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Application of reaction calorimetry toward understanding the large scale chemistry of ethyl diazoacetate

Jerry D. Clark^{*}, Ajit S. Shah, James C. Peterson, F. Michael Grogan, Stephanie K. Camden

Monsanto Co., 800 N. Lindbergh Blvd., St. Louis, MO 63167, USA

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Abstract

Ethyl diazoacetate is an important organic chemistry synthon, but its use as an industrial intermediate is limited due in part to the safety concerns associated with its instability and high reactivity. Reported are the reaction calorimetry results obtained from a new ethyl diazoacetate preparative method, the results from its use in a novel, exothermic reaction and the application of this data toward process development, a successful pilot plant campaign and full-scale reactor design. The results indicate that, given the proper engineering design, in situ preparation and use of ethyl diazoacetate solutions can be used at production scale without significant risk. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Ethyl diazoacetate; Reaction calorimetry; Process development; Beta keto ester; Hazards analysis

1. Introduction

Ethyl diazoacetate is an important two-carbon synthon for organic chemistry [1–13], but its use as a large-scale, industrial commodity is limited due to safety concerns. The material safety data sheet [14] indicates that this reagent is shock sensitive, flammable and toxic. Chemically, diazocarbonyl compounds are also known to be very reactive [1–13]. Thus, when ethyl diazoacetate was envisioned as a potential starting material for the industrial preparation of a novel Monsanto agrochemical, a risk assessment study of its preparation and use was undertaken.

2. Results

The thermal stability characteristics of ethyl diazoacetate were investigated by accelerated rate calorimetry (Fig. 1) and differential scanning calorimetry (Fig. 2). These results correlated well [15,16]. Onset self-heating temperatures were found to be 100 and 98°C, respectively, and were not affected greatly by dilution. However, the maximum temperature rise rate was greatly affected by dilution. Measured values ranged from 0.3°C/min for 11 wt.% ethyl diazoacetate to 129°C/min for 90–95% ethyl diazoacetate. The calculated heat of reaction was –178 kJ/kg from the ARC experiments and –168 kJ/kg from the DSC experiments. Asymmetry in the DSC curve indicates that the decomposition of ethyl diazoacetate is a complicated series of reactions.

Detonation studies [16] of ethyl diazoacetate (Fig. 3) concluded that at concentrations approaching

^{*} Corresponding author. Fax: +1-314-694-1621.

E-mail address: jerry.d.clark@monsanto.com (J.D. Clark).

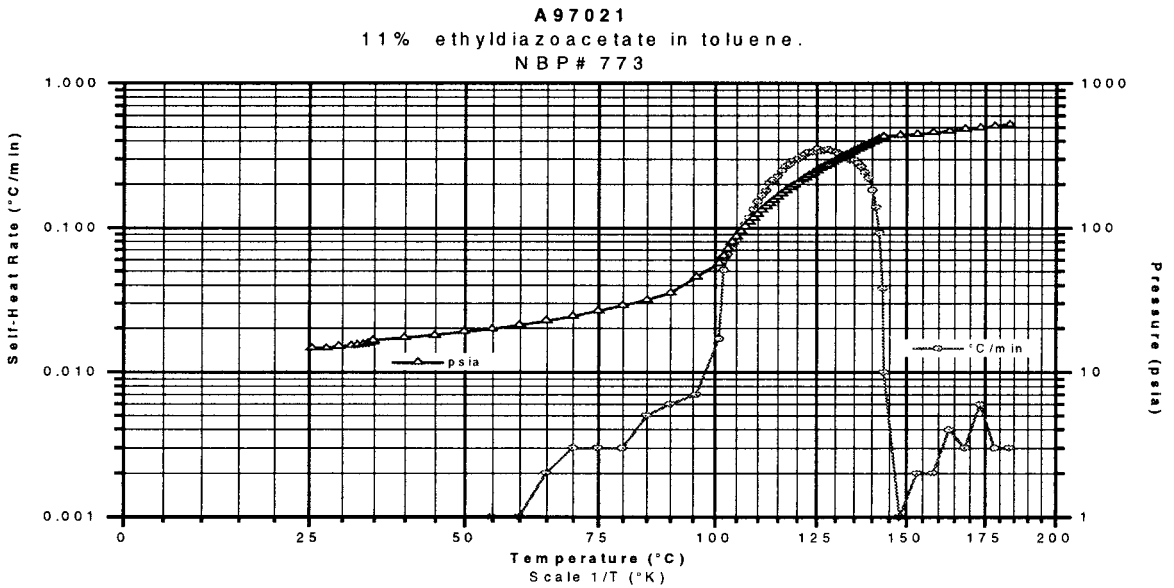


Fig. 1. ARC data for 11% ethyl diazoacetate solution in toluene.

