

Evaluation and Optimisation of the Reagent Addition Sequence during the Synthesis of Atrazine (6-Chloro-*N*²-ethyl-*N*⁴-isopropyl-1,3,5-triazine-2,4-diamine) Using Reaction Calorimetry

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Abstract:

The sequence of reagent addition and associated heats of reaction during the synthesis of the important herbicide atrazine (6-chloro-*N*²-ethyl-*N*⁴-isopropyl-1,3,5-triazine-2,4-diamine) from cyanuric chloride, isopropylamine, and ethylamine have been investigated by means of calorimetric and analytical methods. Sodium hydroxide was used as proton scavenger in this procedure. The best addition sequence found was the concurrent addition of amine and NaOH, keeping the amine in slight excess at all times. Using this feed sequence, the reaction becomes feed-controlled, and provided that a proper level of mixing can be maintained in the reactor, a high degree of control over reaction selectivity is obtained.

Introduction

Triazines are the most widely used herbicides in the world today. Atrazine (**1**) a 1,3,5-triazine, is a selective systemic herbicide that is used to control broad-leafed weeds and perennial grasses in crops such as maize, pineapple, and sugarcane.¹ Although there is some debate as to its toxicity and impact on the environment, the use of atrazine has numerous advantages over many other herbicides including a low risk of crop injury (implying higher crop yields) and low treatment costs.² Because of these and other positives, the world market for atrazine is worth over \$400 million at the user level.¹ Industrially, atrazine is produced in a two-stage reaction of cyanuric chloride **2** with isopropylamine (IPA) and ethylamine in an alkaline medium as has been described by Pearlman and Banks³ (Scheme 1). The reaction is exothermic and is carried out in a two-phased mixture of water and organic solvent (typically xylene or toluene). The water acts as a heat sink, as a reactant carrier for the amines and sodium hydroxide, and as a solvent for the byproduct, sodium chloride. The organic solvent acts as a solvent/dispersant for the starting material, organic reagents, intermediates, and reaction product.

The least reactive amine, isopropylamine, is first reacted with **2** to reduce the occurrence of disubstitution of the organic substrate. To reduce hydrolysis of **2**, the reaction temperature is kept below 5 °C during this step. In the second step of the reaction, the intermediate, 2,4-dichloro-6-isopropylamine-1,3,5-triazine, **3**, is reacted with ethylamine to

produce **1**. This step is usually carried out at higher temperatures (<30 °C).

One disadvantage of this process is that several side reactions may occur during the synthesis of **1**, leading to the formation of a number of unwanted side products. The major impurities that are formed are propazine, **4** (6-chloro-*N*²,*N*⁴-diisopropyl-1,3,5-triazine-2,4-diamine, Scheme 2), simazine **5** (6-chloro-*N*²,*N*⁴-diethyl-1,3,5-triazine-2,4-diamine, Scheme 3), hydroxytriazines **6**, **7**, and **8** (Scheme 3), and tris-triazines such as **9** (Scheme 4).

In particular, the presence of impurities **4** and **5** in the final product (although herbicides in their own right) renders the atrazine product less effective because of their lower solubilities, thus emphasizing the importance of a highly efficient and selective method for the production of high-grade atrazine.

Another disadvantage of the industrial process for the preparation of **1** is that the selectivity and yield of the product is not consistent from one batch to the next.

The purpose of this study was therefore to investigate and optimise the reagent addition sequence for the synthesis of atrazine such that the product may consistently meet technical specifications by minimising the formation of side products as far as possible. For this purpose, reaction calorimetry was used to monitor the rate of reaction (as a function of total energy released). These results were compared to those obtained for the chemical analysis [high performance liquid chromatography (HPLC)] of reaction mixtures to define the most suitable addition sequence.

In this investigation, power compensation calorimetry was selected as the most appropriate technique with which to study this reaction, whereby a constant temperature differential ($\Delta T \approx 10\text{--}30$ °C) is set up between the reactor contents (reaction mixture) and the reactor jacket. This is achieved through the use of an internal heater to heat and keep the reaction mixture at the desired temperature. The jacket temperature (controlled via an external heating/cooling system) is set at the desired lower temperature. The principles of power compensation calorimetry^{4,5} are best illustrated by means of the schematic representation of the experimental arrangement shown in Figure 1.

