combination of the two ('impacted friction') during handling/processing of materials. Sensitivity to friction may be assessed using the Koenen friction apparatus in which the sample is placed on a porcelain tile and dragged under a loaded porcelain stylus. Unstable materials tend to glow or even ignite at the point of contact. Impact sensitivity is typically assessed via the Fallhammer test in which the response of the sample to sudden energy input from a falling weight is investigated. Such tests can indicate whether, for example, decomposition is likely to be initiated by the accidental grinding of a material against a vessel wall by an impellor blade.

Electric sparks, typically arising from the sudden dissipation of a static charge, represent another common initiation source for unstable materials. Many of the organic powders encountered within the pharmaceutical industry exhibit high resistivities and such materials can readily become highly charged during handling. This charge can be retained for long periods with a consequent risk of static discharge. This presents a particular hazard if the sample has a low minimum ignition energy. The electric spark test, in which

the sample is subjected to a spark energy at three discrete levels (4500, 450 and 45 mJ), gives an indication of susceptibility to spark initiation. Materials showing a tendency to ignite at the lowest energy require further testing in order to determine whether antistatic or fully conducting conditions are required for safe handling.

The train fire test or flash point determination described in section 2.4 above examine the sensitivity of a material to direct ('naked') heat sources. Behaviour on contact with an indirect heat source can be assessed via the Koenen tube test. The test material is held in a 24 mm diameter tube fitted with an orifice plate (typically with a 2 mm diameter hole), and is subjected to heating from four gas burners. An 'explosion' occurs when the tube fragments into at least three pieces. The minimum orifice diameter to cause this is determined. This allows the sample to be categorised in terms of explosibility.

Probably the most appropriate test to determine whether a substance is explosive is to subject it to a detonative shock. In the 50/60 tube test the sample, in a tube of 50 mm internal and 60 mm external diameter, is subjected to the shock of a high explosive or detonator. The behaviour of the sample is assessed in terms of the propagation of the shock, as shown by the condition of the steel tube.

2.6.2 Dust Explosibility Test [13]

Many powders which appear benign when examined via the strategy outlined above can undergo explosive decomposition when a powerful ignition source (such as a static discharge) arises in a situation where the material is dispersed in a plentiful supply of oxygen. Such behaviour can be assessed via the 20 litre sphere test. The test assembly comprises a partially evacuated 20 litre spherical explosion chamber into which the sample is introduced from a highly pressurised storage vessel through a pneumatically operated outlet valve incorporating a dispersion device. The ignition source, comprising a chemical igniter, is actuated shortly after dispersion of the dust into the test chamber. Transducers allow explosion pressures to be monitored over a range of dust concentrations. This, in turn, gives access to the maximum attainable explosion pressure and the maximum rate of pressure increase and allows the powder to be classified in terms of explosion hazard. The data obtained are valuable in assessing explosion relief venting requirements.

2.6.3 Adiabatic Dewar Testing [14, 15]

Although ARC is particularly adept at detecting the phenomenon of bulk instability (section 2.5 above), and can usually define reliable safe storage/transportation conditions, there are occasions when the technique is insufficiently sensitive to detect subtle, but often highly significant exothermic activity typically occurring in the 'embryonic' stages of a decomposition. This is basically due to the inherent thermal inertia of the ARC system which serves to suppress the observed self-heating rate of the sample, thus preventing high sensitivity data acquisition. This can result in the undesirable situation of extrapolation of the time to maximum rate plot to give access to SADT values. In cases where this is thought to be of dubious reliability, this problem can be overcome by utilising adiabatic dewar testing. This is a technique which can approximate very closely to true adiabaticity i.e. ϕ values are very close to 1 (cf. typical values in the range 1.8–2.5 for ARC). This results in at least an order of magnitude improvement in sensitivity [11] relative to conventional ARC. The simplest apparatus comprises a dewar flask (often 500 ml) containing the sample closed with a highly insulating lid and placed in an oven whose temperature distribution should be as uniform as possible. The sample and oven temperatures are measured by separate thermocouples and displayed on a recorder. The oven is heated to the desired test temperature and the temperature rise of the sample due to self-heating subsequently monitored as a function of time. More sophisticated test methods allow operation at elevated pressures and under highly adiabatic conditions via the use of an 'adiabatic shield' (in which the oven temperature is regulated to follow closely that of the sample). Results obtained from such techniques can reliably be applied to large scale vessels and can give direct access to SADT values.

3. Case study - silver salt

In order to illustrate the value of this stability screening strategy a real-life case study investigated in the author's laboratory using the techniques outlined above, is presented below.

The material in question was a silver salt β -lactam synthetic precursor to a compound closely related to penicillins. Practical constraints dictated that it was to be temporarily stockpiled, prior to progressing the synthesis. It was, therefore, essential to characterise the compound in terms of thermal stability in order that safe conditions for bulk storage could be defined.

Stability was also of great importance from a processing point of view as it was proposed to dry the material by heating to 40–50° in a steam oven.

A survey of relevant literature failed to reveal any thermal stability data relating to silver (or other heavy metal) salts of this type.