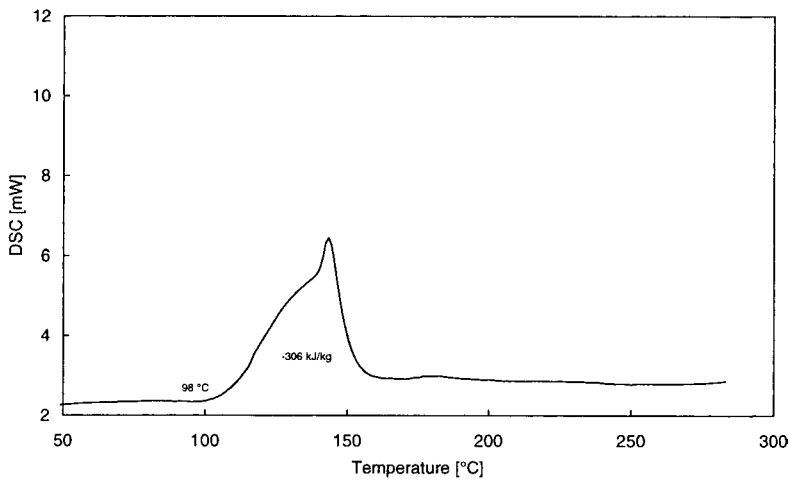


Fig. 2. DSC data for 20% ethyl diazoacetate solution in toluene.

100%, the booster initiated shock wave was not substantially supported by ethyl diazoacetate. The tube deformations patterns and a fast decrease to zero wave velocity *did not indicate detonation* of this compound under the test conditions. The impact of these results on scaling implies that the *ethyl diazoacetate mixture can be used at a production*

scale without significant risk of a condensed phase detonation.¹

¹The runaway and vent behavior of this system was also studied. Methods employed, but not discussed in this report, were controlled runaway and vent monitor experiments, and vent calculations based on a homogeneous vessel model. See [16].

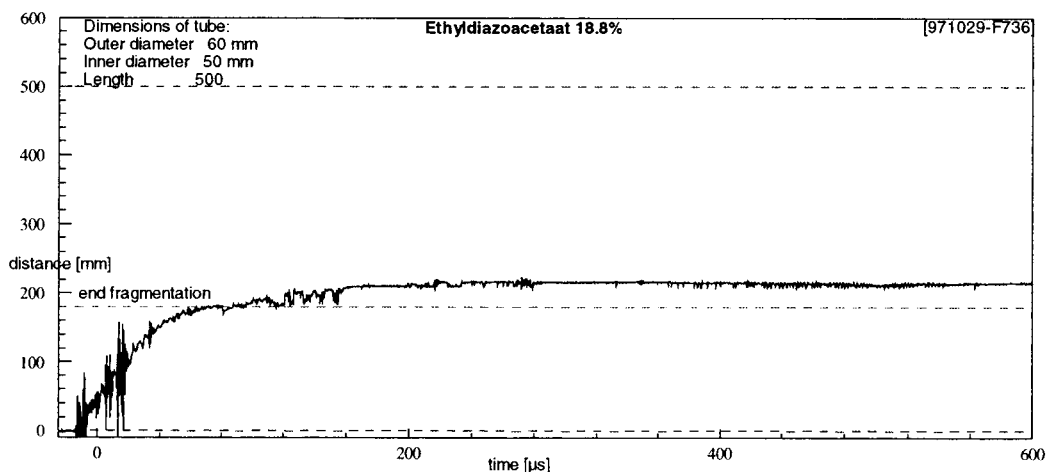
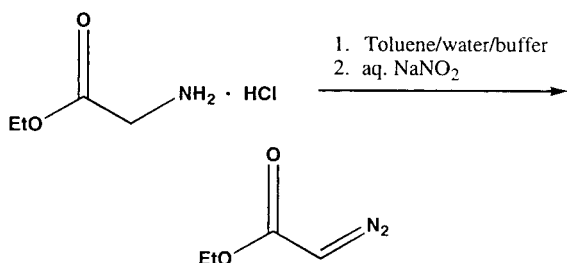


Fig. 3. Ethyl diazoacetate detonation studies. Shock wave velocity pattern along the tube.