Equation 1 summarises the heat balance around the reactor at the start of the experiment under steady state (before the

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(1) See: <http://www.pan-uk.org/pestnews/Actives/atrazine.htm>.

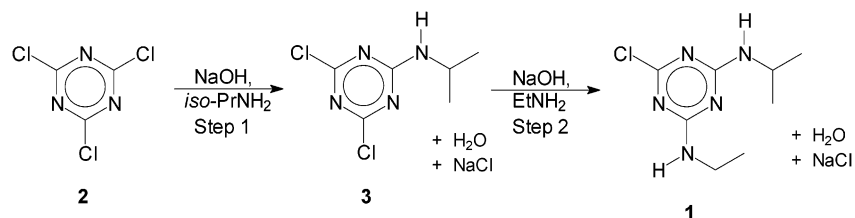
(2) See: <http://www.lenjohnson.com/atrazine.html>.

(3) Pearlman, W.; Banks, C. K. *J. Am. Chem. Soc.* **1948**, *70*, 3726.

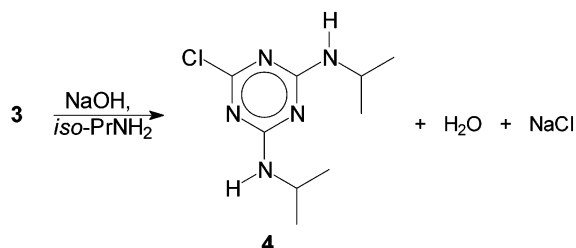
(4) Singh, J. *Process Saf. Prog.* **1997**, *16*, 43.

(5) *Ullman's Encyclopedia of Industrial Chemistry*, 6th ed.; Wiley-VCH: Weinheim, 2001; electronic release: <http://www.wiley-vch.de/vch/software/ullmann/>.

Scheme 1. Preparative route for the production of atrazine 1



Scheme 2. Formation of the side product propazine 4 from 3



reaction begins, i.e., Q_R , the heat released/taken up by the reaction mixture, is equal to zero).

$$Q_p(o) = Q_{Rem} + Q_L \quad (1)$$

where $Q_p(o)$ is the heat supplied to the reactor contents via the internal heater, Q_{Rem} is the heat retained in the reactor, and Q_L is the heat lost to the jacket and surroundings. When the reaction begins, the electrical power must be adjusted to compensate for heat absorbed or released during the reaction so as to maintain a constant reactor temperature. Equation 2 is thus a simplified representation of the essence of power compensation calorimetry.

$$Q_p = Q_p(o) \pm Q_R \quad (2)$$

This heat output/uptake of the reaction can then be followed directly as a function of time by simply monitoring the amount of power supplied to the internal heater.

Because of its simplicity, power compensation calorimetry is useful for the study of reaction rates, heats of reaction, reaction progress, and mixing (mass transfer) characteristics

Scheme 3. Formation of side products simazine 5 and hydroxytriazines 6, 7, and 8 from 2

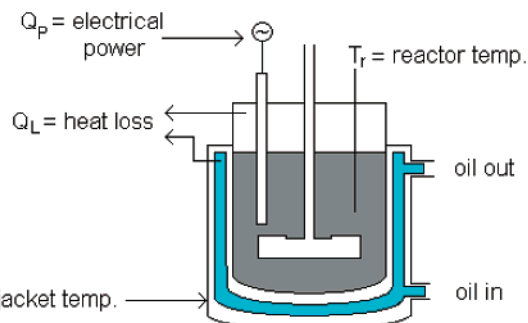
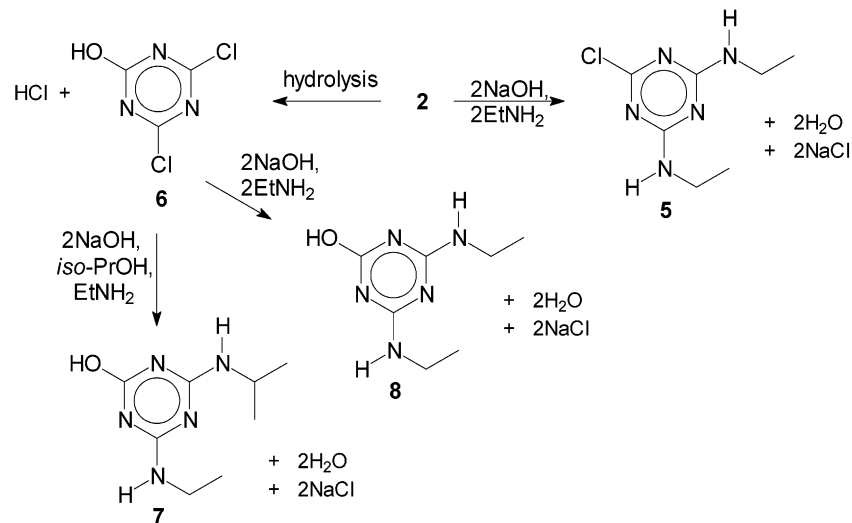


