

Safety and Environmental Reports

An Unexpected Incident with *m*-CPBA

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Abstract:

This contribution describes an unexpected incident that occurred during oxidation of sulfide to sulfoxide using *m*-CPBA (*m*-chloroperoxybenzoic acid) as oxidant in DMF as a solvent on a pilot-plant scale. Investigation in the incident indicated that initial exotherm by *m*-CPBA in DMF, followed by formation of *m*-CBPO (*m*-chlorobenzoyl peroxide) in a large amount, led to instability of the system.

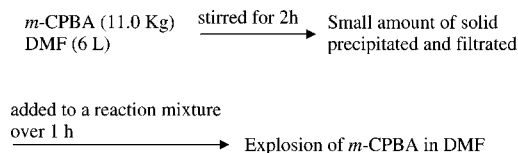
Introduction

m-CPBA is a widely used oxidant both in organic synthesis and pharmaceutical manufacturing.¹ The material is reported stable under room temperature with a melting point of 92 °C.² Oxidative transformations using *m*-CPBA were commonly conducted in DMF as a solvent without serious concern³ whilst a few reports show instability of this system.⁴ When we used *m*-CPBA in question on pilot-plant scale to transform sulfide to sulfoxide, an unexpected incident took place. The vessel was first charged with 6.3 L of DMF and 11.0 kg of *m*-CPBA. A small amount of insoluble material was identified and isolated by filtration after the mixture was stirred for 2 h. After that, the filtrate was slowly added to the reaction mixture. One hour later after the beginning of addition of the solution, the temperature in the vessel of *m*-CPBA in DMF suddenly rose, involving gas evolution, and then the explosion occurred. After the incident, the material insoluble in DMF was identified as *m*-CBPO.⁵ The incident was suspected to be caused by *m*-CBPO contaminating *m*-CPBA and/or generated from *m*-CPBA. The entire incident is diagrammed in Scheme 1.

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- (5) ***m*-CBPO (*m*-chlorobenzoyl peroxide)**: ¹H NMR (200 MHz, CDCl₃): δ 7.48 (t, 2H, *J* = 7.9), 7.65 (ddd, 2H, *J* = 8.0, 2.0, 1.0), 7.97 (dt, 2H, *J* = 7.8, 1.1), 8.06 (t, 2H, *J* = 1.8); ¹³C NMR (100 MHz, CDCl₃): δ 127.0, 127.9, 129.8, 130.3, 134.5, 135.1, 161.8. MS (EI, *m/z*): 157, 156, 155.

Scheme 1. Chart of the entire incident



Results and Discussion

With this unexpected incident, we evaluated *m*-CPBA applied to a pilot-plant scale synthesis from several safety viewpoints. To our surprise only 0.2% of *m*-CBPO was found to contaminate the *m*-CPBA in question. The *m*-CPBA was first evaluated by impact sensitivity testing (IST) and differential thermal analysis (DTA) studies. IST study showed that this reagent itself was stable and the decomposition was expected not to involve severe exotherm. The material melted at 89 °C and was stable at the temperature of <97 °C according to the results of DTA studies (Figure 1). The stability of a mixture of *m*-CPBA in DMF was also examined by DTA studies. The mixture initiated decomposition at 83 °C as shown in Figure 2. This result showed the possibility that solvents might affect the decomposition point of *m*-CPBA although no explosive feature was foreseen at this point. We suspected that DMF as solvent played an important role for the incident. Nevertheless, the mechanism of the incident was still unclear since *m*-CBPO was totally removed in advance and no precipitation was identified

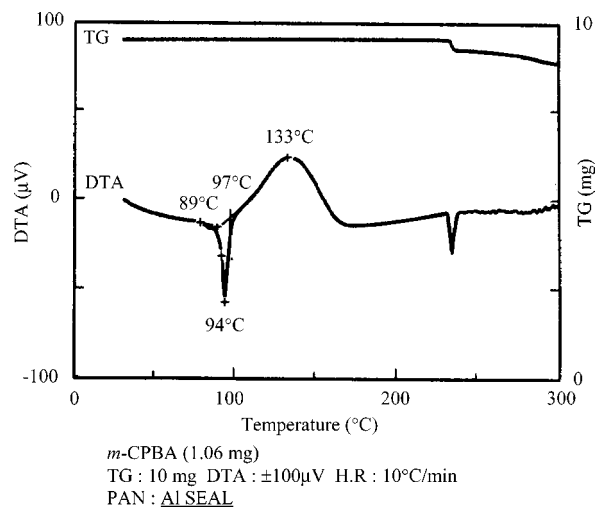
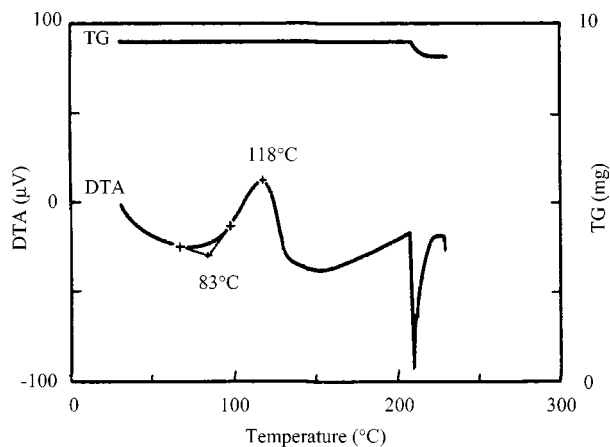


