

THE SEARCH FOR ACTIVE PHARMACEUTICALS: ACCELERATING PROCESS DEVELOPMENT

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Present patent arrangements limit the time that innovative pharmaceuticals manufacturers have to recover development costs via protected sales. An overall reduction in the time taken to get new pharmaceutical products to market gives an increase in the protected sales period. This adds to the pressure to cut process development time. The authors describe a new calorimeter that not only facilitates accelerated process development without jeopardising process safety, but also yields useful process information at a very early stage in the development. The calorimeter was checked for systematic errors using a recognised test reaction, before being used to investigate some of the parameters of a synthetically useful diazotisation reaction.

INTRODUCTION

At present, patent law and practice allow innovative pharmaceuticals developers 16 years of protection from the date of application. This means that developers can sell a new medicine at a monopoly (i.e. high) price during the period of protection. In theory, this arrangement means that the drug development costs can be recovered in a realistically reasonable time. In practice, what actually happens is that it takes, typically, between 5 and 10 years to

- refine the synthesis,
- check for any number of possible toxic effects,
- carry out clinical trials to a standard high enough to satisfy the licensing authorities that the drug has a beneficial effect for patients and that it has no unacceptable side effects, and
- demonstrate improved cost-benefits for medical service providers.

The overall effect is to reduce the length of time available for recovery of the considerable development and testing costs.

It is easy to see that a reduction in the time taken for any stage of development and testing is likely to improve the chances that a particular drug will eventually pay for its own research and development. More complex molecules now in development call for more complex syntheses. In turn, the pressure is on to optimise each stage of the manufacturing process as quickly as possible. One means of improving the yield of information at each stage is simply careful control and monitoring of parameters such as temperature, pressure, pH and so on. This can reduce the number of experiments rejected through, for example, inadequate temperature control. Another way of speeding up development is to increase the number of experiments that can be run in parallel. This paper describes

a new multi-vessel system equipped to allow accurate calorimetric measurements on individual vessels, which gives significant advantages to users:

- Accurate calorimetry at a very early stage in the development
- Multiple parallel experiments allow for Statistical Experimental Design
- Computer control provides for reproducible temperature profiles

The calorimeter has been designed for completely automatic operation using an x-y-z robot for making additions to, and taking samples from (e.g. for analysis) the individual reactors, and gives good results at the 1 mmole scale. As reliable data can be gathered earlier in the product development cycle, the costs and delays associated with scaling-up to pilot and pre-production scales can be reduced significantly.

CALORIMETER DESIGN

OPERATING PRINCIPLE

The calorimeter vessel uses the well-known Power Compensation¹ method:

A constant cooling load is applied to the calorimeter vessel. An actively controlled heater balances the cooling, controlling the calorimeter contents at some defined temperature. The power dissipated through the heater is measured with reasonable accuracy and stored periodically in a computer data file for subsequent analysis. Once the system has achieved a steady state, the control system is applying a constant amount of power to offset, or compensate for the cooling.

If the equilibrium is disturbed, for instance by a chemical reaction occurring within the vessel, the controller must change the amount of power fed to the heater in order to keep the calorimeter contents temperature constant. This is a quantitative effect, so that if the reaction liberates energy at the rate of a watt, the change in the heater power will be one watt. At the end of the experiment, the deflection of the heater power from the baseline value over the period of the reaction can be integrated to give a measurement of the heat liberated by the chemical reaction.

In principle, there are few restrictions on the temperature range that can be accommodated by the new design. In the present design, the thermocirculator could be used between -40°C and 200°C : this limits the operating temperatures in the individual vessels to between -35°C and 205°C . The glass vessels may have other restrictions due to the material of construction (Pyrex glass). The original specification required that the instrument should cover as wide a temperature range as possible.

BLOCK DESIGN

Each of the reactors was placed in a close-fitting hole in a custom-designed² aluminium block, which was drilled to allow free flow of heat transfer oil throughout its bulk.

