ELSEVIER Thermochimica Acta 255 (1995) 9–16

thermochimica
acta

Reaction calorimetry at low temperatures

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Received 20 September 1994; accepted 4 October 1994

Abstract

A new heat flow reaction calorimeter for use at low temperature and some applications of this device are described. Isothermal and temperature-programmed experiments can be carried out down to −90°C with this calorimeter. These characteristics make the calorimeter especially useful for safety assessment and optimization of chemical processes under low temperature conditions.

Keywords: Low temperature; Reaction calorimetry; Safety; Thermal safety

1. Introduction

A knowledge of thermal properties is necessary for the development and design of safe chemical processes. Reaction calorimetry is an appropriate engineering tool for the determination of dissipated heat release rate, enthalpy of reaction and thermal accumulation. The utilization of reaction calorimetry is common practice today, but the equipment commercially available allows operation only in the temperature range between −30 and +250°C.

In pharmaceutical production, some reactions are performed at low temperature (down to −90°C). For that purpose, a low temperature reaction calorimeter has been developed in our laboratory.

The aim of this paper is the presentation of experimental results and of the software used for data evaluation.

SSDI 0040-6031(94)02141-4

2. Calorimetric principle

The reaction calorimeter for low temperatures works according to the heat flow principle [1,2]: the temperature difference $\Delta T = T_R - T_J$ between the contents of the reactor R and the jacket J is continuously measured. A fast thermostat regulates the jacket temperature for a rapid exchange of heat across the reactor wall, so that the entire heat exchanged across the reactor wall is measured. This heat release rate is proportional to the measured temperature difference. The proportionality factor (U.A) has to be determined by calibration, which is done simply by switching on a built-in electrical resistance heater with a known power production and measuring the resulting temperature difference. In this way, the heat flow rate across the reactor wall Φ_{ex} is given by Eq. (1)

$$\Phi_{ex} = U.A.(T_R - T_J) \tag{1}$$

where the proportionality factor is the coefficient of heat transfer.

The determination of the heat release rate is based on the heat and mass balances for the reactor. When a reaction is carried out below the boiling point of the reaction mixture, the overall heat flow rate balance is

$$\Phi_r = \Phi_{ex} + \Phi_{accu} + \Phi_{dos} + \Phi_{loss} - \Phi_c \tag{2}$$

where Φ_r is the reaction heat flow rate, Φ_{accu} is the heat accumulation rate in the reaction mass through temperature increase, Φ_{dos} is the heat flow rate due to the dosage of reactants, Φ_{loss} is the heat flow rate dissipated through the internal fittings, and Φ_c is the heat flow rate supplied by calibration heating (electrical power).

3. Instrument

The basic requirements of a reaction calorimeter appropriate for safety assessment and process development applications include operation under isothermal and temperature-programmed conditions, simultaneous or sequential additions of several chemical feed streams, and efficient and adjustable agitation of the reaction mixture.

The working principle of this calorimeter is shown in Fig. 1. A further, detailed constructional diagram is shown in Fig. 2.

The calorimeter consists essentially of an agitated glass reaction vessel A with a jacket containing a heat transfer medium, a heat exchange loop in which the heat transfer medium is circulated at a very high rate, thanks to a pump B, and a temperature controller. The chosen heat transfer fluid is methylcyclohexane. The melting point of this liquid is very low (−126.4°C) and its viscosity allows operation at low temperatures. Moreover, its boiling point is relatively high (101°C). In this way, the reaction calorimeter can be operated over a wide temperature range (between −90 and +40°C).

