



Continuous hydrogenation of halogenated nitroaromatic compounds in a micropacked bed reactor

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Abstract

The selective hydrogenation of halogenated nitroaromatic compounds is of great importance in the fine chemical industry. However, the hydrogenation reactions in commonly utilized batch reactors suffer from the undesired dehalogenation, resulting in higher requirement for subsequent separation processes and severe corrosion to industrial fatalities. In this work, a H-flow system with the micropacked bed reactor was developed for the selective hydrogenation of halogenated nitroaromatic compounds and the reduction of 3,4-dichloronitrobenzene was selected as the model reaction. With the optimal hydrogenation conditions, the yield of 3,4-dichloroaniline was obtained as high as 99.8% under mild conditions. With this strategy this flow system was successfully employed to the reduction of other chlorinated nitroaromatics also demonstrating low dehalogenation. The H-flow system enables negligible dehalogenation and remarkable yield of target product with higher efficiency and lower energy cost compared with the batch reactor.

Keywords Hydrogenation · Dehalogenation · Continuous flow · Micropacked bed reactor

Introduction

Selective catalytic hydrogenation of halogenated nitroaromatic compounds is the most widely used method for the synthesis of halogenated anilines, important intermediates in the pesticides, herbicides, drugs, pigments and dyes industry [1–7]. Currently, most catalytic reduction processes in the chemical industry are performed in batch reactors because of the simple structure [8]. However, traditional batch hydrogenation protocols have several drawbacks for the heterogeneous hydrogenation of halogenated nitroaromatics. For instance, slow gas–liquid–solid mass transfer results in long reaction time (3–12 h), in particular for the large reactor [8]. Besides, multiple gas replacements and catalyst separations are required in a batch production, leading to labor-intensive work and increasing risk of safety issues. Most importantly, due to lengthy reaction time and severe back mixing [9], it's

challenging for batch reactors to realize the selective hydrogenation of halogenated nitroaromatics to corresponding halogenated anilines without dehalogenation which accelerates the corrosion of reactors and reduces catalysts' stability [10]. Although in some cases, additives could attenuate hydrodehalogenation, they could also reduce catalytic activity toward the reduction of nitro group, necessitating higher temperature and pressure [11]. Hence it is desired to develop an efficient method for the selective hydrogenation of halogenated nitroaromatic compounds.

Continuous flow technology is among the most valuable advances in the chemical industry due to inherent advantages on the improved product quality and yields, effective suppression of side reaction by precise control of reaction conditions, lower energy and space requirement, smaller reactor volume and increased safety [12–16]. Additionally, micropacked bed reactor, as a promising tool for the gas–liquid–solid reactions, has shown several advantages such as uniform temperature distribution, intensified mass transfer and improved safety while maintaining the plug flow characteristics and fixed bed catalyst immobilization [17–21]. Patrick et al. [1] developed a continuous-flow platform for the selective hydrogenation of 1-iodo-4-nitrobenzene using Raney-Co catalyst. Compared with batch

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reactor, selectivity was greatly improved, and less than 2% dehalogenation product was detected owing to the precise control of residence time. Todor et al. [22] proposed a continuous flow system with new $\text{Co}_3\text{O}_4/\text{NGr@CNT}$ as catalysts in a micropacked bed reactor for the reduction of 4-iodonitrobenzene. The results showed that main product (4-iodoaniline) was obtained without any detectable dehalogenation at full conversion, which proved the effectiveness of continuous-flow micropacked bed system on the highly selective hydrogenation of halogenated aromatics. Feng et al. [23] adopted continuous-flow technology for the hydrogenation of crizotinib intermediate using Raney Ni as the catalyst. Consequently, side reactions such as dehalogenation and debenzoylation were inhibited eminently and desired product was obtained with high selectivity (99.9%) and high conversion (99.5%). Hannes et al. [24] selected the hydrogenation of 1-iodo-4-nitrobenzene as the model reaction and evaluated reaction performance under batch and continuous flow modes. Experimental results indicated that the yield of 4-iodoaniline in continuous flow system were 10% higher than that in batch reactor, verifying the superiority of continuous flow for the selective hydrogenation of halogenated aromatics. Therefore, the continuous flow system based on micropacked bed reactor would offer excellent mixing efficiency and great control over residence time and temperature, improving reaction selectivity remarkably and minimizing excessive hydrogenation which results in undesired dehalogenation.