Concomitant with these studies, work directed toward development of a new preparation of ethyl diazoacetate from ethyl glycinate hydrochloride was well underway. Published procedures [17–20] were undesirable because these methods employed halogenated solvents and gave rise to lower-than-desired yields and product quality. Thus, extensive work within Monsanto led to the discovery of a new ethyl diazoacetate preparation method [21]. This new method consistently gives excellent quality ethyl diazoacetate in yields of 89–91%. The product is isolated as a solution in a hydrocarbon-based solvent such as toluene at concentrations as great as 30 wt.%.



The Mettler RC1 Reaction Calorimeter study of this preparation measured a moderate heat of reaction of -96 kJ/g mol of ethyl glycinate hydrochloride (-66 kJ/kg of solution), and a mild to moderate adiabatic temperature increase of 31°C (Fig. 4). Heat accumulation after complete aqueous sodium nitrite addition was measured as 2 kJ/kg . This repre-

sents only a 1°C adiabatic temperature potential [22,23]. The data also indicated that the reaction was essentially complete 15–30 min after dosing was stopped.

The next objective was to model a new industrial application of ethyl diazoacetate, the preparation of a specific beta keto ester. However, there was concern about the thermal stability of the specific aldehyde to be utilized. This prompted further investigation (see Footnote 1). Accelerated rate calorimetry (Fig. 5) and differential scanning calorimetry (Fig. 6) on the aldehyde correlated well [15,16]. The onset self-heating temperatures were found to be 105 and 110°C , respectively, with a second, less energetic, exothermic reaction noted in both experiments. The accelerated rate calorimetry indicated that this second reaction began at approximately 250°C , whereas differential scanning calorimetry indicated that this reaction began at 305°C . Nevertheless, the trends are similar. The calculated heats of reaction for both exothermic reactions from the DSC experiment were -373 and -213 kJ/kg , respectively [16].

The detonation properties and thermal stability of a mixture of ethyl diazoacetate and the aldehyde were also measured at a mole ratio of 1.4–1, respectively. Process feasibility studies indicated that this ratio denoted the optimum reagent stoichiometry for the beta keto ester preparation; therefore, this ratio represented the highest hazard potential before the introduction of catalyst. The detonation test (Fig. 7)

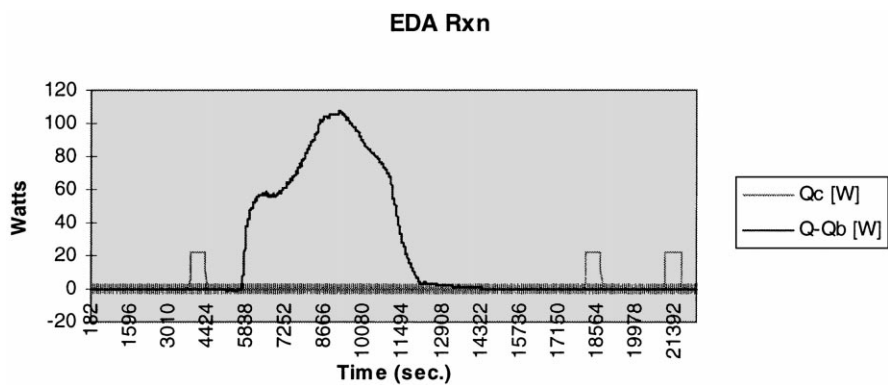


Fig. 4. Ethyl diazoacetate preparation. RC1 calorimetry data, watts vs. time.

