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Safety Evaluation of Sodium Borohydride in Dimethylacetamide

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Abstract:

The thermal stability of sodium borohydride ($NaBH_4$) in dimethylacetamide (DMA) was examined by comparison with $NaBH_4$ in dimethylformamide (DMF), which is known to cause a violent runaway reaction. DMA is more thermally stable than DMF as a solvent for $NaBH_4$ based on consideration of the decomposition onset temperature and sensitivity to impurities.

Introduction

$NaBH_4$ is traditionally used as a chemoselective reagent for reducing aldehydes and ketones to alcohols.[1] As its reducing power can be adjusted by the choice of solvents and additives, $NaBH_4$ is used for various reductive reactions.[2] It is widely used as a reducing agent for organic synthesis not only in the laboratory but also on an industrial scale.[3]

The safety and ease of handling $NaBH_4$ is better than that of other reducing agents such as aluminum hydrides, but its reduction reactions generate large amounts of heat and hydrogen gas which need to be controlled. Control is possible by using semibatch operations in multipurpose reactors, as done by pharmaceutical companies, to prevent runaway reactions. The following three procedures have been reported as semibatch-type operations of $NaBH_4$ reduction: (1) $NaBH_4$ is added to the substrate layer,[4] (2) the substrate is added to the $NaBH_4$ layer,[5] (3) methanol, as an initiating reagent and solvent to dissolve $NaBH_4$, is added to a mixture of the substrate and $NaBH_4$.[6] The first semibatch procedure is the safest as it essentially avoids $NaBH_4$ accumulation, but solid $NaBH_4$ addition from an open hole on the reactor is an unsafe operation and requires a special sealing device to prevent a hydrogen explosion.[4]

For multipurpose reactors, addition of a $NaBH_4$ solution to the reactor is recommended as this does not require an opening operation or a special device. A highly concentrated $NaBH_4$ solution is preferred because a high throughput process leads to cost reduction. Solvents such as water, alkylamines, methanol, DMF, and DMA can dissolve 10 g or more of $NaBH_4$ per 100 g at ambient temperature.[7a] Basic aqueous solutions of $NaBH_4$ are relatively stable and the most environment-friendly, but in many cases, organic compounds are not soluble in aqueous solutions, and thus organic solvents have been used for $NaBH_4$ reduction.

While dilute solutions of $NaBH_4$ in DMF can been used without incident, a violent exothermic reaction has been reported involving a saturated solution and resulting in spontaneous ignition of the flammable gases evolved.[2i,3a,7] Although DMA is recommended as a substitute for DMF, detailed safety assessments of $NaBH_4$ in DMA have not been reported. Here we report on the assessment of the stability of $NaBH_4$ solution in DMA using a differential scanning calorimeter (DSC), an accelerating rate calorimeter (ARC) and a SuperCRC reaction microcalorimeter. The safety was evaluated by comparison with the DMF solution of $NaBH_4$.

Results and Discussion

The stability of $NaBH_4$ solutions in DMA and DMF was examined by DSC experiments. A sealed SUS crucible was

Table 1. **DSC results of $NaBH_4$ solution in DMA and DMF**

entry	solvents	additives	additive amount [wt %]	decomposition-onset temp [°C]	decomposition energy [J/g]
1	DMA[a]	−	0	216	573
2		H_2O	0.38	218	559
3		MeOH	0.60	215	603
4		HCOOH	0.39	201	515
5		HCOOH	3.43	196	506
6		iron rust	0.46	218	533
7	DMF[b]	−	0	189	757
8		H_2O	0.51	186	827
9		MeOH	0.46	182	634
10		HCOOH	0.45	175	662
11		HCOOH	3.64	152	604
12		iron rust	0.83	189	751

[a] 11.7 wt % solution (6.39 g of $NaBH_4$ in 48.09 g of DMA). [b] 15.7 wt % solution (1.30 g of $NaBH_4$ in 7.00 g of DMF).[7a]

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Table 2. **ARC results of $NaBH_4$ in DMA and DMF**

solvents	onset T (°C)	T_{max} (°C)	P_{max} (bar)	$(\Delta T/\Delta t)$ max (°C/min)	$(\Delta P/\Delta t)$ max (bar/min)	TMR[c] (min)	ADT24[c] (°C)	ΔT[c] (°C)	Φ
DMA[a]	125	201	24	79	40	35	111	306	4.03
DMF[b]	95	201	18	547	59	1	74	429	4.05