The hydrogenation of 3,4-dichloronitrobenzene (3,4-DCNB) was selected as the model reaction and the product 3,4-dichloroaniline (3,4-DCAN) is a significant intermediate in dye and pigment industry [25, 26]. In general, the

reduction of 3,4-DCNB proceeds via the nitroso compound and hydroxylamine to 3,4-DCAN [27]. Dehalogenation of the nitro raw material is possible to occur at any step during the reaction pathway, but the dehalogenation of the more electron-rich product (3,4-DCAN) is commonly faster. Another pathway can accrue from condensation of these intermediates [28]. For instance, nitroso and hydroxylamine intermediates can condense to form azoxy compounds. Besides, nitroso intermediate can also react with 3,4-dichloroaniline to form diazo compound. These compounds could be reduced to 3,4-dichloroaniline through a hydrazo intermediate. The complex reaction pathways are depicted in Scheme 1. Hence it's a challenge for the highly selective hydrogenation of 3,4-dichloronitrobenzene.

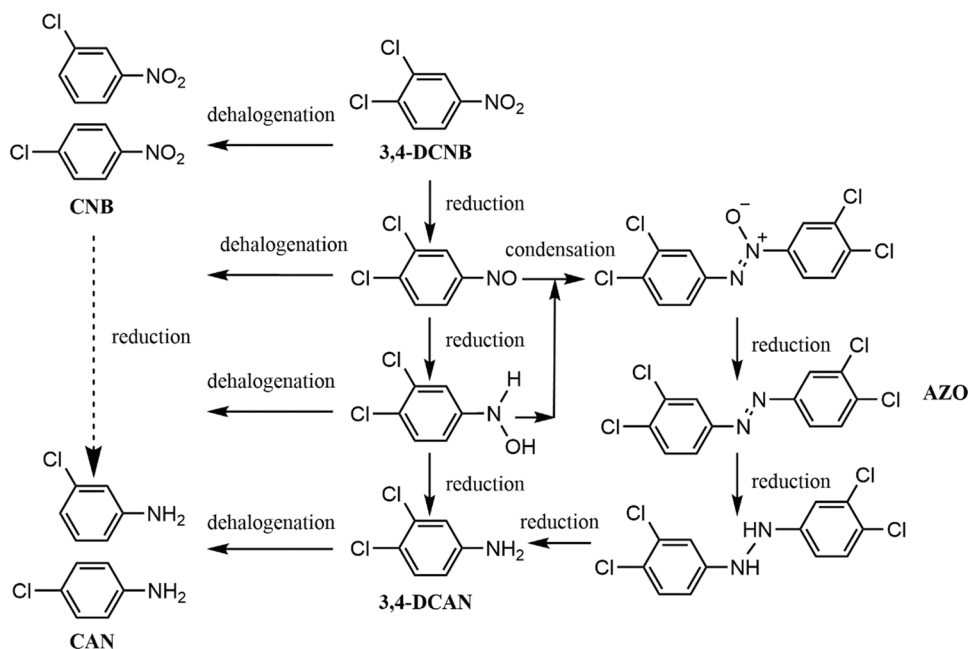
In this study, a H-flow system based on a micropacked bed was developed for the selective hydrogenation of chlorinated nitro aromatics. The catalysts and reaction parameters suitable for the reaction were screened and some relevant chloronitrobenzenes were also applied to demonstrate the efficiency and high selectivity with this H-flow system.