The validity of an oxygen balance calculation was questionable, owing to the lack of any obvious strongly oxidising functional groups within the molecule. Notwithstanding this, the value indicated, –110, potentially placed the material in the MEDIUM category with regard to explosion hazard. Great care was, therefore, exercised in performing subsequent studies.

The DSC profile of the silver salt (Fig. 14) obtained in crimped aluminium pans under an atmosphere of flowing nitrogen, was an immediate cause for concern. Even utilising a nonequilibrium technique of relatively low sensitivity, exothermic activity was detected from as low as 95° upwards, decomposition occurring via a very large symmetrical exotherm up to 165°. Energy release was considerable ($-530 \text{ J}\cdot\text{g}^{-1} \cong 270 \text{ kJ}\cdot\text{mol}^{-1}$) and no significant endothermic events appeared to precede the decomposition. A virtually identical profile was obtained under an air atmosphere (and in high pressure pans), and it was, therefore, clear that atmospheric oxygen was not necessary for the decomposition to occur. A TG examination of the material showed a large, rapid weight loss over a corresponding temperature range indicating that copious amounts of volatile decomposition products resulted, posing a potential explosion hazard in, for example, a sealed storage keg.

Train fire testing of the silver salt revealed its particularly alarming flammability properties. Ignition occurred very easily and combustion subsequently propagated exceptionally rapidly via very large, bright yellow flames which were approximately 0.5 metres in height (produced from a 'train' containing only about 10 grams of sample). Copious amounts of dense, black smoke were generated and a great deal of heat was evolved. A small amount of charcoal-like residue remained. The 10 cm test portion of the train burnt in only 6 seconds and the material was therefore classified as **HIGHLY FLAMMABLE**. The compound would consequently pose an extreme hazard on exposure to a local 'hot spot' during processing or storage, ignition occurring very easily, and the entire bulk of material combusting within a very short period of time, liberating large amounts of heat and noxious decomposition products.

The bulk stability of the silver salt was investigated via an ARC study. Due to ARC's enhanced sensitivity (at least an order of magnitude superior relative to DSC [11]), exothermic activity was detected from a considerably lower temperature than in the DSC study. Figure 15 shows the sample self-

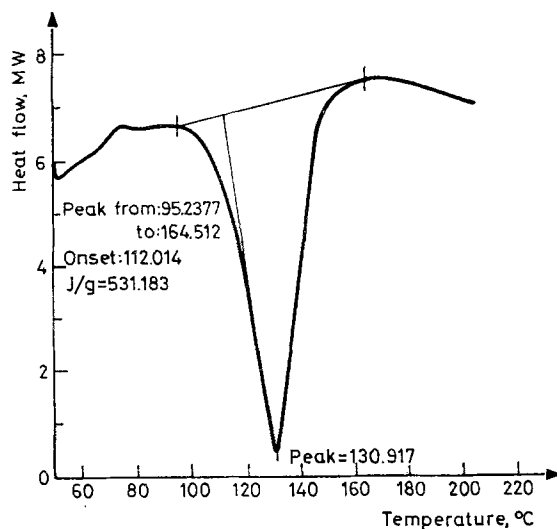


Fig. 14 Silver salt – integrated DSC profile

heat rate vs. $1/T$ plot obtained from the ARC run. First detection of exothermic activity occurred as low as 62° with decomposition subsequently taking place via a large, broad exotherm resulting in the temperature spontaneously rising to 200° . On utilising Eqs 3, 4 and 5 above, this would indicate a maximum temperature of 450° being generated in the worst conceivable case (i.e. a totally adiabatic environment) and corresponds to an approximate enthalpy of $250 \text{ kJ} \cdot \text{mol}^{-1}$ for the decomposition (from Eq. 6), a figure which is in good agreement with that obtained from the DSC data. After a relatively gentle onset to decomposition, the material appeared to undergo virtually instantaneous pyrolysis at 82° , as evidenced by the sudden increase in sample self-heat rate to a maximum of $\sim 400^\circ \text{ min}^{-1}$ at 102° . This pyrolysis was also accompanied by a sudden increase in pressure within the sample bomb to $\sim 450 \text{ psi}$ (30 atmospheres), indicating that a large amount of non-condensable gas was produced on decomposition. This was emphasised by the sudden departure from a straight line of the log pressure vs. $1/T$ plot (Fig. 16), and served to underline the potential explosion hazard posed by the material. However, despite the relatively rapid, markedly exothermic decomposition observed, the activation energy (E_a) for this process calculated using the slope of the initial linear portion of the sample self-heat rate plot in Eq. 7 above, was relatively high at $\sim 195 \text{ kJ} \cdot \text{mol}^{-1}$.