A thermocouple was located in a pocket drilled into the centre of the block to allow temperature measurement and control. The oil temperature was controlled using a proprietary thermocirculator. A classical software-implemented, three-term control algorithm controlled the temperature of the block.

HEATER DESIGN

Originally, power compensation calorimeters were built with heaters fitted inside the calorimeter vessel. This arrangement gives the advantage of an extremely small time constant for vessels containing large volumes (sometimes 5 or even 10 litres) of reaction mixture. The major disadvantages surround the construction of the heater,

- It must be small enough to fit into the vessel
- It must not dissolve or otherwise react, or interfere, with the reaction mixture
- Its surface temperature must not lead to charring of the reaction mixture

A number of ways of meeting these criteria have been tried, including use of high chromium steel alloys as the heater outer sheath material or coating a steel heater sheath with an inert material (e.g. PFE and PTFE). The most useful solution, in many ways, has been Pyrex glass as a sheath material, although this slows down the heater response and is not so physically robust as a metal-sheathed heater.

A novel³ feature of the system presented here is an external heater. A diagram of a single reaction cell is given in Figure 1. It was felt that the loss of response speed and reduced reproducibility ($\pm 10\%$) of this feature were acceptable for work conducted at this stage of the product design cycle, and that a little over- or under-temperature could also be tolerated. There were compelling physical reasons for adopting the design however:

- There was very little space available for an internal heater in the 10 cm³ reaction vessel.
- The space above the calorimeter was needed for access by the x-y-z robot.

VESSEL DESIGN

It was not possible to fit the thermometer into the calorimeter in the conventional way, i.e. fitted to, and suspended from the calorimeter lid because the calorimeter top had to fit underneath the moving head of the robot. Figure 2 below gives some idea of the arrangement involving the robot. In the absence of any usable space above the reactor lid, the thermometer pocket was fitted into the side of the reactor vessel.

As designing complex syntheses often involves moisture and oxygen sensitive reagents and intermediates, an existing design of reactor lid, allowing for purging with dry, inert gas was chosen. It was accepted at the design stage that accurate calorimetry would not be possible under conditions with significant positive gas flow rates. This was not felt to be necessarily a problem with the system, as calorimetry was only part of its functionality.

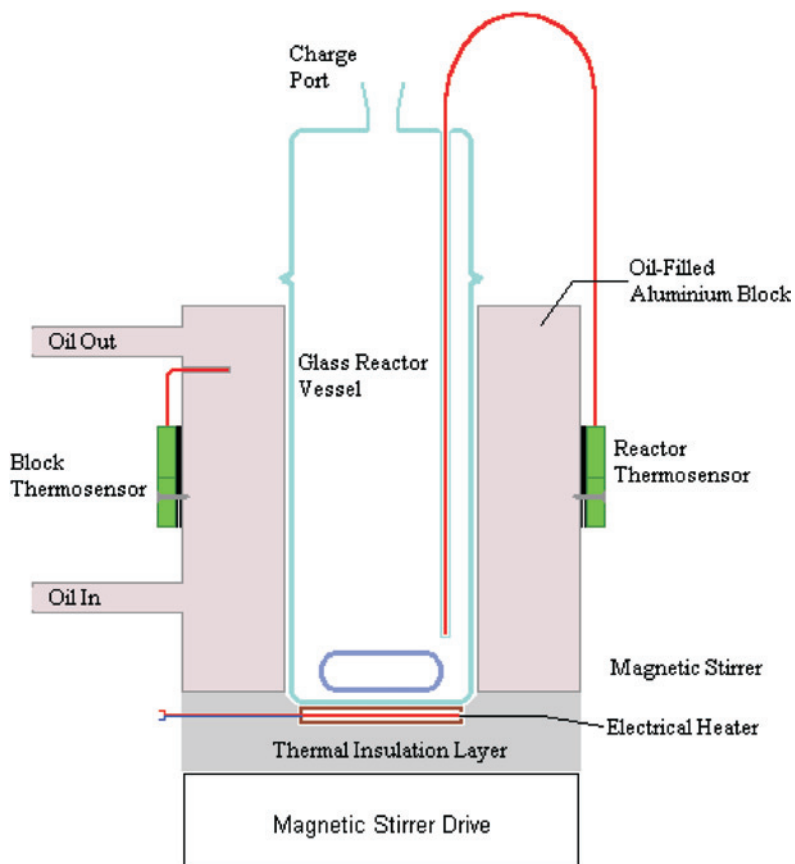


Figure 1. Sketch diagram showing a detail of the reactors. The reactor contents were stirred magnetically, and the temperature was measured using a thermocouple