Figure 1. Schematic representation of the reaction calorimeter.

during reactions. Since control of the reactor temperature is by means of an internal heater immersed directly in the reaction mixture, control is both fast and accurate.

Results and Discussion

Various ways of carrying out the synthesis of **1** have been described in the patent literature; in particular, different reaction media have been used to improve the yield or quality of the final product.⁶ Whichever reaction medium is selected, the first reaction stage is usually carried out with equimolar ratios of cyanuric chloride, amine, and alkali metal hydroxide, while the second stage is carried out with a slight excess of the amine and of the alkali metal hydroxide to ensure the complete conversion of intermediate **3**. In addition to using different reaction media, reagent addition sequences have also been investigated to minimise side reactions and improve the quality of the final product.

The use of reaction calorimetry to optimise the reagent addition sequence during the synthesis of atrazine was the

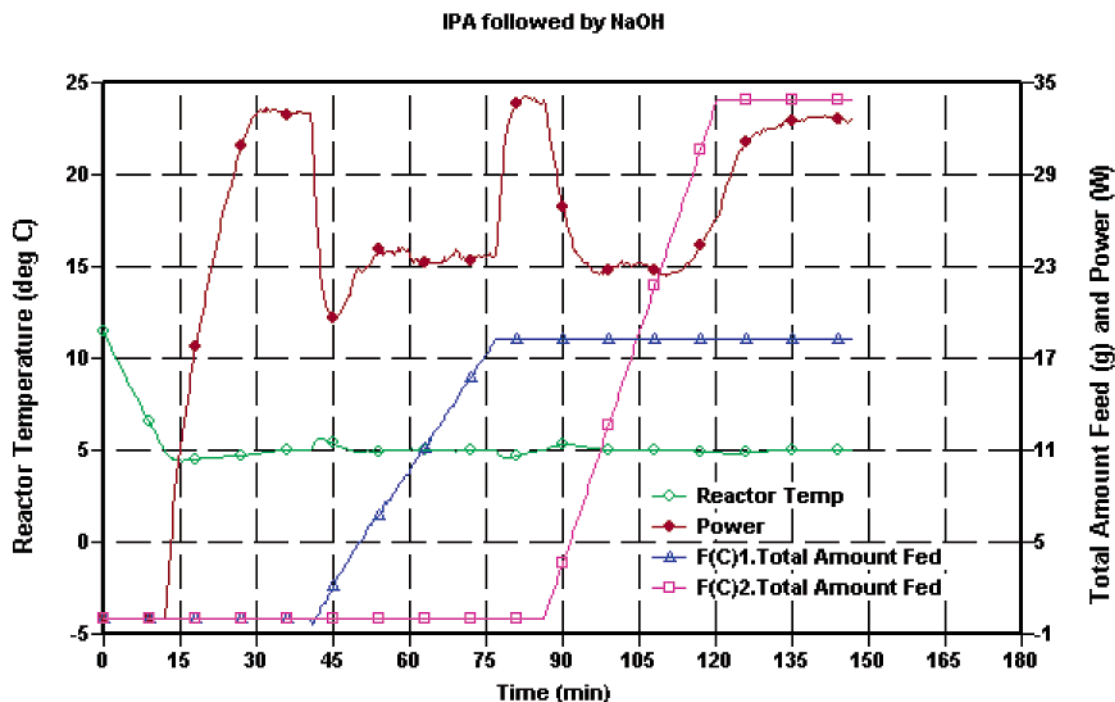
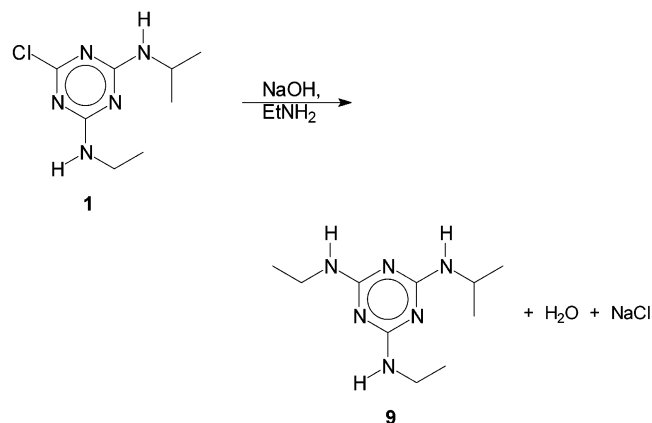