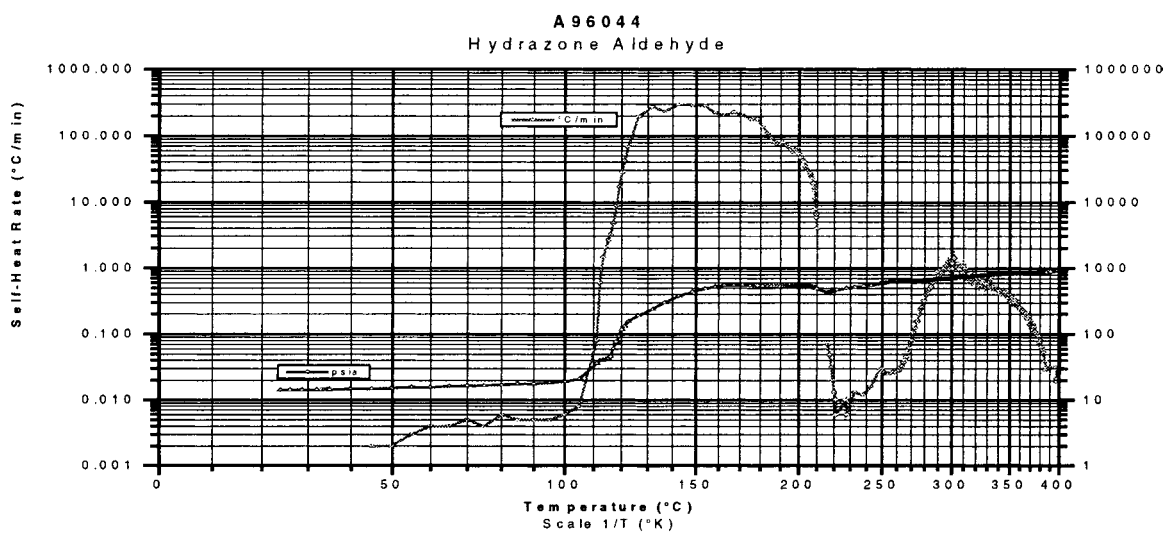


Fig. 5. ARC data for the aldehyde.

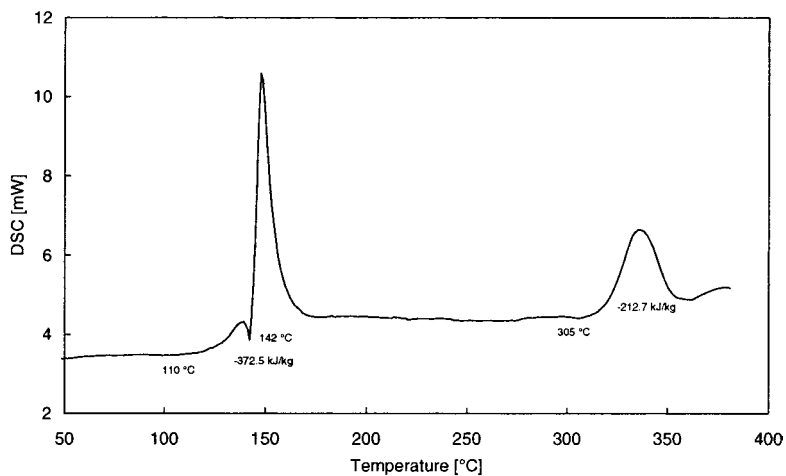


Fig. 6. DSC data for the aldehyde.

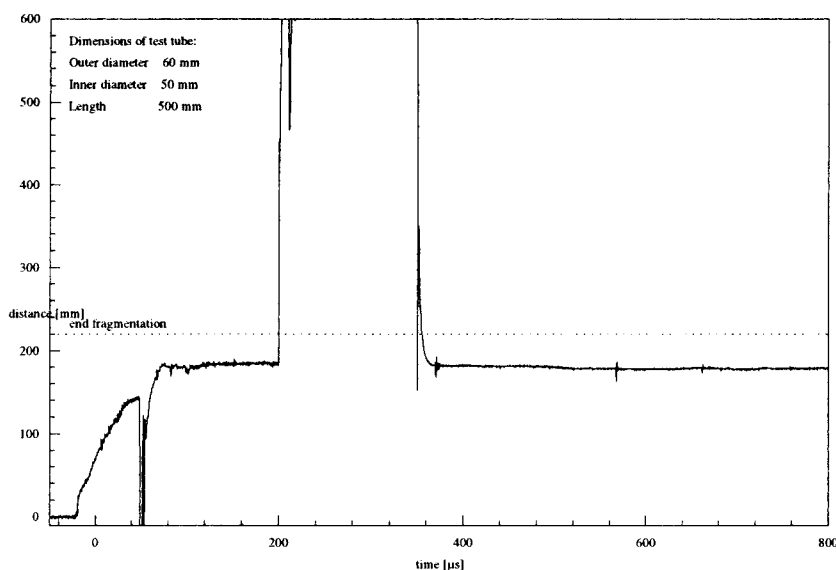
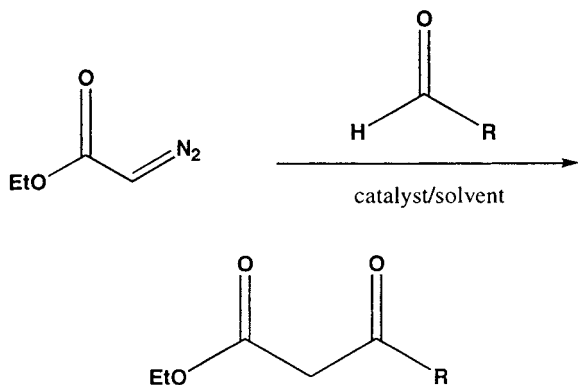