THERMOMETRY

The system was designed to study small amounts of reaction, of the order of 1 mmole, and the physical space allowed for the thermometer probe was limited. Thermocouples were selected as the best thermometers for the application, because they were

- Robust (cf platinum resistance thermometers)
- Accurate enough for the application
- Small enough to fit inside the calorimeter vessels

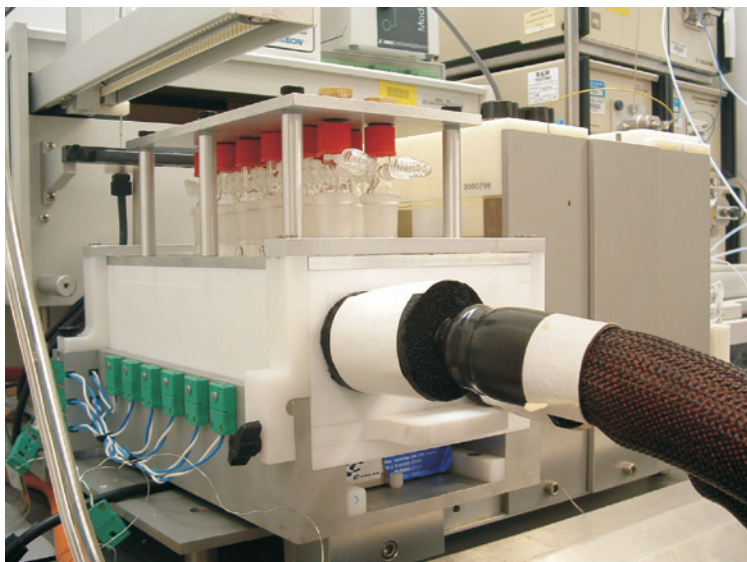


Figure 2. Reactor block sited on the bed of an SK233 x-y-z robot

STIRRING

Efficient stirring is essential for Power Compensation Calorimetry to work. It is necessary to keep the reagents well mixed and to ensure an even temperature within the reactor vessel. This arises because of the relationship between the temperature, the heater power level and the control algorithm that links the two.

Magnetic stirring was selected because

- It takes up no space above the calorimeter vessel
- Very simple engineering beneath the calorimeter vessel
- Does not interfere with the heater arrangement
- Adequate for 7–10 cm³ reaction mixture volumes

POWER MEASUREMENT AND CONTROL

A new power supply was commissioned* that gives a pure direct current output and is easily controlled by the computer control hardware. One of the serious problems overcome on this project was the sheer number of individual conductors that were needed to allow accurate power and temperature measurements (for 12 individual vessels, 74 wires in

*Built in UK to a design commissioned by JBSafety Consultancy. Contact Jim Bickerton for details.

total). The individual power supplies were rated at 3W, and a multi-core cable was found with a suitable number of conductors (4 for each heater). The wires were arranged in 25 twisted pairs to reduce electrical noise. We adopted the four-wire design for each heater to reduce errors from energy losses along the heater cables.

TEMPERATURE CONTROL ALGORITHM

A software-implemented classical three-term control loop calculation was used to control each calorimeter/reactor temperature.

