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THERMAL HAZARDS AND SAFE SCALE-UP OF REACTIONS CONTAINING DIMETHYL SULFOXIDE

T. T. Lam[*]*, T. Vickery and Linda Tuma*

Merck & Co., Inc., P.O. Box 2000, RY818-B101, Rahway, NJ 07065, USA

Extensive thermal analysis has shown that DMSO-containing reaction mixtures can be more energetic and decompose at lower temperatures than pure DMSO. Several processes at Merck using DMSO as a solvent were found to have the onset temperatures of decompositions reduced to the point where it became a thermal and operational hazard. The onset temperature depended on the reagents in the reaction mixture and the thermal history of the mixture. The case studies presented in this paper will include discussion on what process hazards were identified, how the process hazards differ from the pure DMSO hazards, and how to scale up these processes safely.

Keywords: *ARC, decomposition, dimethyl sulfoxide, DMSO, exothermic, thermal hazard*

Introduction

Dimethyl sulfoxide, DMSO, is commonly used as a solvent in many chemical reactions due to its capability to solubilize many inorganic and organic compounds. However, despite of its common use, there have been several serious incidents associated with DMSO reported in the literature both at the laboratory scale and at the industrial scale.

Hall [1] reported a fatal incident in a laboratory in 1991, where DMSO was inadvertently contacted with traces of perchloric acid which resulted in an explosion, fatally injured the technician. The laboratory damage exceeded 60000 German marks. A pilot plant reactor exploded in 1991 [1] during a vacuum distillation of a DMSO mixture containing 5% of 2-bromomethyl-1,3-dioxolane and 7% water. An investigation of the incident indicated that ~0.3% hydrogen bromide (HBr) was found to form during the long-term storage of the mixture. It is believed that HBr catalyzed the DMSO degradation at elevated temperatures, which was then accelerated by its decomposition product, dimethyl sulfide, resulting in rapid temperature and pressure rises. The explosion destroyed the reactor with the reactor cap being blown through several levels of the pilot plant and the reactor body propelled from the first floor to the ground level. The structure damages were over half of a million dollars. Bromides catalyzed DMSO decomposition is known and documented in 'Bretherick's Handbook of Reactive Chemical Hazards' [2]. Other incidents related to DMSO can be found in [1, 2].

Unlike most solvents, DMSO is very reactive and undergoes a violent exothermic decomposition just above its atmospheric boiling point. Reaction mixtures containing DMSO can be much more hazardous than the pure solvent as the DMSO decomposition can become more violent. Several processes at Merck using DMSO as a solvent were found to have the onset temperatures of decompositions reduced to the point where it became a thermal and operational hazard. The onset temperature depended on the reagents in the reaction mixture and the thermal history of the mixture. Due to variation of the onset temperatures and the violent decomposition, processes using DMSO need to be evaluated carefully to ensure their safe scale-up. The case studies presented in this paper will include discussion on what process hazards were identified, how the process hazards differ from the pure DMSO hazards, and how to scale up these processes safely.

Experimental

Various thermal analytical tools were used to assess thermal hazards of processes. These include differential scanning calorimetry (DSC) [3], reactive system screening tool (RSST) [4] and accelerating rate calorimetry (ARC) [5]. The DSC runs were scanned at 5°C min^{-1} from room temperature to ~300°C under a nitrogen atmosphere in a tantalum-lined crucible, which can withstand a pressure of approximately 500 psi. The sample mass in each DSC run was about 5 mg. Detail description on the in-house developed crucible can be found in [6]. The experimental parameters of ARC runs are summarized in Table 3.

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[*] Author for correspondence: Thientu_Lam@Merck.com

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Akadémiai Kiadó, Budapest, Hungary
Springer, Dordrecht, The Netherlands

Case studies

Case study #1 – coupling reaction

Original process

Two bromo-containing compounds were coupled in the presence of copper powder with DMSO as a solvent. All reagents were combined at room temperature, warmed to 50°C and aged for 8.5 h for reaction completion. The process was evaluated for thermal and operational hazards prior to scale-up in the Pilot Plant.

The coupling reaction was not recommended for scale-up as the heat generated from the reaction had a potential to initiate a decomposition exotherm. This decomposition exotherm was accompanied by extremely rapid rates of pressure and temperature increases with a large residual pressure based on the ARC, RSST and DSC data.