Materials and methods

Chemicals

The reactant of 3,4-DCNB ($\text{C}_6\text{H}_3\text{Cl}_2\text{NO}_2$, 99%) was obtained from Zhejiang Dibang Chemical Co. Ltd without any purification. The solvent of methanol (CH_3OH , 99.9%) was purchased from Aladdin-Holdings Group. Hydrogen (H_2 , 99.9%) and nitrogen (N_2 , 99.9%) were supplied by Beijing Beiweng Gas Manufacturing Plant. The platinum/carbon

Scheme 1 Reaction pathways for the hydrogenation of 3,4-dichloronitrobenzene



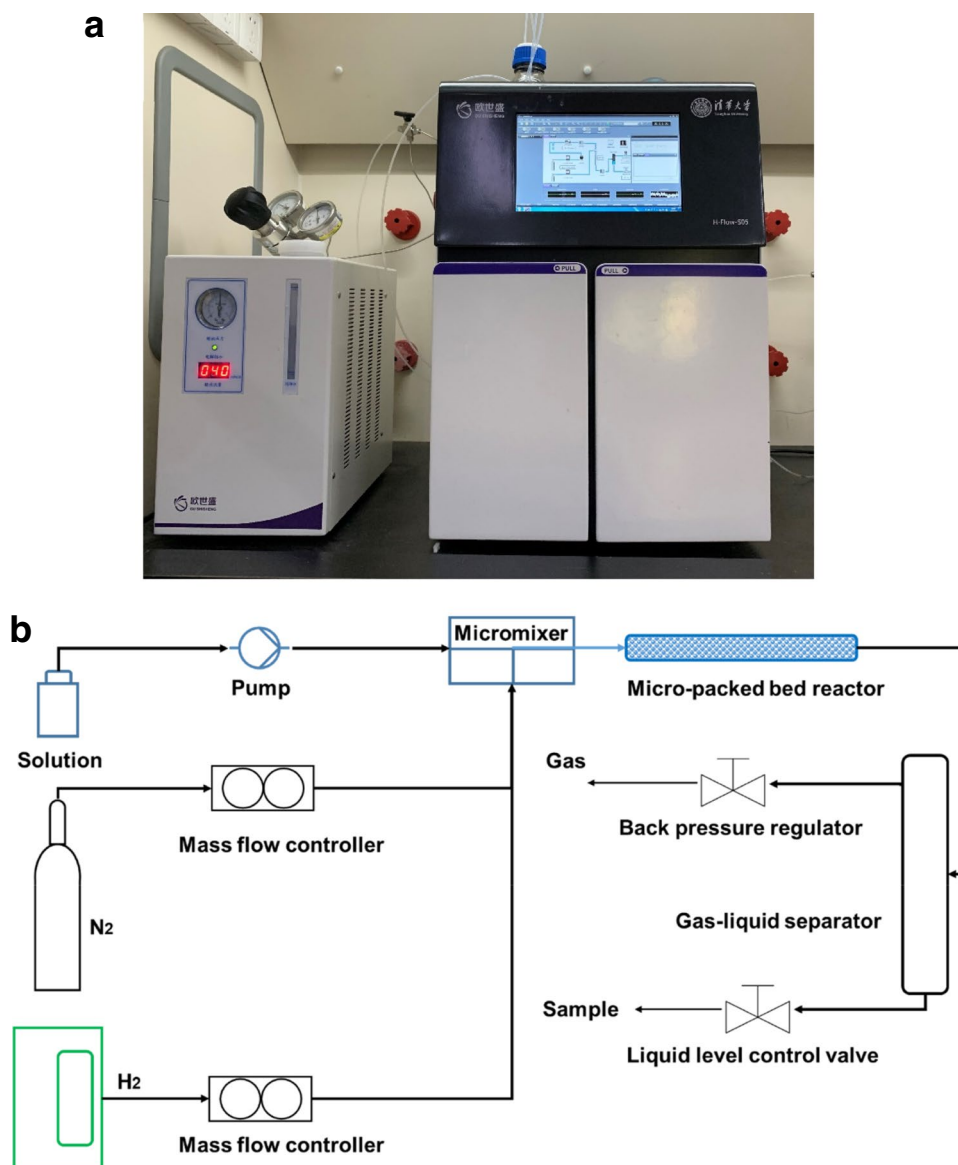
particle catalyst (Pt/C, 5 wt%), palladium/carbon particle catalyst (Pd/C, 5 wt%), Ru/carbon particle catalyst (Ru/C, 5 wt%) and nickel/silica particle catalyst (Ni/SiO₂, 20 wt%) with the average size of 400–500 μm were all acquired from Dalian Institute of Chemical Physics.