A significant level of noise on the thermometer readings has been ascribed to a number of possible sources including:

- Noise caused by the constantly changing magnetic flux of the stirrer drive
- Noise from nearby electrical equipment
- Noise caused by inefficient grounding “loops”

CONTROL COMPUTER — USER INTERFACE

On the controlling computer, a graphical user interface, enjoying all of the advantages of a proprietary operating system was used to provide facilities for the operator:

1. Set up parameters for experiments
2. Plot temperature and power data on screen during experiments
3. Modify the coefficients of the control activities at run time
4. Store numeric data

CALCULATION OF HEAT OF REACTION

In conventional calorimetry, two measurements are needed to find a heat of reaction⁴:

- An adiabatic temperature rise ΔT_{ad} , and
- The amount of energy (normally supplied as electrical energy) needed to raise either the products mixture or the reactants mixture through the temperature interval ΔT_{ad} .

Combining these values in classical Hess' Law fashion gives the heat liberated by the reaction. Classical precision calorimetry dwells on calculating suitable corrections to the observed temperature rise in order to find the truly adiabatic value. Reference 4 discusses many techniques in considerable detail. In power compensation calorimetry, the two measurements are carried out simultaneously as a consequence of the way it works. The resultant power-time curve for the experiment requires relatively little correction as the rate of heat loss to/from the calorimeter is almost constant because the reaction proceeds isothermally. A correction was applied for the addition of a cold liquid to a warm calorimeter. It was calculated using the well-known method of mixtures (amount, specific heat of additive and temperature interval are multiplied to give the actual correction). Values for specific heat capacities were either taken from the literature or estimated using well-documented methods^{4,7}.

PROOF OF THE CALORIMETER

TEST REACTION

A test reaction was used to prove the system worked and was free of systematic errors. The one chosen was that between methanol and acetic anhydride, catalysed by a small amount of sulphuric acid (see Reaction Scheme 1 below).

The observed heat of this reaction is widely reported⁵ as being between -62 and -67 kJ.mol^{-1} of acetic anhydride, depending on conditions of measurement. The reaction has proved invaluable over the past 30 years to compare the many and diverse calorimeters that have been designed for process development and hazards assessment.

TEST PROCEDURE

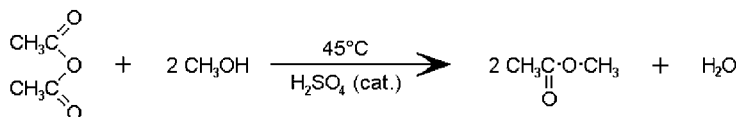
Figure 2 illustrates how the 12-pot instrument was fitted together on the bed of the x-y-z robot. The block containing the reactor vessels was clamped onto a frame carrying the stirrer drives and heaters. Each reactor was charged with 8 cm^3 of anhydrous methanol (containing 0.5 ml.dm^{-3} 98% sulphuric acid), and was closed using the glass top. Once the apparatus had settled into thermal equilibrium, acetic anhydride (1.26 ml, equal to 1.363 g or 13.35 mmol) was added over 20 minutes using the robot-borne syringe.

The control software was set up to run the twelve experiments at 45°C , with the block temperature set at 40°C . Typical power-time and temperature-time curves are shown in Figure 3 below.

TEST REACTION RESULTS

A number of experiments were performed to show that the calorimeter system was capable of measuring the heat of the test reaction reliably. The mean result of a total of 22 individual experiments carried out over a day was $(873 \pm 67)\text{J}$ liberated by 13.35 m.moles of acetic anhydride, giving a specific heat of reaction of $-(65 \pm 5)\text{kJ.mol}^{-1}$, where the quoted error is the standard deviation of the mean of 20 readings. This result indicates that the power measurement system is probably free of systematic errors and offers reasonable reproducibility, given the sample size, of around $\pm 10\%$ of the measurement.