DSC analysis

The liquid and solid phases of the reaction slurry in DMSO before heat-up were analyzed separately via DSC. As shown in Table 1a, both phases contained a low-temperature exotherm initiating at or just above the reaction temperature of 50°C with a moderate heat release rate. The liquid phase had a large thermal energy of 1213 kJ kg^{-1}. The DSC data also showed that the instability of the reaction mixture was not due to the coupled product, as the product in ethanol at the same concentration had a much smaller exotherm that initiated at a higher temperature (62.8 kJ kg^{-1} at 160°C).

RSST analysis

To assess pressure consequences of this exotherm, an RSST run on the pre-reaction slurry was performed. The RSST results showed two exotherms, one just below the reaction temperature with a low pressure increase rate and one above the reaction temperature accompanying by extremely rapid rates of pressure and temperature increases (Table 1b). A large residual pressure was also measured from the RSST run, indicating significant amounts of non-condensable gases were generated. The first exotherm was likely the heat of reaction. The heat of reaction was measured independently on an Omnical CRC calorimeter at –84 kJ mol^{-1} with an adiabatic temperature rise of ~30°C.

ARC analysis

The ARC run in the heat–wait–search (H–W–S) mode on the pre-reaction slurry in DMSO also detected two exotherms. The first exotherm initiated before ~50°C, the programmed start temperature of the ARC run. The maximum self-heat rate of this exotherm was only ~0.14°C min^{-1}. This first exotherm was ended at ~70°C, at which point a second exotherm was detected. The maximum rates of temperature and pressure increases

Table 1a Coupling reaction – DSC results

Sample description	Initiation temperature/°C	Exotherm size/kJ kg^{-1}	Heat release rate
	Pre-reaction slurry in DMSO		
Supernatant	85	1205.8	moderate
Wet solids	50 210	142.7 22.6	moderate slow
	Pre-reaction slurry in DMF		
Supernatant	50 125 235[a]	9.2 174.5 49.0	slow moderate moderate
Wet solids	50 220	56.5 45.2	moderate moderate
Final product in ethanol	160	64.4	slow

[a] The exotherm initiated immediately after the conclusion of the previous exotherm.

Table 1b Coupling reaction – RSST results (scanning mode)

Sample#	Atmosphere	Initiation temperature[a]/°C	Max. (d*T*/d*t*)/ °C min^{-1}	Max. (d*P*/d*t*)/ psi min^{-1}	Max. pressure inc./psi	Residual pressure[b]/psi
Pre-reaction mixture in DMSO	nitrogen (16 psi initial)	~40 ~154	26.1 513.2	0.43 2607.5	50.0	17.0
Pre-reaction mixture in DMF	nitrogen (16 psi initial)	~50 ~175 ~217	7.7 12.7 234.3	0.5 1.5 6.0	19.1	9.6

[a] The accurate initiation temperature can be determined by other methods.

[b] Residual pressure indicates generation of non-condensable gases upon decomposition.

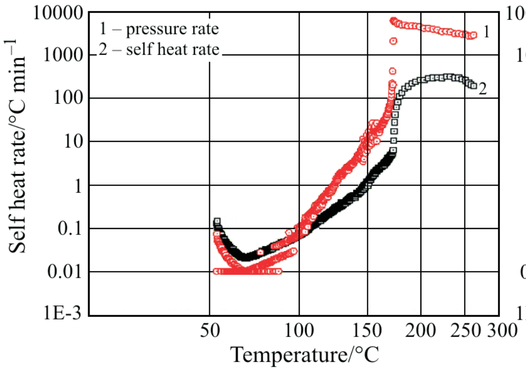

Fig. 1a Coupling in DMSO – ARC run

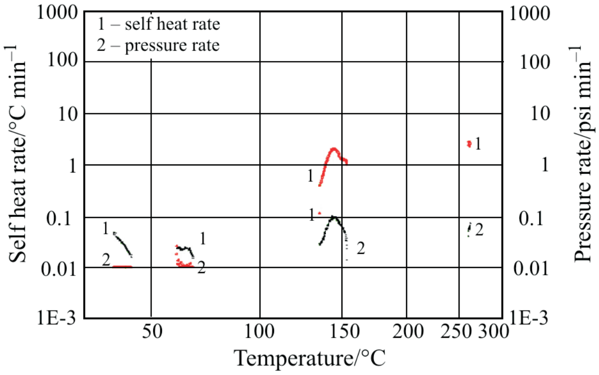

Fig. 1b Coupling in DMF – ARC run

associated with the second exotherm were extremely high, ~310°C min^{-1} and ~6100 psi min^{-1}, respectively (Fig. 1a). This exotherm possessed a thermal energy of ~523 kJ kg^{-1}, which had potential to increase the batch temperature by ~250°C adiabatically. There was evidence of large amounts of non-condensable gases being generated based on the large residual pressure of 450 psi upon cooling down to 20°C at a 53% fill in the test cell.