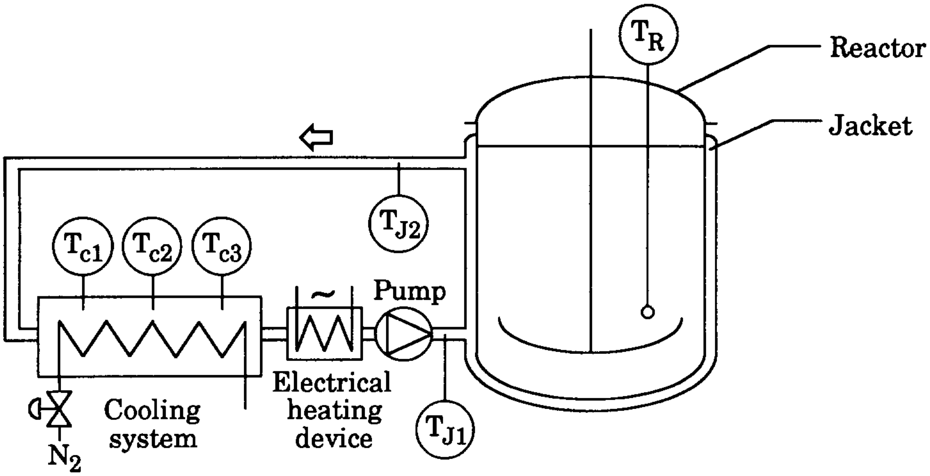
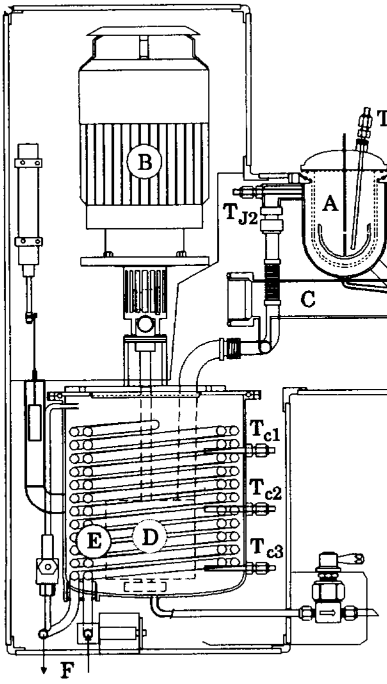


Fig. 1. Working principle of the reaction calorimeter.

The temperature in the calorimeter is controlled through simultaneous cooling and heating of the circulating methylcyclohexane. The temperature of the circulation loop ($T_{c_1-c_3}$) is adjusted by varying the feed rate of liquid nitrogen that



A	**: Reactor**
B	**: Methylcyclohexane pump**
C	**: Electrical heater**
D	**: Methylcyclohexane reservoir**
E	**: Heat exchanger N_2/Methylcyclohexane**
F	**: Liquid nitrogen inlet and outlet**
T_{J1}	**: Temperature of the cooling medium inlet (jacket)**
T_{J2}	**: Temperature of the cooling medium outlet (jacket)**
$T_{c1\text{-}c3}$	**: Temperature sensors in the methylcyclohexane reservoir**

Fig. 2. Detailed constructional diagram of the reaction calorimeter.

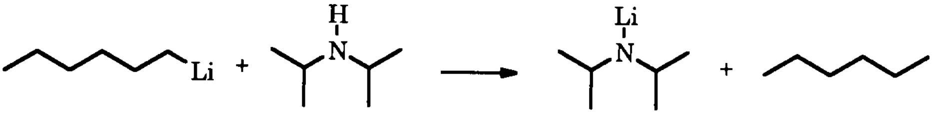


Fig. 3. Synthesis of lithium diisopropylamide.

circulates in a spiral tube E immersed in the methylcyclohexane reservoir D. The system is buffered by heating from an electrical resistance heater C in order to fine-tune the reaction temperature. A PI (proportional/integral) algorithm is used for the control of the cooling/heating system.

The temperature of the contents of the reactor T_R is measured directly by a Pt-100 sensor. The jacket temperature T_J is calculated as the average of the temperatures at the inlet and the outlet for the cooling medium

$$T_J = (T_{J_2} + T_{J_1})/2 \quad (3)$$

The useful volume of the reactor is between 50 and 300 ml. The observed detection threshold of this reaction calorimeter is 0.25 W.

All functions of the calorimeter are operated by a personal computer (IBM PC compatible). The microprocessor controller comprises a digital interface controller (I/O). Communication between the computer and titration devices is provided by RS232 serial ports.

A cooled storage tank is available beside the reaction vessel in order to store a thermally sensitive reactant. This reactant can then be dosed into the reactor during the course of a chemical reaction.

4. Computer software

Computer software was written to facilitate convenient interaction between the operator and the reaction calorimeter. All operations and temperatures during the

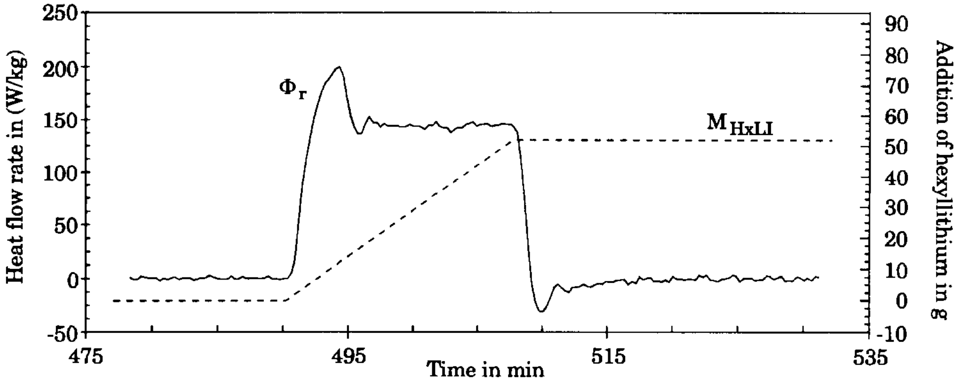


Fig. 4. Rate of heat production for the synthesis of lithium diisopropylamide.