To show that all of the individual calorimeters had identical characteristics, a comparison was made of the differences between each measured value and the mean



Reaction Scheme 1. Methanolysis of acetic anhydride, a standard reaction for testing calorimeters to be free from systematic errors

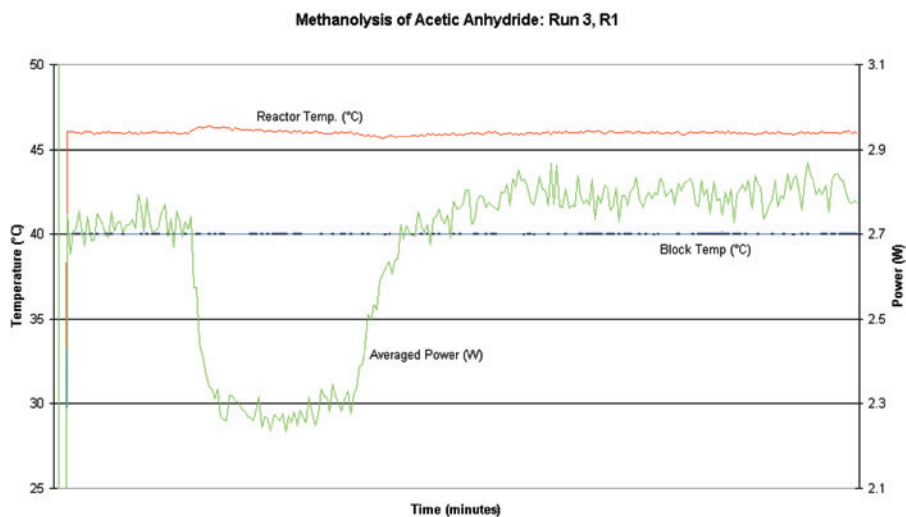


Figure 3. Plot of temperature and power vs time for a typical experiment

for a series of measurements. This is shown in the plot in Figure 4 below. Aside from a few instances of remarkably large errors, there are no indications that any of the reactors are consistently higher or lower than the mean for a series of experiments. None of the individual calorimeters was consistently in error, leading to the conclusion that they are all free of systematic errors linked to particular positions in the block.

IMPROVEMENTS IN DESIGN ARISING FROM THE TEST REACTION EXPERIMENTS

PROBLEMS IDENTIFIED DURING TEST REACTION RUNS

Following an analysis of the test reaction results, it was considered that errors could arise if an individual calorimeter vessel was moved relative to its heater pad during an experiment. Close observation of the action of the robot arm during dosing showed that sometimes a reactor vessel was lifted slightly as the robot-arm pulled the syringe needle out of the septum after dosing. Slight finger pressure applied to the top of each reactor at the end of an experiment series occasionally resulted in a small amount of downward movement — of the order of 0.5 to 1 mm. This observation supported the view that sometimes the calorimeter vessels were being lifted slightly during the run. This effect probably accounted for a number of erroneously high figures.

Individual Deviations from the Series Mean (%)

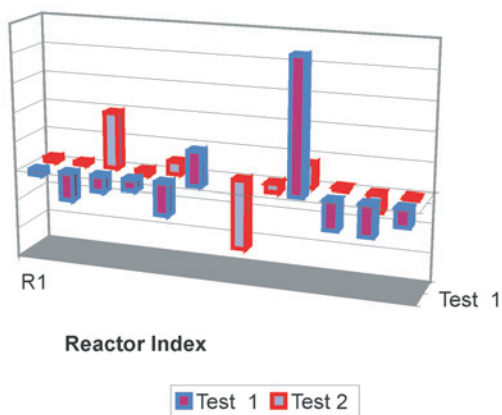


Figure 4. 3D plot of differences between reactors for four series of experiments. The errors across the data sets do not show any specific trends, so it is inferred that there are no systematic errors attached to the system or the block

In instances where the reactor was slightly moved, but still within range of the heater pad, an increase in the base level of heating required to balance the cooling load was seen. On integrating over a period of time, this deviation appeared as a large positive increase in measured compensation power, from the time that the reactor vessel had moved. Where the calorimeter vessel was lifted clear of the heater altogether, then heater signal, struggling to meet the cooling load, increased rapidly to 100% and remained unchanged until the end of the experiment.

A similar explanation for the occasional low result is also possible. If the calorimeter vessel were not in good contact with the heater during the period before the dosing, then the baseline value for the power compensation heat balance would be higher than if the vessel were firmly seated. If the downward force applied by the robot moved the vessel onto the heater pad, then the baseline power value, masked by the effects of the chemical reaction, would fall again. This would integrate to give a false, low value at the end of the experiment.