Figure 1. DTA result of *m*-CPBA as a powder.



m-CPBA (40g) in DMF (38mL)
 TG : 10mg DTA : $\pm 100\mu\text{V}$ H.R : $10^\circ\text{C}/\text{min}$
 PAN : AL SEAL

Figure 2. DTA result of *m*-CPBA in DMF as a solvent.

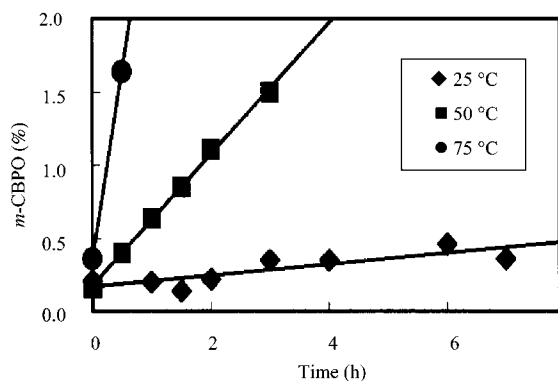
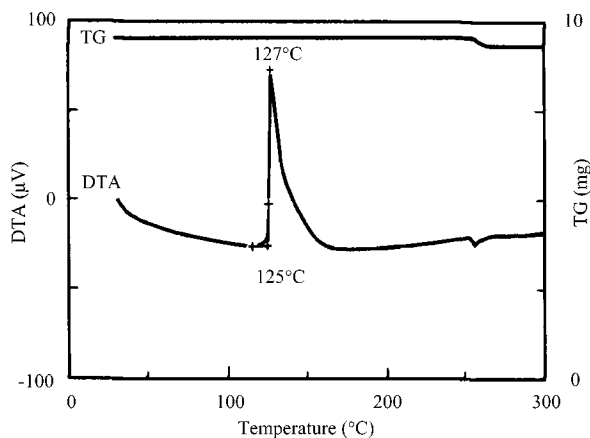


Figure 3. Amount of *m*-CBPO in DMF as solvent.



m-CBPO (0.97 mg)
 TG : 10 mg DTA : $\pm 100\mu\text{V}$ H.R : $10^\circ\text{C}/\text{min}$
 PAN : AL SEAL

Figure 4. DTA result for *m*-CBPO.

before the incident during the actual pilot-plant scale manufacturing. In addition it was also difficult to understand that the very small amount of *m*-CBPO could lead the system to explode.

During our continuous efforts to clarify the explosive features of this system we discovered that the amount of *m*-CBPO significantly increased in DMF as a solvent under high-temperature conditions (Figure 3). As shown in Figure 4, a severe explosion was foreseen by the DTA study when

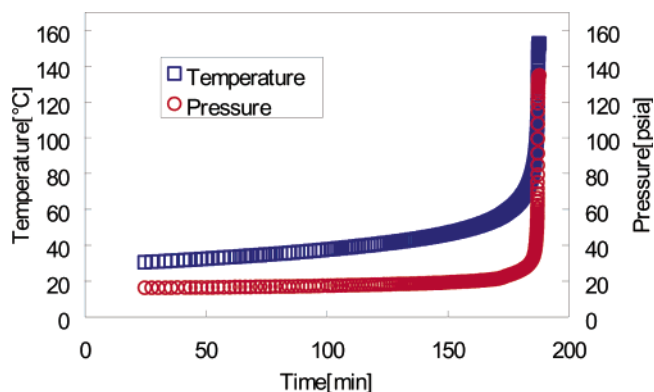


Figure 5. ARC result of *m*-CPBA in DMF as a solvent.

