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# Thermal Hazard Evaluation of 4-Methoxybenzyl Chloride (PMB-Cl)

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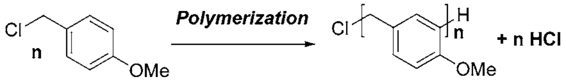
## Abstract:

**Thermal stability testing of 4-methoxybenzyl chloride is described herein, from which safe storage and handling conditions have been defined.**

## Introduction

Benzyl and benzyl-derived protecting groups are widely used to protect alcohols, amines, and other heteroatom functionalities.[1] The 4-methoxybenzyl (PMB) group, in particular, is widely used in carbohydrate chemistry and offers the advantage of cleavage under oxidative, reductive, or acidic conditions. It is commonly introduced by the reaction of 4-methoxybenzyl chloride (PMB-Cl) with the substrate under basic conditions.[2,3] There have been a number of reports in the literature of safety incidents with PMB-Cl,[4,5] thought to have resulted from the runaway polymerization of the material (Scheme 1), with concomitant release of HCl gas and overpressurization, which can result in the rupture of storage containers. Bretherick's Handbook of Reactive Chemical Hazards reports that benzyl halides lacking an electron-withdrawing group on the aromatic ring are prone to undergo autocatalytic Friedel−Craft polymerizations.[6] This polymerization is accelerated under acidic conditions and can also be catalysed by iron. Ballard and Hollyhead have also reported the controlled polymerization of PMB-Cl.[7] This reagent can be obtained from commercial suppliers stabilized with solid potassium or calcium carbonate, which neutralizes any HCl produced, with the aim of preventing the conditions in the storage container becoming acidic and, therefore, protecting against uncontrolled polymerization. However, the nonstabilized form can also be obtained. The Sigma-Aldrich MSDS recommends that PMB-Cl be stored refrigerated, but this is not the case with all suppliers.

*Scheme 1.* **Polymerization of PMB-Cl**



We intended to use PMB-Cl for a multi-kilogram scale process in our pilot plant and, thus, engaged in testing the thermal stability of this reagent, to ascertain safe storage and handling conditions. We present here the data from these studies, which we believe will be of value to the chemical community with respect to the safe use of this reagent in the laboratory and on a larger scale.

## Experimental Methods

Three techniques were used to evaluate the stability and degradation of PMB-Cl.

**Differential scanning calorimetry (DSC)** was used to determine exothermic onset conditions, either as a function of temperature or as a function of time at a constant temperature. The DSC runs were made on TA Instruments 2920 DSC cells, operating under TA Instruments' Thermal Advantage software, Ver. 1.1 A. A reusable pressure-tight cell,[8] made of either Hastelloy B-2 or tantalum-lined Hastelloy B-2, was used.

A FAI **Reactive System Screening Tool (RSST)** was used to characterize the exothermic polymerization with some external heat input in terms of rates of temperature and pressure increase as a function of temperature. The RSST runs were made using a standard FAI RSST, with version 1.4 of the control software. A standard 10 mL glass test cell was used for all the runs.

A **Gas Evolution Test Cell (GETC)** was used to measure the rates of pressure generation under isothermal conditions. The GETC (patent pending) consisted of a 150 mL Whitey Hastelloy C-22 sample cylinder equipped with a 0−60 psig Ashcroft K-8 pressure transducer and a Whitey ball valve as a charge port. The sample was charged to the GETC, and the port was sealed. The GETC was then placed in a constant temperature bath for 24 to 120 h, and the pressure was monitored.

The PMB-Cl used was purchased from Sigma-Aldrich, catalog number 270-245. For the "stabilized" experiments,

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(1) Greene, T.; Wuts, P. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp 88, 581, and 639.