[a] 11.7 wt % sulution (6.39 g of $NaBH_4$ in 48.09 g of DMA). [b] 15.7 wt % solution (1.30 g of $NaBH_4$ in 7.00 g of DMF).[7a] [c] Φ corrected.

used, and a heating rate of 10 °C/min was applied. The results are shown in Table 1. The $NaBH_4$ solutions in DMA and DMF showed severe decomposition beginning at 219 and 189 °C with associated decomposition heat of 573 J/g and 757 J/g, respectively (entry 1 and 7). Adiabatic temperature rises of 287 and 378 °C, respectively, had been calculated by estimating a heat capacity of 2 J/(g·K).[8] These exothermic phenomena were observed on reducing amides to amines by $NaBH_4$,[7b] and the difference of the heat values and adiabatic temperature rise depended on the concentrations of $NaBH_4$ in the solvents.

Addition of H_2O and MeOH has been reported to not influence the decomposition-onset temperature, while addition of formic acid has been shown to decrease it.[7c] Both were reconfirmed (entries 8−11). With increasing formic acid contamination of the DMF solution, the decomposition-onset temperature decreased from 189 °C to 175 °C and 152 °C with addition of 0.45 and 3.64 wt %, respectively (entries 10 and 11). On the other hand, in DMA solution, the decomposition-onset temperature decreased from 216 °C to 201 and 196 °C with addition of formic acid of 0.39 and 3.43 wt %, respectively (entries 4 and 5). This shows that the formic acid contamination affects the decomposition-onset temperature more severely in DMF than in DMA.

Safety assessments of $NaBH_4$ in DMF and DMA were done using ARC techniques.[9] Although the ARC experiment for DMA solution was performed starting at 50 °C and heating the sample to 350 °C using a heat step interval of 5 °C and a waiting period of 10 min as a standard procedure (Figure 1a), the procedure for DMF solution was changed to using a heat step interval of 2 °C and a waiting period of 6 min to detect rapid heat generation (Figure 1b).

An exothermic phenomenon of $NaBH_4$ in DMA solution was detected at 125 °C (temperature increase rate 0.02 °C/min) with a maximum temperature increase rate of 79 °C/min at 183 °C. $NaBH_4$ in DMF solution showed more rapid decomposition than in DMA solution, and an exothermic phenomenon was detected at 95 °C (temperature increase rate 0.02 °C/min) with a maximum temperature increase rate of 547 °C/min at 137 °C. The times to the maximum rate (TMR; corrected by Φ) were 35 min at 125 °C in DMA and 1 min at 95 °C in DMF, respectively. These results are summarized in Table 2.

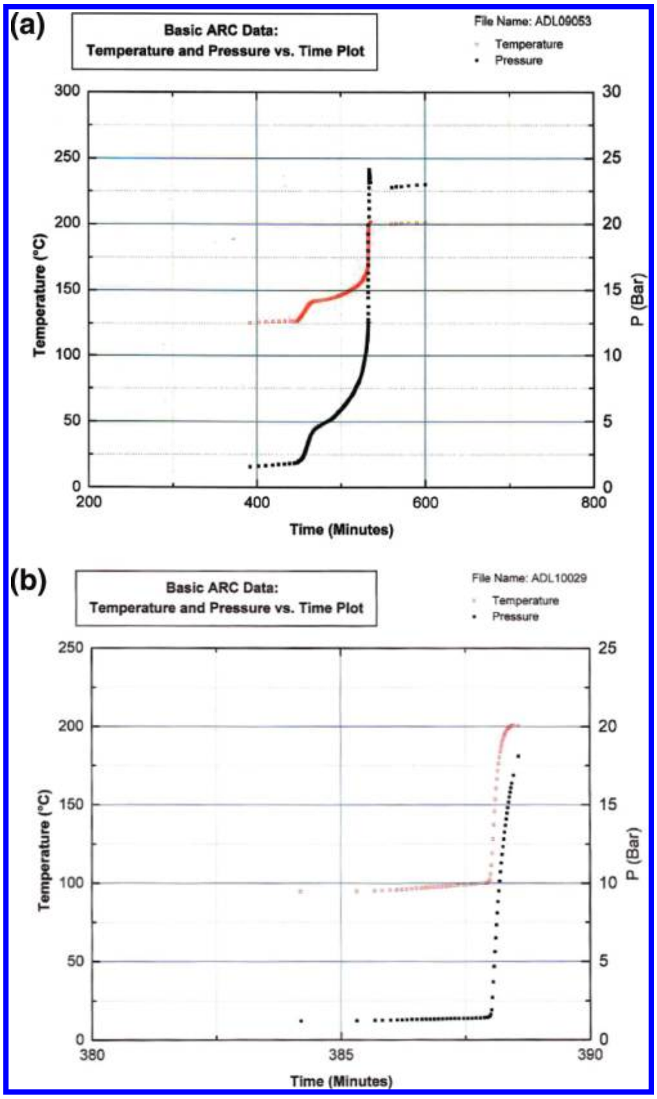

Figure 1. **(a) ARC data for $NaBH_4$ in DMA (11.7 wt %). (b) ARC data for $NaBH_4$ in DMF(15.7 wt %).**