Experimental setup

A schematic overview of the continuous flow platform (H-Flow 10, Ou Shi Sheng (Beijing) Technology Co. Ltd.) was shown in Fig. 1. Liquid flow was supplied by a plunger pump with maximum flow rate of 9.99 mL/min and maximum pressure of 10 MPa. H₂ gas from the hydrogen generator (Ou Shi Sheng (Beijing) Technology Co. Ltd.) and N₂ gas from the regulated cylinder were fed through two mass flow controllers (Beijing Sevenstar Electronics Co.

Ltd.) with maximum flow rate of 100 sccm. Liquid was pre-heated to reaction temperature and then mixed with gas prior to entering the micropacked bed reactor (Length: 24.0 cm, inner diameter: 5.5 mm, outer diameter: 13.9 mm) which was wrapped by the heating jacket vertically. A condenser was placed on the downstream of reactor to remove excessive heat from the product and hydrogen. Following that the mixture entered the gas–liquid separator and product was collected in the collection vial. A back pressure regulator was connected with the top of separator to control system pressure while a liquid level control valve was installed at the bottom of separator to avoid undesired overflow to gas outlet. System parameters (pressure, temperature and flow rate) were all set to required values using online control modules while transient reaction conditions were shown on the screen by the online monitor modules.

Fig. 1 **a** Picture of H-Flow system. **b** Schematic of the H-Flow system based on the micropacked bed reactor for the selective hydrogenation of 3,4-DCNB



The reactant (3,4-DCNB) was prepared as a specific concentration with the solvent. The micropacked bed reactor was prewetted by pure solvent, then followed by N_2 to replace gas in the system. After that H_2 was introduced into H-Flow and the system pressure was gradually increased to the required value, ensuring the pressure drop between mass flow controller and back pressure regulator less than 0.5 MPa to protect the mass flow controller. Meanwhile, the system temperature was increased to the required value. When all the desired parameters were achieved, the solution of reactant was delivered in the system and the system achieved a steady state after at least three times of liquid residence time, then the sample was collected. When all the experiments had been completed, the heating jacket was turned off and system pressure was reduced to atmospheric pressure by releasing the back-pressure regulator. After the system was depressurized, a mixture of N_2 and methanol was transported through the micropacked bed reactor to fully remove residual gas–liquid mixture and catalyst was stored in a nitrogen atmosphere.

Analytical method

The sample was analyzed offline utilizing gas chromatography (shimadzu, GC-2014) with an FID detector and a Shimadzu RTX-5 capillary column (length: 30 m, diameter: 0.32 mm, film thickness: 0.25 μ m). The samples were diluted and measured under the following conditions: the injection temperature, 280 °C; the column temperature, 50–110 °C, 20 °C/min, 110–150 °C, 10 °C/min, 150 °C, 4 min, 150–250 °C, 20 °C/min; the detector temperature, 280 °C. The sample volume for all analysis was 1 μ L. Based on these analytical conditions, the retention times of the reactants and products were as following: CAN (*m*-chloroaniline and *p*-chloroaniline), 5.8 min; CNB (*m*-chloronitrobenzene and *p*-chloronitrobenzene), 7.4 min; 3,4-DCAN, 8.5 min; 3,4-DCNB, 7.8 min; AZO, 13.3 min. For the most experiments, no 3,4-DCNB was detected by gas chromatography, hence the conversion was treated as 100%. Therefore, the selectivity of product could be calculated as follows:

$$S = \text{selectivity} = \frac{C_A}{C_A + C_B + C_C + C_D} \times 100\%$$

where, C_A , C_B , C_C and C_D were the concentrations of 3,4-DCAN, CAN, CNB and AZO in the samples, respectively.