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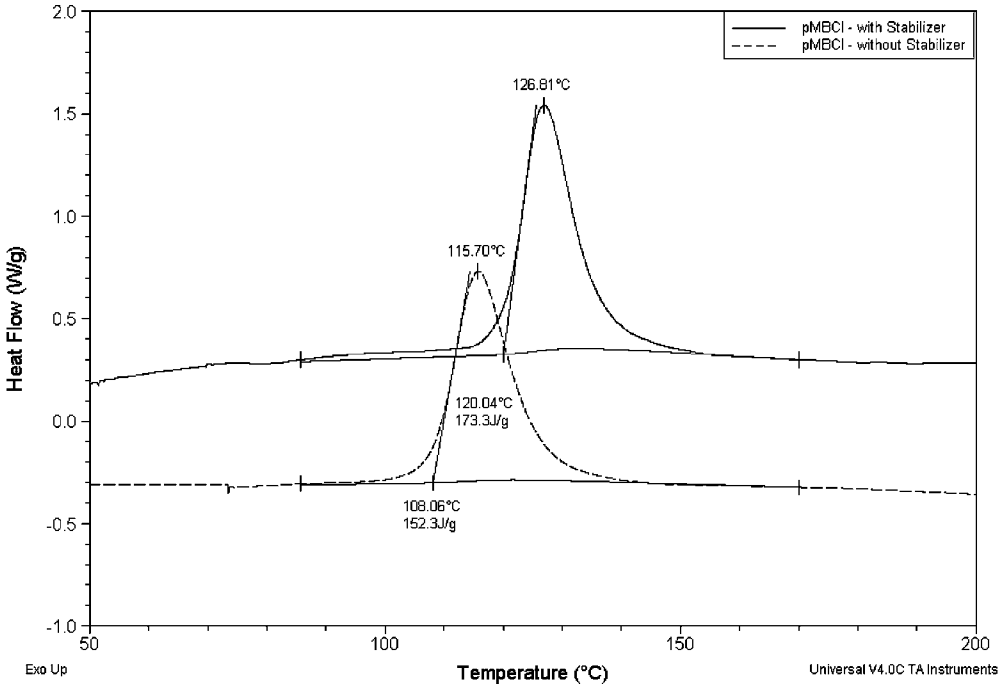

*Figure 1.* **Scanning DSC at 5 K/min.**

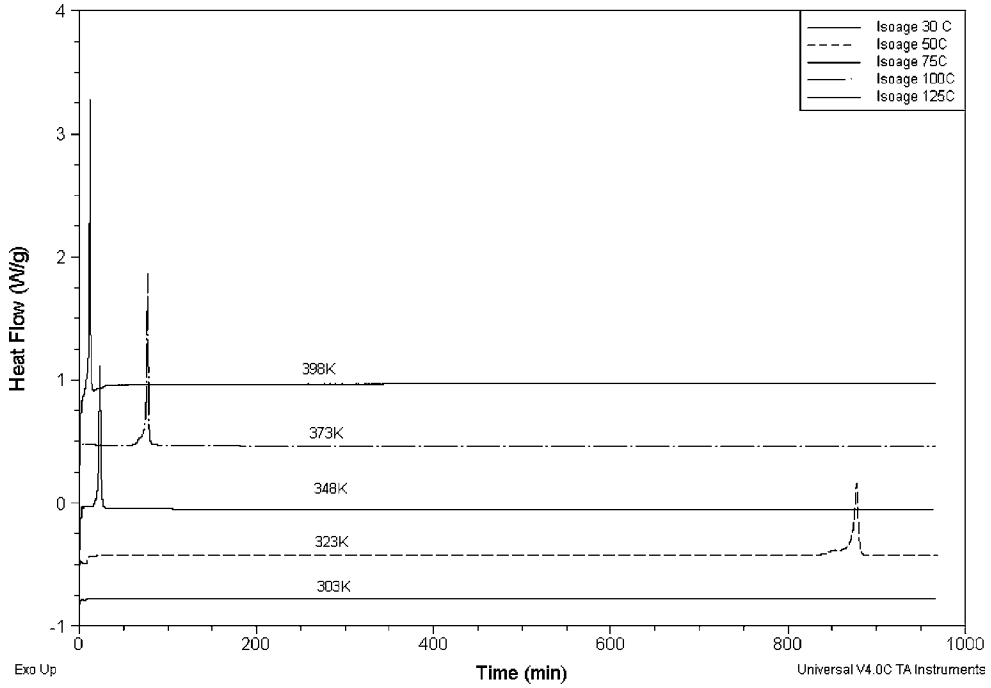

*Figure 2.* **Isothermal ages of unstabilized PMB-Cl.**

5 wt % potassium carbonate, taken from the Sigma-Aldrich sample bottle, was added to the test.