Revised process

Due to the identified serious thermal runaway, it was recommended not to scale up the reaction and to investigate other solvents. The reaction was revised with only one change, DMSO was replaced by dimethylformamide (DMF). The 85°C exotherm seen in the DMSO system occurred at a higher temperature in the DMF system, and the exotherm size was reduced by seven folds, according to the DSC data of the pre-reaction stream (Table 1a). The pre-reaction slurry was subjected to an H–W–S ARC run. The decomposition exotherm was detected in the DMF system but at a higher temperature, 135 *vs*. 70°C for the DMSO system. The maximum rates of temperature and pressure increases associated with this exotherm were insignificant, <0.1°C min^{-1} and <2.0 psi min^{-1}, respectively (Fig. 1b). The RSST data showed the same comparison between the DMF and DMSO systems (Table 1b). The process in DMF was amendable for scale-up.

Thermal hazards comparison of coupling reaction to pure DMSO

The decomposition seen in the coupling reaction was far more serious than that from pure DMSO. Unexpectedly, the onset temperature of the decomposition was significantly reduced to 70°C as opposed to 195°C for pure DMSO. The energy and pressure releases as well as the generation rates were all much higher than the pure system. The maximum rates of temperature and pressure increases of the decomposition were 300°C min^{-1} and 6000 psi min^{-1} for the coupling reaction compared to 3°C min^{-1} and ~100 psi min^{-1} for pure DMSO (Figs 1c and d). The presence of copper bromide, a by-product from the coupling reaction, might be responsible for the severe decomposition as bromides are known to catalyze DMSO decomposition. In a separate study, it was found that one of the bromo-compounds and copper also interacted with DMSO, producing mixtures with larger decomposition exotherms and lower initiation temperatures. The combination of destabilizing reagents contributed to the severity of the decomposition seen in this reaction system.

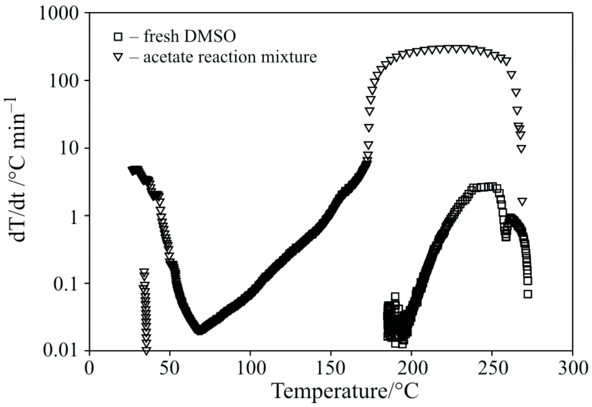

Fig. 1c Coupling reaction *vs*. pure DMSO, temperature rate

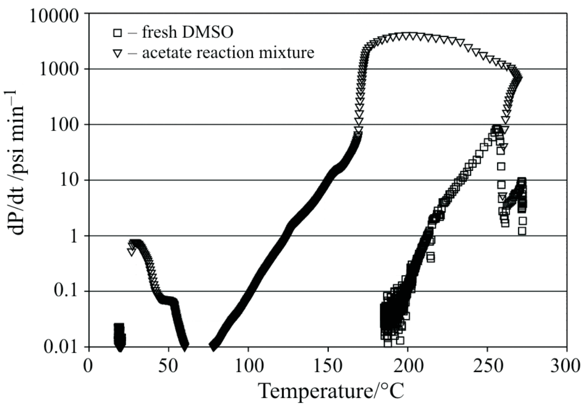

Fig. 1d Coupling reaction *vs*. pure DMSO, pressure rate

Case study #2 – fluoride displacement reaction

Original process

DMSO was used as a solvent in a coupling reaction involving a fluoro-compound and a quinone in the presence of potassium *tert*-butoxide. The reagents were charged at room temperature, heated to 150°C, and aged there for 20 h using an oil bath of 170°C. This reaction was evaluated for thermal and operational hazards prior to its scale-up. It was found that this reaction was not safe for scale-up due to potential of a thermal runaway at the proposed operation conditions.