Figure 2. Energy profile obtained for the consecutive addition of IPA followed by NaOH (F(C)1 = IPA feed, F(C)2 = NaOH feed).

Scheme 4. Formation of the tris-triazine side product **9** from **1**



primary interest of this investigation. The main focus of this optimisation was 2-fold. First, it was of interest to determine whether a lower temperature than 30 °C could be used during the second step to reduce possible hydrolysis of the mono-substituted intermediate **3**, particularly at the start of the second addition sequence when the pH of the mixture is relatively high. Second, the objective was to reduce reactor residence times, especially at lower reaction temperatures. In this regard, the time required to complete the reaction after the reagents (amine and base) had been added was of direct interest.

The following addition sequences were thus investigated for the two reaction steps during the synthesis of atrazine:

(A) all the required amine added first, followed by base addition for each reaction step;⁷

(B) all the base added first, followed by addition of the required amine for each reaction step;⁶ and

(C) concurrent addition of amine and base, whilst maintaining a slight amine excess relative to the base.⁸

Addition Sequence A. Consecutive Addition: Amine Before Base. Figure 2 shows the calorimeter output obtained for the consecutive addition of isopropylamine (IPA) followed by base (NaOH) (step 1 of the synthetic procedure).

The drop and rise in the power output by the internal heater during the addition of amine is very sharp, giving almost a square-shaped energy profile. This is typical of reactions where the rate of the chemical reaction is fast and is not mass-transfer limited.⁹ (Small variations in Q_p both before and between feeds are possibly due to the overall heat-transfer coefficient which is, in turn, dependent on the physical properties (heat capacity, viscosity, etc.) of the reactor contents and also on the wetted area (which increases as materials are added to the reactor)). Under these conditions, the reaction is feed-controlled, and the rate of the reaction is equal to the rate of reagent addition. In contrast, the fall and rise of the power output by the internal heater during the addition of NaOH is more rounded, indicating a slight, but detectable, difference between rate of reagent addition and reaction rate. Typical addition rates for the particular experimental setup were IPA at 8.3×10^{-3} mol min⁻¹ and NaOH at 0.01 mol min⁻¹. The total energy released during the addition of IPA and NaOH was 100.4 kJ mol⁻¹ and 84.7 kJ mol⁻¹ of cyanuric chloride, respectively. No attempt was made to proportion the energy between the main reactions involved (IPA with cyanuric chloride and HCl with IPA, or NaOH with the hydrochloride salt of IPA and NaOH with HCl) during either addition.

(6) Messori, V.; Francese, R.; Esposito, R. U.S. Patent 4,275,204, 1981.

(7) Haschke, H.; Schreyer, G.; Schwarze, W.; Suchsland, H. U.S. Patent 4,058,662, 1977.

(8) Baldi, L.; Ferrari, C.; Francese, R. U.S. Patent 4,099,006, 1978.

(9) Singh, J. *Process Saf. Prog.* **1997**, *16*, 225.