## Results and Discussion

First, differential scanning calorimetry (DSC) was carried out on both stabilized (with 5 wt % $K_2CO_3$) and unstabilized PMB-Cl. Scans were collected at 5 K/min (Figure 1). Without stabilizer, a detectable exotherm was observed at 341 K, with a heat release of 152.3 J/gm charged. As expected, stabilized material showed a detectable exotherm at the higher temperature of 363 K, with a heat release of 173.3 J/gm. Both the stabilized and unstabilized material have large exotherms initiating below 100 °C, which could indicate decomposition at typical room temperature (293−298 K).

To determine the actual initiation temperature, a series of isothermal age experiments were run on the unstabilized PMB-Cl. By determining how much the exotherm decreases in size during a 16 h age at given temperatures, the rate of decomposition can be estimated.

The shape of the heat flow graphs (Figure 2) indicates that PMB-Cl undergoes autocatalytic decomposition. In a standard isothermal age experiment, where the decomposition is not autocatalytic, the heat flow is at a maximum when the sample initially reaches the age temperature, then the

***Table 1.*** **Time to maximum rate in isothermal ages of unstabilized PMB-Cl**

| age temperature (K) | time to maximum rate (min) |
|---|---|
| 303 | >1000 |
| 323 | 830 |
| 348 | 22 |
| 373 | 54 |
| 398 | 11 |

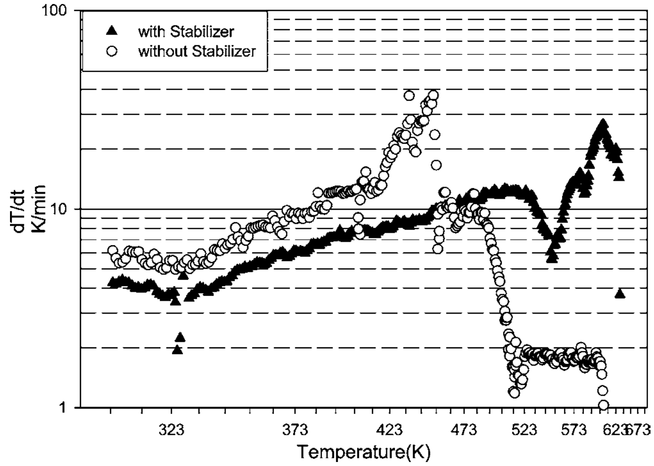

***Figure 3.*** **Rate of temperature change vs temperature.**

heat flow decreases with time. In our experiments, the reaction rate at the age temperature was initially not detectable. Then the rate began to increase after a period of time, indicating that a reaction product was catalyzing the decomposition. The primary variable affecting the decomposition is temperature (Table 1). The trend was for time to maximum rate to decrease as temperature increased: at 348 K and above, the exotherm initiated within 1 h, whereas, at 323 and 303 K, it took 14 h or more. Lot-to-lot variation may explain why the 373 K run took longer to initiate than the 348 K run.

In all of the thermal analysis testing, the samples were unstirred, and there were no data on the pressure consequences of the exotherms. To address this, the RSST was used to study PMB-Cl in a stirred system with a large vapor space. The rates of temperature change (Figure 3) and pressure change (Figure 4) as a function of temperature indicate that the potassium carbonate stabilizer is very effective in a stirred system. The RSST tests showed that there is significant pressure generation associated with the decomposition, 0.26 mol of gas per mol of PMB-Cl. In the stirred, partially vented RSST, the onset temperature appears to be higher than that in confined systems (413 K without stabilizer, 493 K with stabilizer).

So far, our experiments showed that PMB-Cl undergoes autocatalytic decomposition; 16 h at 323 K can be enough to trigger decomposition in unstabilized, unstirred material. We also found that potassium carbonate is an effective stabilizer and that agitation increases the stability of the system. The final test was selected to mimic what would happen to a bottle of stabilized, unstirred PMB-Cl stored refrigerated, at room temperature, and at 308 K. The GETC was used to measure pressure generation during ages at these temperatures.