Safe storage conditions for the silver salt were derived from the \emptyset -corrected time-to-maximum rate vs. $1/T$ plot (TMR plot) for the decomposition

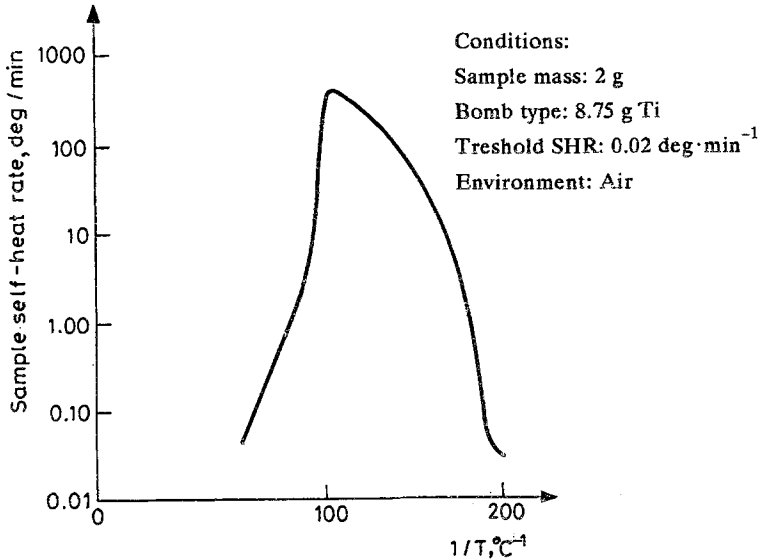


Fig. 15 Silver salt - ARC sample self-heat rate plot for decomposition

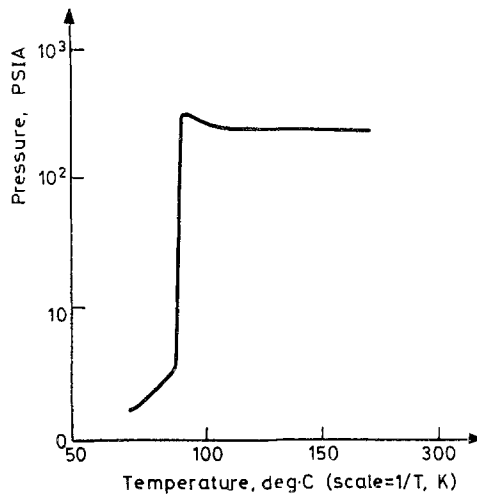


Fig. 16 Silver salt- ARC log pressure vs. reciprocal temperature plot for decomposition

(Fig. 13). As explained in section 2.5 above, the TNR values for the three typical storage keg sizes were obtained from the TMR plot utilising their respective time constant values. The TNR values were then used to calculate the SADT corresponding to each bulk size utilising Eq. 8. This, in turn, allowed maximum safe storage temperatures to be recommended. The data obtained are summarised in Table 4.

Table 4 Silver Salt Bulk Stability Data

Bulk Size, kg	TNR, °C	SADT, °C	Maximum storage temperature, °C
10	55	50	30
20	50	45	25
36	45	40	20

These figures, although undesirably low, are not as bad as may have been expected in view of the poor thermal stability indicated during the above hazard screening. This is primarily due to the relatively high activation energy required for the decomposition; a parameter which is highly influential in Equation 8 above.

In the light of the data obtained on subjecting the silver salt to the above tests, the following recommendations were put forward:

(i) Due to the highly flammable nature of the compound great care was required in avoiding exposure to potential sources of ignition (arising, for example, from friction, static discharges etc.) Processing via milling/grinding was strongly discouraged.

(ii) The proposed drying procedure was completely unacceptable - heating this material, which can begin exothermic decomposition from temperatures at least as low as 60°, to 40–50° in a steam oven (a potential source of temperatures up to 100°) clearly posed a serious explosion hazard. Desiccation under vacuum was adopted as an alternative method.

(iii) Bulk storage of the material at ambient temperature should only be performed in pack sizes of up to 5 kg. Large bulks required active cooling. (In fact 20 kg lots were stored for a number of months at 0° without incident.)

Application of this relatively simple hazard screening strategy was, therefore, readily able to generate safe conditions for the processing and storage of a potentially hazardous synthetic intermediate.

* * *

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Zusammenfassung — Es wird eine relativ einfache Methode zur Ermittlung der Wärmeempfindlichkeit isolierter synthetischer Zwischenprodukte und Endprodukte beschrieben, wie sie innerhalb eines großen Arzneimittelunternehmens vorkommen. Als Screening-Verfahren wurde DSC unter sorgfältig kontrollierten Bedingungen angewendet, um jegliche Neigungen festzustellen, die eine Substanz bezüglich einer signifikanten exothermen Zersetzung haben kann. Verdächtige Proben wurden weiterhin mittels Verbrennungstests und ARC untersucht; die ermittelten Angaben erleichtern die Charakterisierung im Hinblick auf Entzündungs- und Entflammbarkeitseigenschaften sowie Massebeständigkeit. Es wird weiterhin eine in der Praxis durchgeführte Studie beschrieben, um die Anwendung dieses Verfahrens bei einem unbeständigen synthetischen Zwischenprodukt zu illustrieren, für welches sichere Verfahrens- und Lagerungsbedingungen ermittelt wurden.