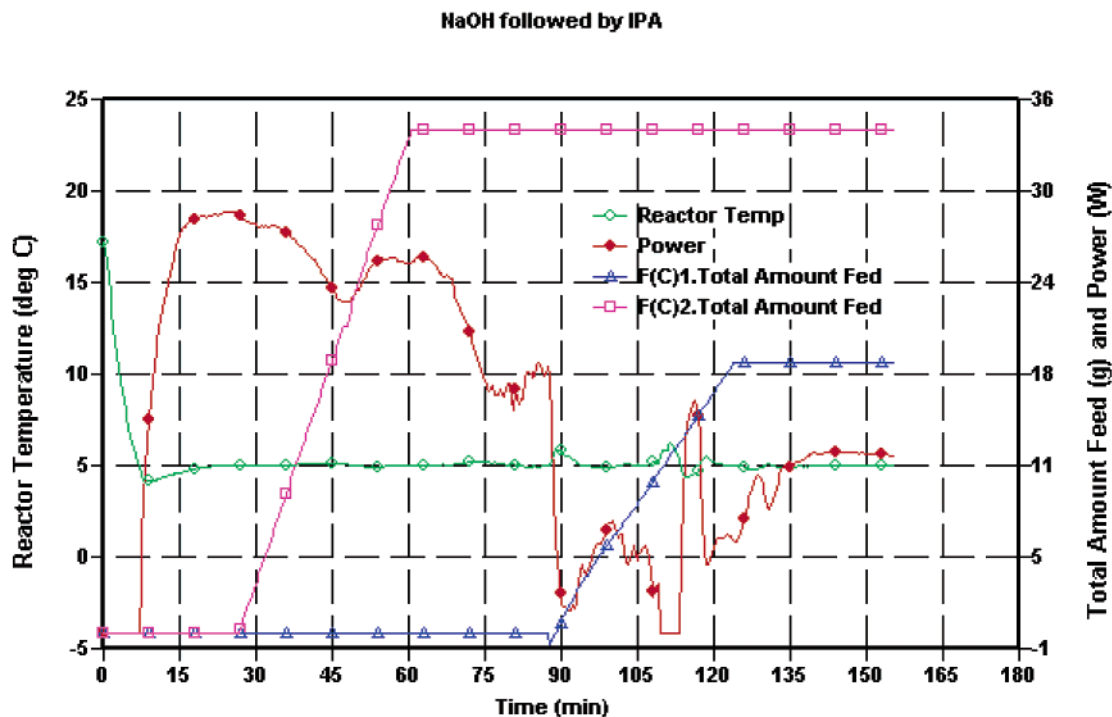


Figure 3. Energy profile obtained for the consecutive addition of NaOH followed by IPA (F(C)1 = IPA feed, F(C)2 = NaOH feed).

The second step of the reaction was then carried out using the same addition sequence as described above, i.e., ethylamine was added first followed by the addition of the NaOH.

Reasonably good results (isolated yields of atrazine and product purities) were achieved using this addition sequence. Typically, yields in excess of 97% (based on the initial amount of cyanuric chloride charged) were obtained with atrazine purities of >98%, provided the rates of reagent addition were slow enough to ensure proper mixing at all stages.

Addition Sequence B. Consecutive Addition: Base Before Amine. Figure 3 shows the calorimeter output obtained for the consecutive addition of first base (NaOH) followed by IPA (Step 1 of the synthetic procedure). The energy output curve obtained for this addition sequence displays a number of undesirable features. First, there is a considerable drop in the power baseline after the addition of NaOH, indicating poor mixing, and hence poor heat transfer for the resultant two-phased reaction mixture. Second, the power output during the amine addition step becomes highly erratic as the amount of amine added increases. The reason for this became apparent when the reactor was opened: large clumps of solid had formed in the reactor, thereby preventing the effective dissipation of heat. (The rates of addition of the two components were similar to that described in the previous experiment.)

After completing the second step of the process, carried out with the same sequence of addition, analytical results obtained confirmed the poor performance of this addition sequence. Typical isolated yields were always low (<80%) with significant amounts of the side products simazine (1.0–3.0%) and propazine (15–20%) being formed. No attempt was made to determine the energy released using this addition sequence.