DESIGN IMPROVEMENT

A clamp was designed to hold the 12 vessels firmly in place on the heater pads during the experiment. The studies on the industrially useful synthesis reaction described below were carried out with this clamp in place — the clamp, taking the form of a flat plate, can be seen in Figure 2 below.

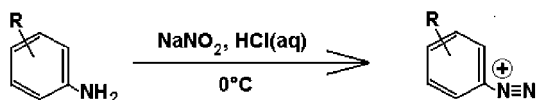
STUDY OF A SYNTHETICALLY USEFUL REACTION

DIAZOTISATION REACTIONS GENERALLY

Diazotisation reactions are synthetically useful as they yield reactive materials that are useful intermediates for a range of products. Diazomethane is a most versatile and useful reagent in organic chemistry, despite being highly toxic, dangerously explosive and impossible to store for any length of time. There are no high quality heat of formation data available for diazonium compounds, and there are few reported data for enthalpies of reaction. For the purposes of process development, high quality data are not required, which is just as well because the quantities of material available for such measurements are not always adequate for precision calorimetry.

DIAZONIUM ION FROM ARYL AMINES

The preparation of diazonium salts from aryl amines is well documented in many undergraduate texts (See Reaction Scheme 2 below).



Reaction Scheme 2. The general diazotisation of aryl amines by nitrous acid. Specific amines may require different conditions

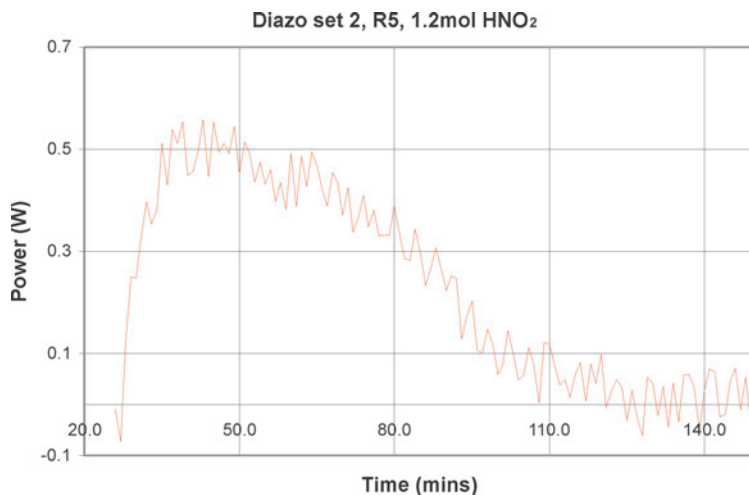


Figure 5. Typical power-time profile from a diazotization experiment

Aryl diazonium salts are also known to be very unstable so typically the reactions are carried out at 0°C. The controlled decomposition can be used in chemical synthesis to great effect, for the purposes of introducing halides, nitriles, hydroxyl groups etc. into the aromatic ring. This means that aryl diazonium salts are both valuable intermediates and unstable compounds. Like the preparative method, the hazards of making and using diazonium compounds are well documented⁶. Investigation of this reaction at the millimole scale of development has been carried out using the new calorimeter.

Table 1. Summary of results from 2 sets of experiments on the diazotization reaction

Data Set	Total Energy (J)	Amount of HNO ₂ (mol ratio)	Vol. & Conc. of HNO ₂ added	Yield (%)	£ _R H (kJ.mol ⁻¹)
Diazo 1					
R2	396	1.3	0.343 cm ³ of	72.5	348
R5	342	1.3	5.625M		301
R11	389	1.3			342
R12	481	1.3			423
R7	341	1.5	0.418 cm ³ of	65.8	330
R8	377	1.5	5.625M		365
R9	434	1.5			420
R10	422	1.5			409
Diazo 2					
R3	406	1.2	0.471 cm ³ of	65	398
R4	414	1.2	4.000M		406
R5	431	1.2			423
R6	442	1.2			433
R1	395	1.3	0.510 cm ³ of	76.5	329
R2	417	1.3	4.000M		347
R11	454	1.3			378
R12	438	1.3			365
R7	412	1.4	0.549 cm ³ of	74.7	352
R8	225	1.4	4.000M		192
R9	178	1.4			152
R10	352	1.4			300

Note: The yields were obtained from working up the final solutions in each group of 4 calorimeters, as the amounts of material were so small (0.00674 moles per four reactors), and so yields are quoted for each group of 4 experiments.