progress of the reaction are graphically displayed. The software allows the adjustment of the regulating parameters. Moreover, additions of reactants with a dosimeter, temperature ramps and calibrations can be monitored with this program. The data are saved on the hard disk of the computer with a time interval between 1 and 20 s.

Evaluation of the experiments is carried out with evaluation software developed by our laboratory for the Contraves Contalab reaction calorimeter. This software allows the determination of the various parameters necessary for the safety assessment of a chemical process [3].

The standard curves, such as those of reactant dosage, reaction temperature and heat flow rate profile, are represented clearly by a graphical display. Furthermore, the thermal accumulation is determined as a function of the extent of reaction. Accumulated heat, adiabatic temperature increase and MTSR (Maximal Temperature that can be reached by the Synthesis Reaction) are routinely calculated and plotted. Thus, the safety assessment of a chemical process is qualitatively improved and technically simplified.

Some of the outstanding characteristics of this software are

(1) compliant editing of the process data and physical constants (i.e. dosage and specific heat capacities) at all stages of the evaluation;

(2) easy graphical setting of the baseline by means of a zoom function;

(3) all measured data curves (e.g. temperatures and mass of added reactants) can be superimposed during the evaluation, allowing better definition of the baseline;

(4) weighting of the calibration factors over an evaluation range according to weight of dosage, time or temperature.

5. Examples

5.1. Synthesis of lithium diisopropylamide

Polar organometallic compounds are indispensable for the synthetic chemist. These reagents are simple to prepare with high specificity and yet react quite easily with a great diversity of substrates. Lithium diisopropylamide (LDA) is a useful, relatively non-nucleophilic strong base. It can be used as a single electron donor or as a hydride donor. LDA is prepared by the reaction of alkyllithium on diisopropylamine [4–6]. A hexyllithium solution was used for the synthesis [7]. The stoichiometric equation of the synthesis is shown in Fig. 3.

5.2. Mode of operation

Tetrahydrofuran and diisopropylamine were introduced into the reactor, and this mixture was cooled to $-40°C$. A first calibration of the reaction calorimeter was performed, and a 30% hexyllithium solution ($T = 20°C$) was added over 20 min. After a stirring period of 20 min, a second calibration was carried out.

Table 1
Synthesis of LDA: heat of reaction

	$\Delta_r Q$/(kJ mol^{-1})
Experiment 1	-145.5
Experiment 2	-146.9
Experiment 3	-145.7
Average	(-146.0 ± 0.9)

5.3. Results

The measured heat flow rate Φ_r and the added mass of hexyllithium solution M_{HxLi} are shown in Fig. 4. The reaction is almost wholly controlled by the addition of the reactant. The measured values of the heat of reaction are summarized in Table 1.

5.4. Preparation of metallated 2,1,3-benzoxadiazole

Metallated 2,1,3-benzoxadiazole is an important intermediate compound for pharmaceutically active dihydropyridine derivatives. These latter compounds are effective vasodilators and antihypertensives.

The metallated intermediate is prepared by the reaction of 2,1,3-benzoxadiazole with an organic base, e.g. lithium diisopropylamide [8]. The reaction is preferably carried out in a solvent which exhibits aprotic behaviour towards very strong bases. This solvent is usually a polar solvent such as tetrahydrofurane. Appropriate reaction temperatures are between -50 and -100°C. The reaction must be performed under anhydrous conditions and preferably under an inert atmosphere. The stoichiometric equation of this synthesis is shown in Fig. 5.

5.5. Experimental

The previous reaction mixture (lithium diisopropylamide) was cooled below -70°C. After a further calibration, a solution of 2,1,3-benzoxadiazole in tetrahydrofurane ($T = -15$°C) was added to the reactor over 13 min. After a stirring period of 20 min, a last calibration of the calorimeter was performed.

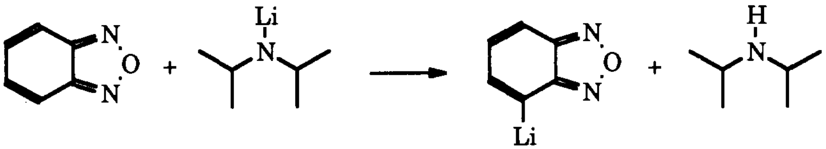


Fig. 5. Synthesis of metallated 2,1,3-benzoxadiazole.