Addition Sequence C. Concurrent Addition: Amine Kept in Slight Excess Relative to Base. In both steps of this experiment, addition of amine commenced first (at the same approximate addition rates as specified earlier), followed by the addition of base one minute after initiating the addition of amine. At these rates, the addition of amine then terminates prior to that of the base. Figure 4 shows the calorimeter output obtained for the concurrent addition of IPA followed by base (NaOH) (step 1 of the synthetic procedure).

The energy output curve for this addition sequence is very similar to the one obtained for the addition of amine alone (Figure 2). The square-shaped energy profile is again indicative of a dose-controlled reaction rate. Also, there is no evidence of product coagulation interfering with mixing or heat dissipation. The total energy released was found to be $176.1 \text{ kJ mol}^{-1}$ of cyanuric chloride, in good correlation with the consecutive addition of first IPA followed by NaOH.

Analytical results obtained for syntheses carried out using this addition sequence were generally excellent. Isolated yields were typically >97% (based on the initial amount of cyanuric chloride added) with both the simazine and propazine contents of the reaction product being <1.2%.

The results obtained for the two addition sequences A and C indicates improved performance over addition sequence B. This is most probably the result of decreased mixing efficiency upon the addition of large volumes of water prior to the addition of amine. Whilst the sequences A and C give comparable results in terms of yields and quality, sequence C is more time-efficient, provided heat transfer can be properly controlled on larger scales due to the greater instantaneous heat load. Hence, good mixing will also be essential to ensure minimisation of side reactions, particularly the formation of simazine and propazine. Also of interest is

Simultaneous addition of IPA and NaOH

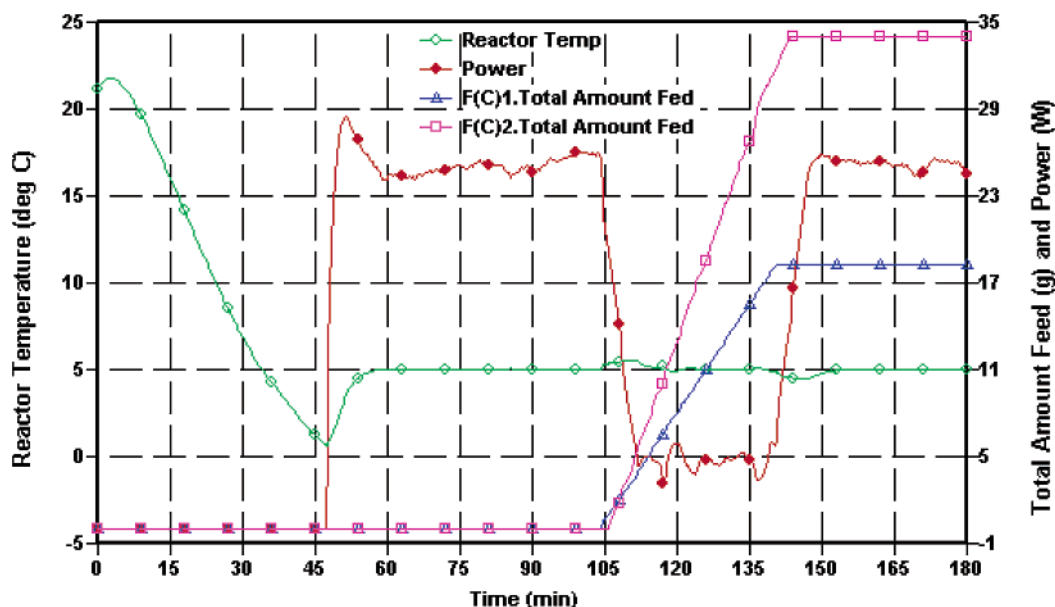


Figure 4. Energy profile obtained for the concurrent addition of IPA and NaOH (F(C)1 = IPA feed, F(C)2 = NaOH feed).

the observation that the reactions require very little post-addition time (ca. 10–15 min) despite the fact that low temperatures are maintained (0 and 15 °C for steps 1 and 2, respectively).