As a general rule, a TMR of more than 24 h at the processing temperature (ADT24) is considered to be acceptable in a manufacturing facility, providing sufficient time for corrective action, if the cooling system, stirring apparatus, or other critical utilities are unexpectedly interrupted. Clearly, the $NaBH_4$ solution in DMA at 11.7 wt % concentration should be handled at under 111 °C.

We examined the preparation of $NaBH_4$ solution in DMA using a SuperCRC reaction microcalorimeter. The heat of dissolution of $NaBH_4$ was measured by charging 1.7 mL (1.6 g) of DMA to 0.21 g of $NaBH_4$ in a SuperCRC at 25 °C (Figure 2a). This gave a heat of dissolution of $NaBH_4$ in DMA of 56 J/g, and the adiabatic temperature rise was estimated to be 28 °C (specific heat = 2J/(g·K)[8]). On monitoring the $NaBH_4$

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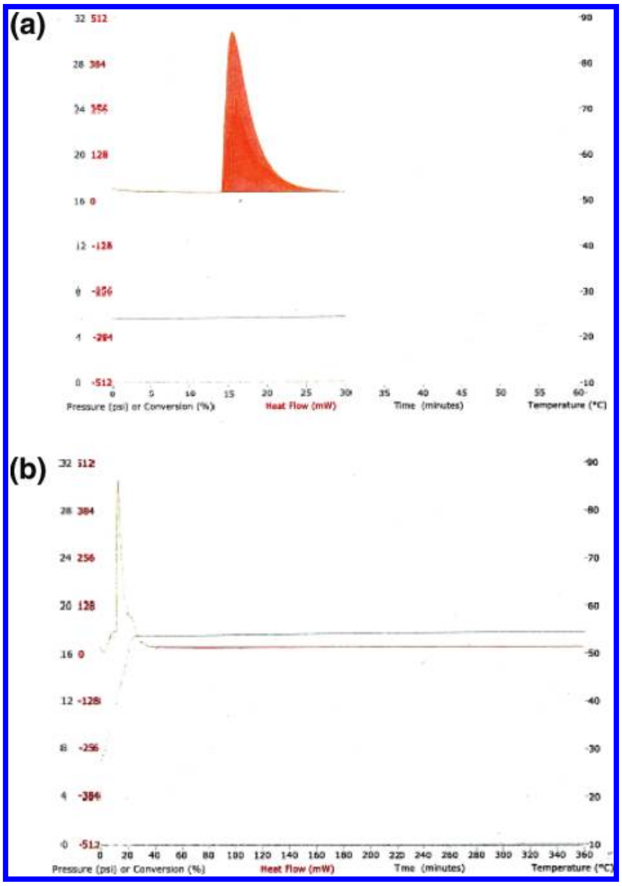

Figure 2. **(a) SuperCRC data for heat of dissolution. (b) SuperCRC data for stability at 55 °C over 6 h.**

solution in DMA at 55 °C for 6 h, no generation of heat was observed (Figure 2b). The maximum temperature for preparation of $NaBH_4$ solution in DMA was estimated to be 53 °C, from the sum of the ambient temperature of 25 °C and the adiabatic temperature rise of 28 °C. The results clearly show that preparation of $NaBH_4$ solution (11.7 wt %) in DMA at ambient temperature with effective stirring did not lead to a risk of a runaway reaction.

Conclusion

Our findings showed that the decomposition-onset temperature of $NaBH_4$ in DMA is about 30 °C higher than in DMF, formic acid contamination affects the decomposition-onset temperature less severely in DMA than in DMF, and the adiabatic decomposition rapidity of $NaBH_4$ in DMA is slower than DMF. ADT24 of 11.7% $NaBH_4$ solution in DMA was estimated to be 111 °C, and thus, it should be handled at this temperature or lower. We were able to safely handle 11.7 kg of $NaBH_4$ solution in 88 kg of DMA to reduce an ester in our plant.

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