Fig. 7. Detonation studies for a 1.4:1 ethyl diazoacetate and aldehyde mixture. Shock wave velocity pattern along the tube.

once again implied that the mixture can be used at a production scale without significant risk of a condensed phase detonation [16]. The tube deformation patterns and a fast decrease to zero wave velocity did not indicate detonation of this compound under the test conditions. The apparent peaks in the signals reflect noise in the test and do not suggest detonation properties. Differential scanning calorimetry (Fig. 8) of the mixture measured a heat of reaction of -259 kJ/kg with a self-heating onset temperature of 94°C .



Having determined the thermal properties and detonation risk of all the reaction components save

the catalyst, the research now turned to a study of the beta keto ester preparation itself [1–13,24,25]. Mechanistically, the reaction proceeds by way of Lewis acid catalyzed activation followed by reversible addition. The intermediate formed undergoes 1,2-hydrogen migration with loss of nitrogen to yield the desired beta keto ester [1–13]. Typically reactions of diazocarbonyl compounds with aldehydes are carried out in a halogenated solvent with tin(II) chloride [24] or some other Lewis acid [1–13,25] as catalyst, but, as mentioned above, the use of a halogenated solvent was prohibited. Thus, results of our extensive process feasibility studies [26] found the reaction to proceed very effectively in a hydrocarbon-based solvent such as toluene. These studies also included a survey of more than 20 Lewis acids. Once the optimum Lewis acid and solvent was determined, an investigation on the effect of payload was also carried out. No effect on yield and product quality was observed for payloads as great as 20 wt.% aldehyde. However, a measurable effect on cycle time was realized for higher payloads due to insufficient mass transfer.

RC1 calorimetry study of the beta keto ester preparation began with a simple “baseline” experiment. The Lewis acid and aldehyde were added sequentially to a solution of ethyl diazoacetate. Although this

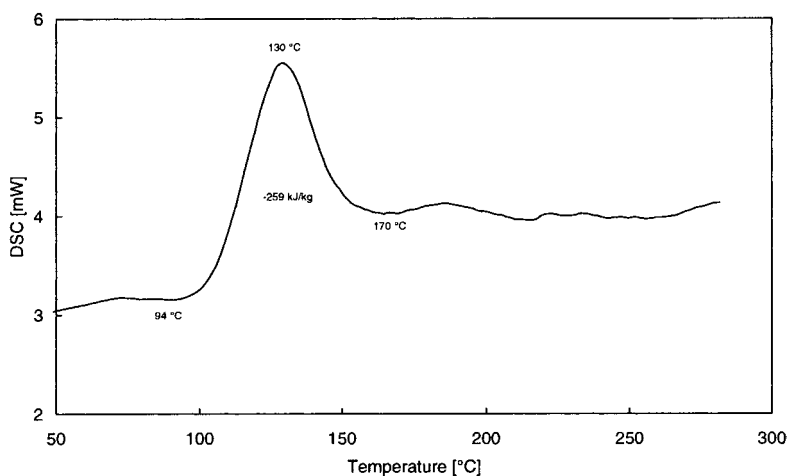


Fig. 8. DSC data for an ethyl diazoacetate and aldehyde mixture.