Results and discussion

Catalyst screening

Selectivity was particularly important in the hydrogenation of 3,4-DCNB, as the 3,4-DCAN was prone for the excessive reduction to form undesired dechlorination byproducts which were difficult to separate in the post-treatment process. Employing suitable catalyst for the hydrogenation was crucial to increase the selectivity. It has been reported that noble metals Pd, Pt and Ru were frequently utilized in the selective hydrogenation of halogenated aromatics[29]. Alumina was generally treated as a preferable support due to the high mechanical resistance and strong interaction with supported metals, but it showed quite low stability to the HCl generated in the reaction[30]. Hence, activated carbon, owing to the high resistance towards the HCl was selected as the support. In addition, Raney Ni was also commonly used in the hydrogenation, however, it was highly pyrophoric since the catalyst would combust spontaneously when contacting with the air[31]. Therefore, in the experiments, Ni/SiO₂ was chosen to substitute the Raney Ni catalyst for the selective hydrogenation of 3,4-DCNB. The summary of reaction performances was given in Table 1.

Severe dehalogenation was observed even at mild temperature when adopting Pd/C catalysts, and AZO was also detected in the products. As the temperature was increased

Table 1 Product composition for the continuous hydrogenation of 3,4-DCNB with different catalysts

Temperature/°C	Catalyst	3,4-DCAN	CAN	CNB	AZO
40	Pd/C	7.26	72.6	12.78	6.34
	Ni/SiO ₂	44.36	0.00	0.00	55.64
	Ru/C	81.77	2.35	0.00	15.89
	Pt/C	99.48	0.03	0.13	0.27
50	Pd/C	10.43	58.36	19.54	11.67
	Ni/SiO ₂	75.05	0.00	0.00	24.95
	Ru/C	73.52	1.08	0.00	25.40
	Pt/C	99.41	0.24	0.13	0.16
60	Pd/C	9.88	53.24	21.34	13.72
	Ni/SiO ₂	90.03	0.00	2.01	7.96
	Ru/C	85.34	10.22	1.83	2.61
	Pt/C	99.70	0.11	0.09	0.09
70	Pd/C	8.97	52.99	23.09	15.40
	Ni/SiO ₂	90.51	0.00	8.34	1.15
	Ru/C	63.48	36.52	0.00	0.00
	Pt/C	99.55	0.10	0.085	0.24

Reaction conditions: system pressure: 2.0 MPa, mass concentration of reactant: 10 wt%, liquid flow rate: 0.7 mL/min, gas flow rate: 25 sccm, solvent: methanol, catalyst loading: 2.53 g.

to 50 and 60 °C, AZO was gradually reduced to 3,4-DCAN, however, the increase of yield was ignorable. This is because that faster reaction rate of dehalogenation at higher temperature offsets the effect of the reduction of AZO. Therefore, dehalogenated inhibitors or some modifications were employed when using Pd catalysts for the hydrogenation of halogenated nitroaromatics to suppress side reactions [32–34].

Hydrodechlorination byproduct was notably less with Ru/C and Ni/SiO₂ catalyst, and AZO was the main impurity for the temperature below 60 °C with less than 1% 3,4-DCNB was detected, indicating insufficient catalyst activity. On the contrary, for temperature beyond 60 °C, CAN increased surprisingly leading to the reduction in yield for Ru/C. As a result, the maximum yield with Ru/C and Ni/SiO₂ were 85.3% and 90.5%, respectively. The results clearly illustrated that Pd/C, Ru/C and Ni/SiO₂ were not suitable for the selective hydrogenation.

Based on the characteristics and advantages of Pt catalyst for the chemoselective hydrogenation of nitroarenes[35, 36], Pt/C catalyst was employed in the selective hydrogenation of 3,4-DCNB. According to the experimental results, no 3,4-DCNB was detected in GC and the content of two main byproducts (CAN and AZO) were also negligible. Moreover, the yields of 3,4-DCAN were beyond 99% among all temperatures, revealing the extraordinary selectivity and excellent applicability for the hydrogenation of 3,4-DCNB. Hence, Pt/C catalyst was applied for the following researches in this study.

For the optimization of selective hydrogenation of 3,4-DCNB process, the effect of reaction parameters on the reactor performance was studied by comparing the yield and mass fraction of 3,4-DCAN in products under different reaction parameters.