PRACTICAL APPROACH USING THE 12 POT CALORIMETER

The chosen synthesis reaction was carried out at the unusually high temperature (for diazotisation reactions) of 50°C, which was only possible because of the marked stability of the particular diazonium salt formed. Two experiments were carried out yielding a total of 20 successful calorimetric measurements. The aims of the experiments were two fold:

- To determine the effective or overall heat of reaction, and
- To determine the effects of recipe on yield.

Both of these aims are typical of process development and scale-up projects.

EXPERIMENTAL PROCEDURE

In the experiments, each reaction vessel was loaded with 7.5 cm³ solution containing 1.569 mmole of substrate in aqueous acetic acid (90%). The calorimeter was assembled and the computer programmed to control the vessel temperatures at 50°C. Sodium nitrite solution (4.0M, at ambient room temperature, 21°C) was added to each calorimeter cell in turn, the precise amount corresponding to a range of excesses of the reagent. A typical plot of temperature and power data is shown in Figure 3. A derived time-power trace obtained during the experiments is shown in Figure 5.

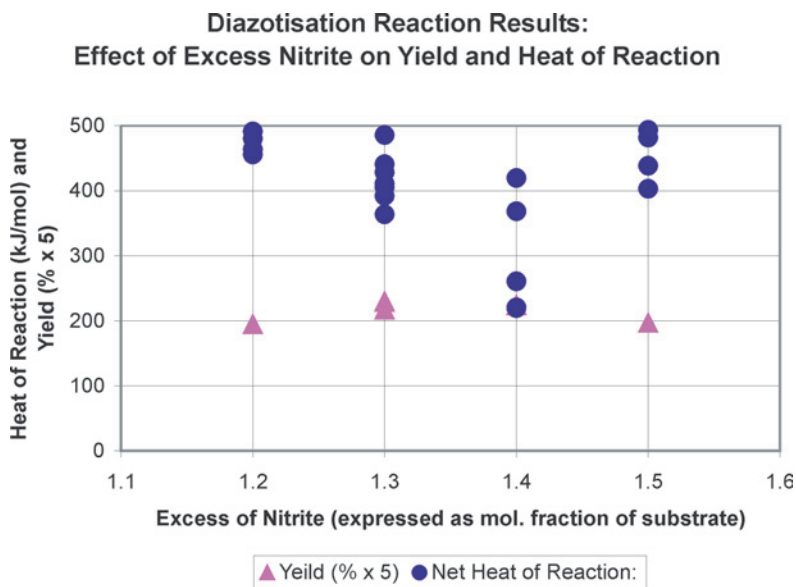


Figure 6. Plot of total heat liberated and product yield vs excess of nitrite for the diazotisation reaction

RESULTS

The results from the two series of experiments are summarized in Table 1. The measured enthalpies and the measured yields are plotted against molar excess of reagent in Figure 6. Even though one or two results are probably spurious, clear trends can be seen for both Yield (peaking between 1.3 and 1.4 molar excess of nitrite), and for observed heat (reaching a minimum at around 1.4 molar excess of nitrite).

CONCLUSIONS

- Power Compensation calorimetry was found to be practical and reasonably sensitive when used with 10 cm³ vessels.
- An exterior heater gave better than expected results, which are more than adequate for the stated aims — i.e. process investigation at a very early stage of new compound development.
- It was possible to determine the effect of molar excess of reagent on the yield and the total heat liberated by the reaction with just two day's experiments.

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