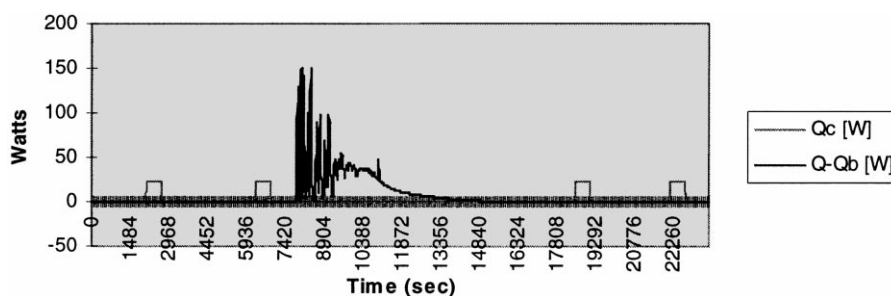
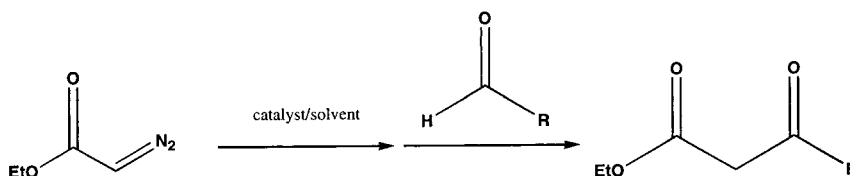


Fig. 9. Beta keto ester preparation. Calorimetry data for sequential addition method, watts vs. time.

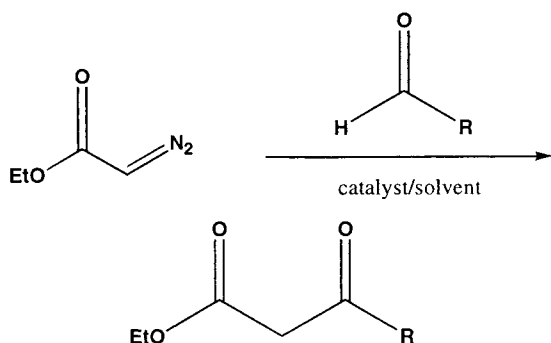
procedure would not be practised in manufacturing, this method of reagent addition minimized the number of chemical and/or physical transformations occurring concomitantly, allowing for better evaluation of each individual contribution to the heat of reaction.

In this experiment (Fig. 9), it was found that the dissolution of the selected Lewis acid catalyst into the

ethyl diazoacetate solution was a weakly endothermic process with a heat of reaction of 1.6 kJ/kg and an adiabatic temperature decrease of 1.2°C. The addition of aliquots of the solid aldehyde to this mixture was, however, very exothermic. The heat of reaction was measured as -155 kJ/kg with an adiabatic temperature increase of 101°C. Additionally, it was observed



that approximately 3 h was required for the reaction to go to completion after all of the aldehyde had been charged. This translates to an adiabatic temperature potential [22,23] of approximately 35°C. Thus, the RC1 calorimetry results clearly indicated that if cooling is lost in a reactor during the course of the aldehyde addition and near adiabatic warming occurs, the temperature within the vessel could approach the onset self-heating temperature of both reactants. This is further complicated by the fact that the rate of ethyl diazoacetate degradation (with nitrogen gas evolution) in the presence of the catalyst increases dramatically as the reaction medium warms to temperatures approaching 20°C! Independent experiments on this degradation behavior showed that greater than 50% of the ethyl diazoacetate was lost in less than a 30 min period at ambient temperature.



Having investigated the “baseline” heat generation profile of this reaction, studies now turned toward minimizing the risk of a runaway reaction by optimizing the dosing conditions. Toward this end,

the simultaneous addition of both the catalyst and the aldehyde to the ethyl diazoacetate solution was assessed. This method of reagent addition did indeed “smooth out” the heat generation profile. It also provided for safer operation because the dosing of the catalyst and aldehyde could be suspended in the event of an emergency such as loss of reactor cooling. Fig. 10 represents the heat release and heat accumulation for a 15 wt.% aldehyde reaction with an addition time of approximately 2.5 h. The heat of reaction was measured as -248 kJ/g mol aldehyde (-205 kJ/kg mixture), with a corresponding adiabatic temperature increase of $+127^\circ\text{C}$.

Analysis of this thermal data indicates that there was 21 kJ/kg of heat accumulation after complete aldehyde addition. This translates to approximately a 13°C adiabatic temperature potential [22,23] or a 22°C decrease from the aforementioned baseline calorimetry study. Furthermore, analysis of the data indicated that employing this method of simultaneous addition decreased the residence time of the unreacted materials from the 3 h observed in the baseline study to approximately 50–60 min.