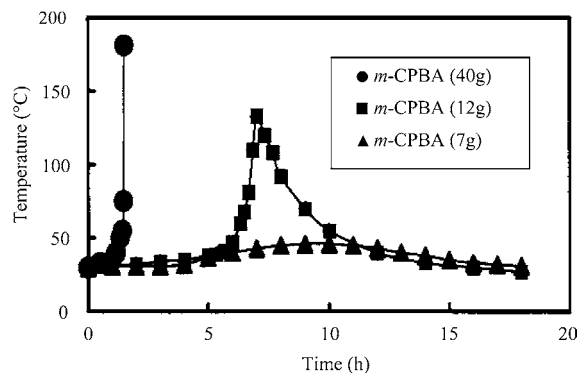


Figure 6. Stability of *m*-CPBA in DMF (38 mL) under adiabatic conditions.

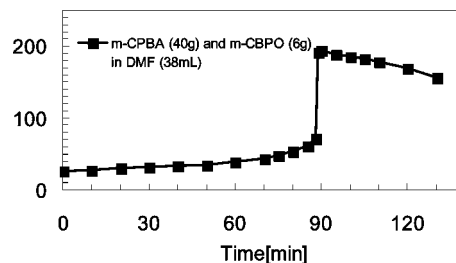


Figure 7. Stability of mixture of *m*-CPBA and *m*-CBPO.

m-CBPO was treated at the temperature of $>125^\circ\text{C}$. Interestingly, ARC studies showed that the mixture of *m*-CPBA in DMF slowly exothermed from ~ 26 to $\sim 70^\circ\text{C}$ over 185 min, and was then followed by acute exotherm to $\sim 200^\circ\text{C}$ over a few minutes involving evolution of white smoke in runs carried out in adiabatic reactors (Figure 5).

With the unexpected result we then investigated the relationships between the decomposition temperature and concentration of *m*-CPBA in DMF as a solvent under adiabatic conditions. As shown in Figure 6 severe exotherm was observed only over 90 min under the conditions of high concentration of *m*-CPBA in DMF (40 g of *m*-CPBA/38 mL of DMF), whilst it took more than 5 h for low concentration conditions (12 g of *m*-CPBA/38 mL of DMF), and there was no exotherm to a significant degree for further low concentration conditions (7 g of *m*-CPBA/38 mL of DMF). These results indicated that the incident occurred due to an initial exotherm by *m*-CPBA in DMF as a solvent under adiabatic conditions that led to producing a large amount of *m*-CBPO; then the temperature rose, and a large amount of *m*-CBPO

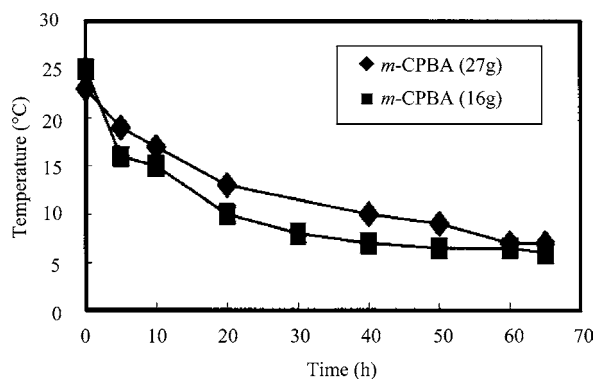


Figure 8. DTA results of *m*-CPBA in CH₂Cl₂ (160 mL).

finally led to the explosion. As a control experiment a mixture of *m*-CPBA (40 g) and *m*-CBPO (6 g) in DMF (38 mL) was investigated. As shown in Figure 7 the temperature of the mixture slowly rose and suddenly in only 95 min a severe exotherm evolved. To develop a safer and more practical process we first investigated alternative solvents to DMF, envisaging avoiding the production of *m*-CBPO. As shown in Figure 8, no exotherm was detected when methylene chloride was applied as a solvent. The improved process using *m*-CPBA as an oxidant in methylene chloride was successfully scaled up to give the product without trouble.

Conclusions

m-CPBA is a classical and well-known oxidant widely used in organic synthesis. This material is usually handled without special attention. Whilst *m*-CPBA itself is a stable and easy-to-handle reagent, it has a possibility of causing an unexpected event especially in DMF as a solvent. Our investigations indicated that the formation of *m*-CBPO led first to a slight exotherm and a large amount of *m*-CBPO produced under high-temperature conditions then led to an explosion. Although the mechanism of *m*-CBPO formation is not clear at this moment, the preparation of *m*-CBPO was dramatically accelerated under high-temperature conditions. An improved process using methylene chloride as an alternative solvent was successfully scaled up to give the product.

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