DSC analysis

The DSC was first used to screen exothermic activities in the pre- and post-reaction samples. Both samples had a large decomposition exotherm of >335 kJ kg^{-1} initiating at ~195°C with moderate to rapid heat release rates (Table 2). Due to the vicinity of the exotherm to the operating temperature and the known severity of DMSO decomposition, ARC testing was performed on the pre- and post-reaction samples.

ARC analysis

The pre-reaction slurry was subjected to a heat–wait–search (H–W–S) test in the ARC from 80 to 180°C. After no exotherm was detected, the slurry was aged isothermally at 170°C, the proposed jacket temperature. The isothermal age was planned for 50 h, which was 2.5 times of the reaction age. However, a thermal runaway occurred after 23 h into the age at 170°C with a rapid rate of pressure increase (350 psi min^{-1}). A large adiabatic temperature rise of 300°C and a residual pressure of 155 psi at 22% fill were measured. The decomposition reaction exhibited autocatalytic behavior. A violent decomposition reaction with an autocatalytic characteristic usually poses a thermal hazard concern and needs to be evaluated thoroughly because the decomposition could occur at a lower temperature if the sample is allowed to age at that temperature long enough. For the pre-reaction slurry, there was no exotherm detected up to 180°C during the H–W–S, but aging the sample at 170°C for 23 h allowed the decomposition reaction to be catalyzed and led to a thermal runaway, producing significant heat and gas (Figs 2a and b).

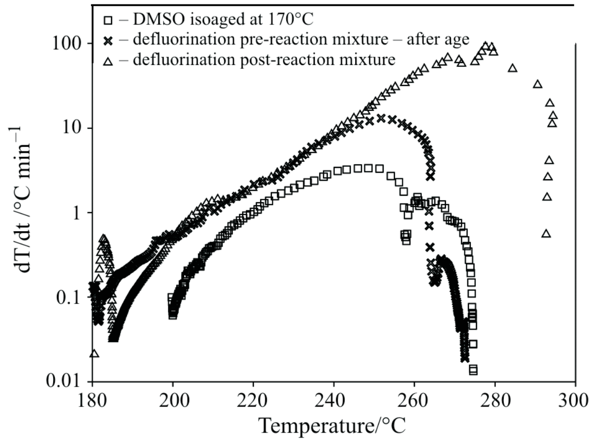

Fig. 2a Fluoride displacement – temperature rate

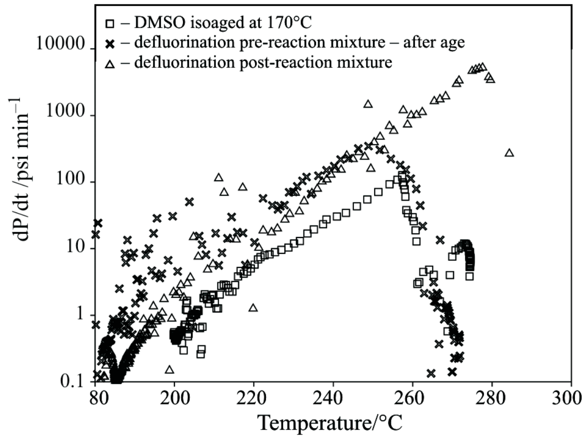

Fig. 2b Fluoride displacement – pressure rate

The product stream was also found to be thermally unstable at the operating temperature when subjected to an H–W–S ARC run (without a prior isothermal age). The onset temperature of the exotherm was detected at 185°C. Higher maximum rates of temperature and pressure increases were measured for the post-reaction mixture compared to that for the pre-reaction sample (Figs 2a and b). Like the pre-reaction slurry, the post-reaction mixture also exhibited autocatalytic behavior. The time to maximum rate of the post-reaction mixture at 147°C was 24 h, which was only 4 h longer than the proposed reaction age time at 150°C. These thermal data suggested that this reaction is not safe for scale-up.

Table 2 Fluoride displacement reaction – DSC results

Sample description	Initiation temperature[a]/°C	Exotherm size/kJ kg^{-1}	Heat release rate
Pre-reaction slurry from the original process	200 195	>325.4 >366.5	moderate to rapid moderate
Pre-reaction slurry from the revised process	205 195	>243.5 >502.1	rapid moderate to rapid

[a] The size of the exotherm could not be determined accurately due to seal rupture.