Experimental Section

General. Cyanuric chloride (Degussa, 99%), isopropylamine (Air Products, Ar-grade), ethylamine (BASF, 70% solution in water), toluene (Saarchem, AR-grade), and NaOH (ACE, CP-grade) were used for synthetic reactions and were used as received. Atrazine (Institute for Organic Industrial Chemistry (IOIC), 98.7%), 2-hydroxyatrazine (Riedel de Haen, 94.7%), 2-hydroxysimazine (Industrial Analytical, 98.5%), propazine (IOIC, 99.7%), and simazine (IOIC, 99.0%) were used as standards in HPLC and were used as supplied.

HPLC Analyses. HPLC analysis was performed on a Hewlett-Packard Series 1100 HPLC instrument, equipped with a dual pump system, variable UV–visible wavelength detector, and auto sampler unit and driven by HP Chemstation LC software. The following conditions were used for the quantification of all five components normally found in atrazine samples:

injector volume	10 μ L
column	Waters Symmetry Shield RP ₈ 4.6 mm \times 250 mm
mobile phase	50:50 acetonitrile/water mixtures
flow rate	0.5 mL/min
total run time	30 min
UV detector wavelength	240 nm

General Method for Atrazine Synthesis. A 500-mL jacketed glass reactor, fully baffled and mechanically agitated and equipped with a water-cooled condenser, was used for syntheses. A 4.50-cm diameter, four-bladed stainless steel impellor was used for agitation at ca. 600 rpm. Circulating

a 20% ethylene glycol solution through the external heating/cooling jacket of the reactor controlled the reaction temperature. For the first step (reaction of cyanuric chloride with IPA), the circulating bath temperature was set to 0 °C to ensure a reaction temperature of <5 °C. The reactor was then charged with toluene (175 g, 1.90 mol) and cyanuric chloride (60.5 g, 0.328 mol). The stirrer was switched on and set to 600 rpm and the mixture allowed to equilibrate for 15 min. IPA (19.2 g, 0.325 mol), as a 70% aqueous solution, and NaOH (28.9 g, 0.325 mol) in water (64 mL) were then added at the required rate (either by means of a dropping funnel or syringe pump) and required addition sequence (as described in the text) such that the reaction temperature remained below 5 °C. The circulating bath temperature was then adjusted to 15 °C, and after equilibration, ethylamine (21.4 g, 0.333 mol) and NaOH (29.8 g, 0.336 mol) were added as before, ensuring the reaction temperature did not exceed 20 °C. After complete addition of the amine and NaOH, the reaction mixture was allowed to stir for a period of 15 min before toluene was removed by vacuum evaporation. Water (400 mL) was then added to the residue to dissolve NaCl, the remaining solid filtered under vacuum, washed with water, and dried between 90 and 100 °C to afford atrazine as a white solid, mp 174–179 °C (lit.,¹⁰ mp 175 °C).

Preparation of Atrazine Using the Reaction Calorimeter. Reaction calorimetry was performed on a Similar, nonisothermal reaction calorimeter (Hazard Evaluation Laboratories). The calorimeter, fitted with a 500-mL stainless steel (SS316) Buchi reactor with bottom drain, a Leeson magnetic driven impellor, and Julabo F32 heater/chiller unit, and two Prominent gamma G/4b metering pumps, was controlled using HEL Winiso software. The circulator (reactor jacket) temperature was set to –5 °C, and the reactor was loaded

(10) See: <http://physchem.ox.ac.uk/MSDS/AT/atrazine.html>.

with toluene (280 g, 3.04 mol) and cyanuric chloride (39.8 g, 0.216 mol). The stirrer was switched on and set to 600 rpm, and the reactor temperature was adjusted to 0 °C by means of an internal calibration rod heater with a 25-mm hot-end before initiating the addition sequence from the Winiso control software. Details of the addition sequences are given in the text, as is information on the yields and purities of atrazine obtained in each case.

Conclusions

The results of this investigation have shown that reaction calorimetry and, in particular, power compensation calorimetry can rapidly and efficiently provide valuable information regarding such issues as reaction rates, mixing efficiency, mass- and heat-transfer problems of reaction systems comprising more than one phase (liquid/liquid/solid). In our case,

such information has led to the rapid determination of optimal addition sequences and rates for the production of 1,3,5-triazine compounds such as atrazine.

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