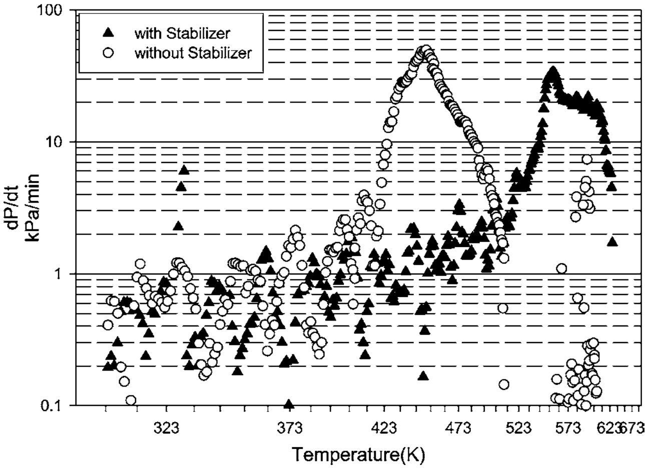

***Figure 4.*** **Rate of pressure change vs temperature.**

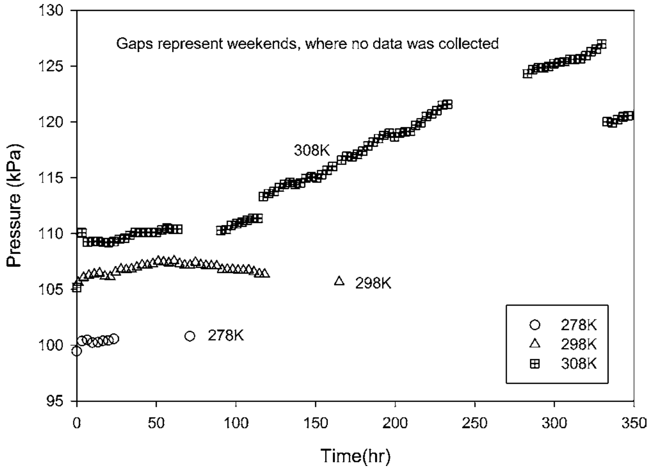

***Figure 5.*** **GETC tests on stabilized PMB-Cl.**

The GETC was charged with stabilized PMB-Cl. The first sample was initially held at 278 K (typical refrigerator temperature) for 3 days (Figure 5). No pressure generation was observed. The same sample was then heated to 298 K and held for 9 days. The lack of significant pressure generation observed indicates that the stabilizer can protect the PMB-Cl for 9 days at room temperature and presumably for longer under refrigerated conditions. A second sample of stabilized PMB-Cl, after 1 h at 298 K, was heated to 308 K. After 3 days at 308 K, pressure generation was observed, which continued over the course of 1 week. Calculation showed that the pressure seen would rapidly pressurize a sealed container to a hazardous level.

## Conclusions

We recommend storage and handling conditions for PMB-Cl based on a model which assumes that PMB-Cl slowly forms HCl at all temperatures. This HCl is neutralized by the carbonate dissolved or suspended in the PMB-Cl. The carbonate is slowly replenished from the reserves at the bottom of the container. If the rate of formation of HCl exceeds the replenishment rate of carbonate, or if the moles of HCl generated exceeds the moles of carbonate present, the excess will catalyze the Friedel−Crafts polymerization and lead to heat generation and the formation of more HCl.

At room temperature, solid potassium carbonate is an effective stabilizer for PMB-Cl, providing at least 9 days of protection: therefore, handling at room temperature during processing prevents only minimal hazard. We infer than it is stable for longer periods under refrigerated storage conditions (2−8 °C) and, therefore, recommend that the material should be refrigerated when not in use. However, above room temperature (>25 °C), the inhibitor does not prevent degradation of the PMB-Cl, and the polymerization of the material with HCl release is possible. Above 35 °C, the polymerization may initiate within hours, depending on the exact temperature and stabilizer level. Since PMB-Cl freezes at 269 K, we recommend that it is not stored in a freezer, as this may cause localized high concentrations of HCl due to limited diffusion to the inhibitor in the frozen state.

Thus we have demonstrated that although PMB-Cl presents a significant hazard, it can be handled and used under the appropriate conditions with minimal risk of incidents.

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