Table 3 ARC experiments parameters

Process	Sample	Bomb MOC	Bomb mass/g	Sample size/g	Test method	phi= $1+(M_bC_b)/(M_sC_s)$
Pure DMSO	DMSO–HWS	C-276	21.53	2.87	H–W–S from 180°C	2.67
	DMSO–isoage	C-276	21.51	3.43	H–W–S from 80 to 180°C, isoage 50 h at 170°C – H–W–S from 115°C	2.39
Coupling	pre-reaction in DMSO	C-276	12.43	8.92	H–W–S from 50 to 300°C	1.28
	pre-reaction in DMF	C-276	12.95	7.49	H–W–S from 50 to 300°C	1.35
Fluoride displacement	pre-reaction mixture	C-276	21.56	2.95	H–W–S from 80 to 180°C, isoage 50 h at 170°C – exotherm detected	2.62
	product solution	C-276	21.57	3.10	H–W–S from 80°C	2.55
	pre-reaction mixture–revised procedure	316L SS	18.20	1.56	~6 days at 110°C H–W–S from 110°C	3.59

H–W–S – heat–wait–search; M_b – mass of the ARC test cell; M_s – mass of the sample in the test cell; C_b – heat capacity of the ARC test cell. C_s – heat capacity of the sample.

Revised process

It was suggested to the project chemist to explore other solvents or to run the reaction at a lower temperature. The revised reaction was carried out at a lower temperature (100 *vs*. 150°C) with a longer age time (70 h *vs*. 20 h) and the 18-crown-6 additive. The pre-reaction mixture was subjected to an isothermal age in an ARC at 110°C (10°C above the reaction temperature) for about 6 days followed by an H–W–S to 250°C. The ARC data showed no gas generation during the age except near the end, when a slight pressure increase was detected. The decomposition was detected at 190°C, which was slightly higher than that from the original process.

A kinetic analysis predicted an adiabatic two-week time to runaway of 142°C for the revised process *vs*. 117°C for the pre-reaction aged sample of the original process. Since the operating temperature was at least 20°C below the temperature at two-week time to runaway and there was insignificant gas generation during the reaction age, the revised reaction was amendable for scale-up. However, restrictions on the reaction temperature and the reaction age time as described in the process procedure were imposed to prevent initiation of the violent decomposition. A high temperature alarm of 110°C was recommended with emergency cooling to be applied if the batch temperature reached 115°C.

Thermal hazards comparison of defluorination reaction to pure DMSO

Pure DMSO was subjected to the same thermal history as the pre-reaction slurry to compare the effect of aging on decomposition of pure DMSO and the reaction mixture. The data showed that the pre- and post-reaction mixtures were less stable than the fresh and aged DMSO. Both the pre-reaction mixture and DMSO exhibited autocatalytic behavior during the 170°C age, but it was much more pronounced in the pre-reaction mixture.

The pressure rate increased from 0.013 to 0.13 psi min^{-1} over 23 h for the pre-reaction mixture compared to the rate from 0.008 to 0.015 psi min^{-1} over 50 h for pure DMSO at the similar fill volume in the test cell. The exothermic decomposition was detected at 200°C for DMSO during an H–W–S after a 50-h age at 170°C. However, in the pre-reaction mixture, the exothermic decomposition was detected after 23 h into the planned 50-h age at 170°C.

The measured heat generation per unit mass of the sample was ~70% higher for the reaction mixtures compared to that for pure DMSO. The reaction mixtures produced about 10% more of non-condensable gases than pure DMSO for each mole of DMSO used in the system. The aged DMSO produced the same amount of non-condensable gases as the un-aged DMSO after corrected for fill fractions.

Conclusions

Several processes using DMSO as a solvent were found to be more hazardous than pure DMSO. The reaction streams had higher energy content than pure DMSO and underwent exothermic decompositions at lower onset temperatures. This combination could lead to a thermal runaway at the operating temperatures. The identified thermal hazards had driven the development of safe and scalable processes.

Processes using DMSO as a solvent, especially at elevated temperatures, should be evaluated carefully for potential thermal hazards. DSC can be used first to identify unknown exotherms. An ARC should then be used to study kinetics of DMSO-mixture decompositions. Since decompositions of mixtures containing DMSO tend to exhibit autocatalytic behavior, it is important to study the effects of thermal history on the decomposition to ensure that these mixtures would not be destabilized and decompose during a prolonged age called by the process. As a rule of thumb, the age time used in a thermal history study should be 2.5 times of the process age time. Once the thermal hazards are identified, a safe operating envelope can be defined and/or development of an alternative, safer, process can be initiated to ensure safe scaleup of processes containing DMSO.

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