Transfer of this technology to the pilot plant [27] proceeded smoothly. The ethyl diazoacetate preparation was scaled to 200 times the size of the RC1 calorimetry studies. A 100 gallon, glass-lined Pfaunder reactor with 50% ethylene glycol cooling was employed. It was found that an average glycol temperature of -8°C was necessary for the chemistry to proceed in the desired fashion. This cooling value essentially confirmed the -9°C value predicted from calculations based on the calorimetry data. A moderate difference was found, however, in the residence time required for complete reaction after aqueous

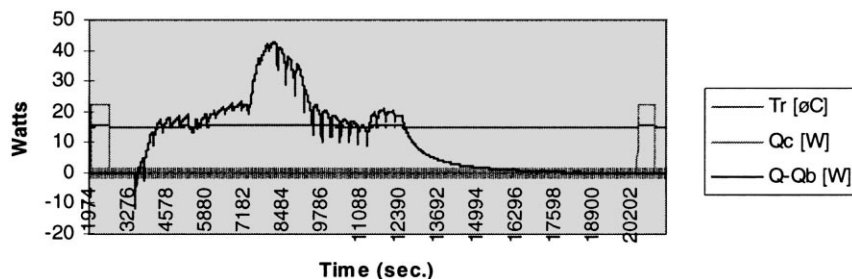


Fig. 10. Beta keto ester preparation. Simultaneous addition method, watts vs. time.

sodium nitrite addition. Stirring for 1 h was required, rather than the 15–30 min observed in the calorimetry studies. This was attributed mainly to the differences between the agitation efficiencies of the two reactors.

Extension of the RC1 calorimetry data to preparation of the desired beta keto ester on a pilot scale was also found to be very efficient; however, at this scale aliquot dosing of the solid aldehyde “by hand” did provide a challenge for the Monsanto operators. The heat of reaction vs. time profile for one of the pilot runs is shown in Fig. 11. The disordered curve, designated line 1, represents the actual dosing profile. The corresponding calculated heats of reaction from each dose are shown. Curve 2 is the corresponding fitted line. This curve is the base used for all further calculations shown.

Monsanto is now in the process of transferring this technology to full scale manufacturing. The data described have been extremely useful for determining future direction. For example, Fig. 11 also depicts the aforementioned heat of reaction vs. addition time profiles extrapolated for full scale reactor design. The curves given are based on calculations employing the same reactor with 50% ethylene glycol as coolant. Curve 3 depicts the heat generation profile for an 8 m³ reactor with a -10°C jacket setting. Curve 4 represents

the dosing time required for the same reactor with -25°C jacket temperature. Curve 5 displays the dosing time required for -30°C cooling and the straight line, curve 6, is a hypothetical cooling in which it is assumed that the heat generation rate is averaged out (i.e., no peak). This last curve, from a safety perspective, represents the optimum conditions for dosing. It depicts a feed controlled or pseudo zero order chemical process in which the heat generation rate is directly proportional to the feed rate. Termination of the feed then gives rise to near zero heat flow, with no accumulation [22,23,28]. As has been noted in the literature, these reaction conditions have an additional attraction. They often are the optimum conditions for “quality and yield. . . because the kinetics of the desired reaction are strongly favored with good selectivity [22,23].”

Having completed the initial stage of pilot studies and while implementing technology transfer, research continues toward further optimization of this chemistry. In an effort to attain the pseudo order reaction conditions just described, our research has returned to the RC1 Reaction Calorimeter. Fig. 12 represents the latest data acquired in pursuit of this goal. In this particular experiment, the reactor containing cooled toluene was simultaneously charged with three inde-