Effect of gas flow rate

In the continuous hydrogenation process, hydrogen flow rate would influence the gas–liquid mass transfer process by increasing the turbulence in the reactor which greatly influences the conversion and selectivity of reaction [37]. In order to investigate the influence of gas flow rate on reaction results, the selectivity and conversion of the reaction under different gas flow rates were studied with Pt/C catalyst and the results were shown in Fig. 2.

It is found that the mass fraction of 3,4-DCAN under different gas flow rates were all beyond 99% except for the experiments under gas flow rate with 22.5 sccm. The CAN and CNB at hydrogen flow rate with 22.5 sccm were slightly higher than other results. The results could be attributed to the longer residence time of liquids in the reactor due to the small gas flow rate. Therefore, gas flow rate of 25 sccm was selected for the following experiments.

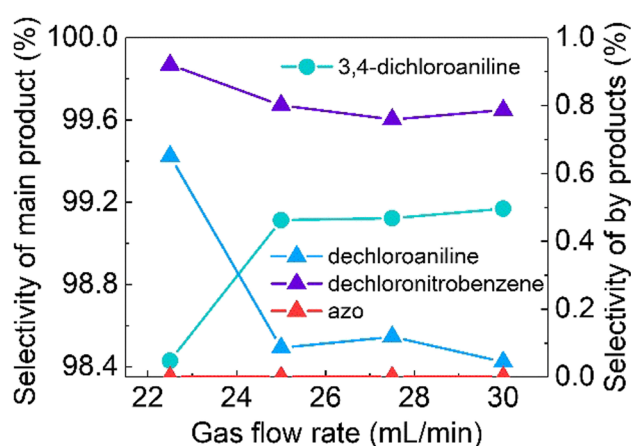


Fig. 2 Product composition for the hydrogenation of 3,4-DCNB at different gas flow rates with Pt/C catalyst. Reaction condition: system pressure: 2.0 MPa, mass concentration of reactant: 10 wt%, temperature: 50 °C, liquid flow rate: 0.7 mL/min, solvent: methanol, catalyst loading: 2.53 g

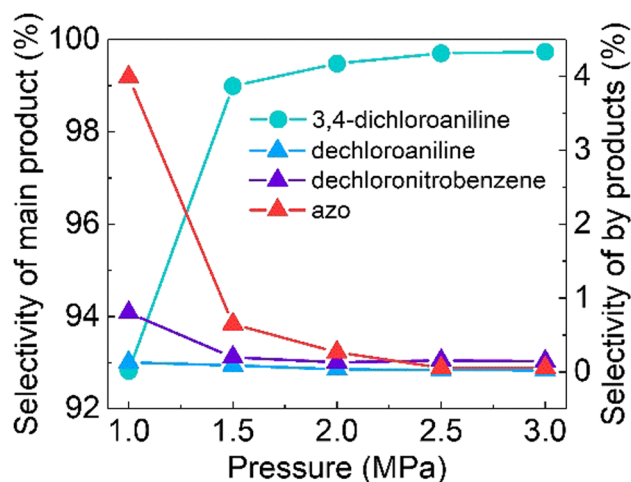


Fig. 3 Product composition for the hydrogenation of 3,4-DCNB at different pressures with Pt/C catalyst. Reaction condition: temperature: 40 °C, reactant mass concentration: 10 wt%, gas flow rate: 25 sccm, liquid flow rate: 0.7 mL/min, solvent: methanol, catalyst loading: 2.53 g

Effect of pressure

Hydrogen pressure would affect the solubility of hydrogen in the solution and gas–liquid mass transfer rate [38]. Inappropriate pressure may accelerate the accumulation of AZO or promote the dechlorination process. Here, the effect of hydrogen pressure on the product composition was studied.

Figure 3 showed that when the reaction pressure was increased from 1.0 MPa to 3.0 MPa, the selectivity of 3,4-DCAN gradually increased to a high value of 99.5% with pressures larger than 2 MPa, and the azoxy compounds declined to less than 0.1%, which was attributed to the

transformation of azoxy compound to 3,4-DCAN. Surprisingly, dehalogenation was also decreased as pressure increased. The reason may be that higher hydrogen pressure increases the amount of active hydrogen on the catalyst which accelerates the reduction of nitro group while the reaction rate of dehalogenation is irrelevant with the hydrogen pressure as pressure higher than 1.0 MPa [30, 39]. The yields of the hydrogenation at different pressures were shown in Fig. 3. The maximal yield of 3,4-DCAN (99.8%) was obtained with the pressure of 2.0 MPa. Hence, the pressure of 2.0 MPa was selected as the optimized condition for the following experiments.