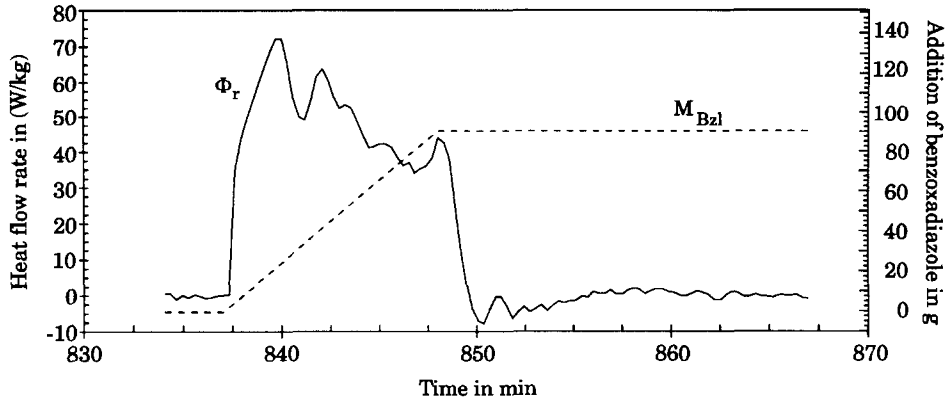


Fig. 6. Rate of heat production for the synthesis of metallated 2,1,3-benzoxadiazole.

Table 2
Synthesis of metallated 2,1,3-benzoxadiazole: heat of reaction

	$\Delta_r Q$/(kJ mol^{-1})
Experiment 1	−49.2
Experiment 2	−49.4
Experiment 3	−50.1
Average	(−49.6 ± 0.5)

5.6. Results

The measured heat flow rate Φ_r and the added mass of 2,1,3-benzoxadiazole solution M_{Bzl} are shown in Fig. 6. The reaction starts atwith the beginning of the addition and is essentially controlled by this dosage. The measured values of the heat of reaction are summarized in Table 2.

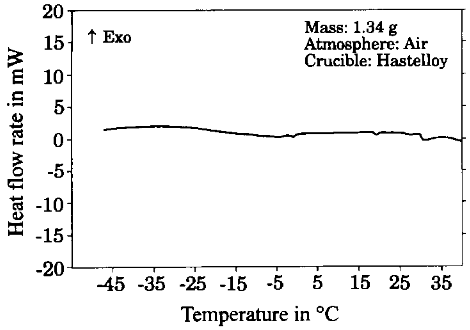
5.7. Thermal stability of the reaction mixture

The thermal stability of the reaction mixture was investigated with a commercial low temperature Calvet calorimeter, the Setaram BT 2.15D. The experimental results of a study of the thermal stability of the reaction mass after the additions of hexyllithium and benzoxadiazole are shown in Figs. 7 and 8.

No exothermic signal relevant to safety was observed during these dynamic experiments (scan rate 0.1°C min^{-1}).

6. Conclusions

This work shows that the new reaction calorimeter allows the measurement of heats of reactions under low temperature conditions. The field of application of this



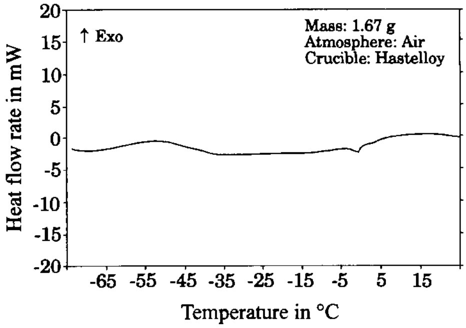


Fig. 7 (left). Dynamic test of thermal stability of the reaction mixture after complete addition of hexyllithium.

Fig. 8 (right). Dynamic test of thermal stability of the reaction mass after complete addition of the benzoxadiazole.

device, together with micro-methods, is the assessment of the thermal safety and the optimization of such types of reaction. The thermal profiles obtained in our laboratory for other chemical manufacturing processes are sometimes much more complex and interesting than those shown in this paper, but these cases cannot be discussed here because of the proprietary nature of the compounds. Our investigations of several chemical processes have demonstrated the power of this computer-driven experimental equipment in providing valuable thermal and kinetic information for a large range of reactions.

Acknowledgement

The author is grateful to Dr G. Suter for helpful criticism during the preparation of this paper.

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