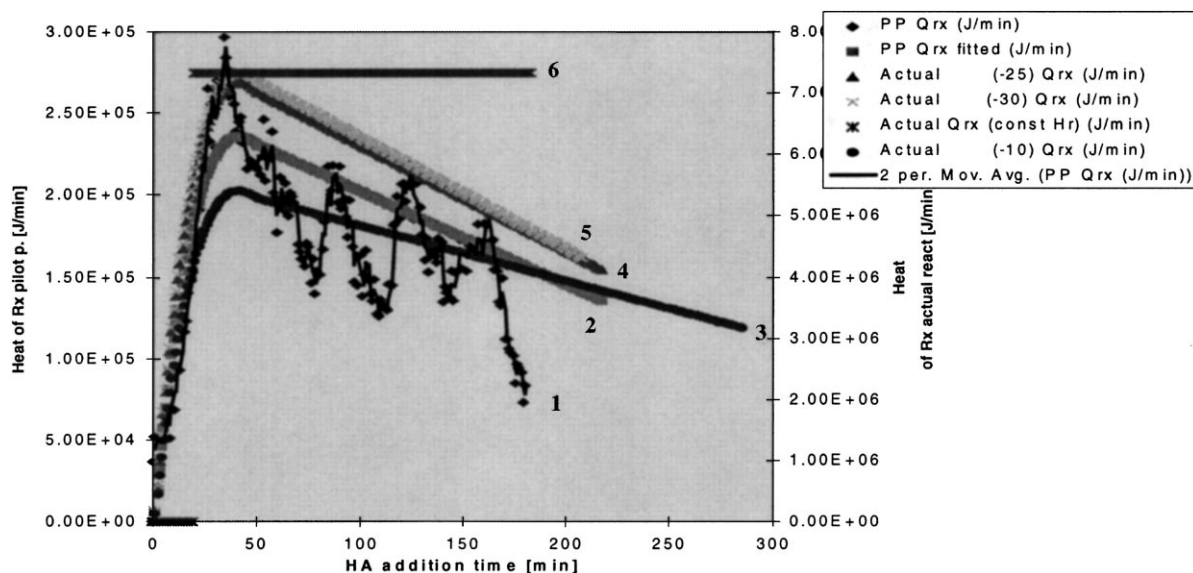


Fig. 11. Beta keto ester preparation. Pilot plant studies and full-scale reactor cooling vs. dosing time.

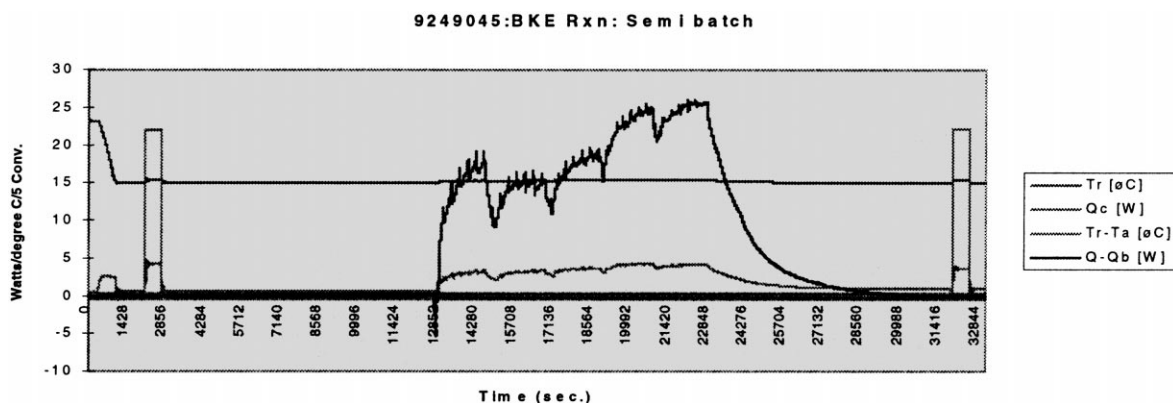


Fig. 12. Semi-batch beta keto ester preparation. Heat release and accumulation data, watts vs. time.

pendent streams: a Lewis acid solution, an ethyl diazoacetate solution and a stoichiometric amount of aldehyde. All reagents were charged over a 2.75 h period, but the aldehyde was added in equal portions every 5 min. The four larger breaks in the heat generation profile represent recharging the catalyst solution stream. Note the rate of heat generation now approaches the straight line or the feed controlled reaction conditions described above. This mode of reagent addition and a method for controlled solid aldehyde addition [29,30] will be the focus of future studies.

3. Conclusion

Thermal stability, reaction calorimetry and pilot plant studies of a new ethyl diazoacetate preparative method and reaction were completed. The results indicate that, given the proper engineering design, in situ preparation and use of ethyl diazoacetate solutions in the preparation of a beta keto ester can be used at a production scale without significant risk.

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