Effect of temperature

Temperature has a large influence on the reaction pathways. Under low temperature, direct hydrogenation that the reduction of nitroso compounds was dominated as the main pathway which inhibits excessive hydrogenation and the generation of AZO, while high temperature accelerates the condensation of nitroso and hydroxylamine intermediates to form AZO. Hence, the effect of temperature was systematically investigated across a large temperature range of 40–160 °C.

As shown in Fig. 4, the full conversion (no 3,4-DCNB was detected in GC) was obtained at all the temperatures and maximum yield of 99.7% was obtained at 60 °C. And then selectivity was decreased to 96.1% at 160 °C. When the reaction temperature was higher than 90 °C, dehalogenation was accelerated, resulting in a remarkable decline in selectivity, including the CAN (more than 0.5%) and CNB (more than 0.25%). The maximal 2.49% CAN and 1.34% CNB were

observed in 160 °C. Based on the optimized reaction temperature, the full conversion and maximum yield of 99.7% were obtained and temperatures below 90 °C were suggested for the application of H-flow system considering the severe corrosion led by HCl.

Effect of liquid flow rate

The liquid flow rate would greatly influence the residence time by changing the liquid holdup in the micropacked bed reactor [40]. And the variation of residence time has significant influence on the dechlorination process and the generation of AZO. For the hydrogenation under long residence time, dechlorination would inevitably appear since target product 3,4-DCAN remaining on the Pt/C catalyst was dehalogenated by the hydrogen absorbed on the catalyst surface. While for the reaction under short residence time, it wasn't sufficient for the 3,4-DCNB and AZO to contact with hydrogen, therefore, they cannot be converted to the desired product.

Figure 5 has shown that when the liquid flow rate varied from 0.4 mL/min to 0.7 mL/min which corresponds to the residence time from 2.2 min to 3.8 min, the yields of 3,4-DCAN were all beyond 99.5% and no AZO was observed in GC. As the liquid flow rate was increased, AZO was generated owing to the shorter residence time to be further reduced to 3,4-DCAN and the yield of 3,4-DCAN declined to 99.3%. In Fig. 6, it was found that maximal yield of 3,4-DCAN appeared under higher liquid flow rate as the temperature increased, indicating that side reaction (dehalogenation and condensation) was accelerated at higher temperature, hence decreasing residence time would diminish the adverse impact. The highest yield of 99.7% was achieved with the

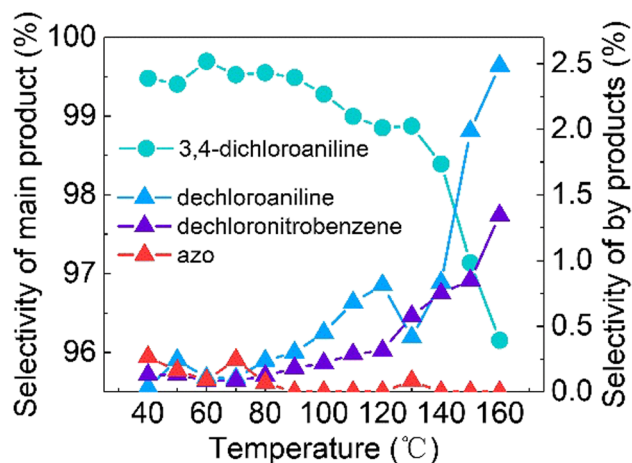


Fig. 4 Product composition for the hydrogenation of 3,4-DCNB at different temperatures with Pt/C catalyst. Reaction condition: system pressure: 2.0 MPa, reactant mass concentration: 10 wt%, gas flow rate: 25 sccm, liquid flow rate: 0.7 mL/min, solvent: methanol, catalyst loading: 2.53 g

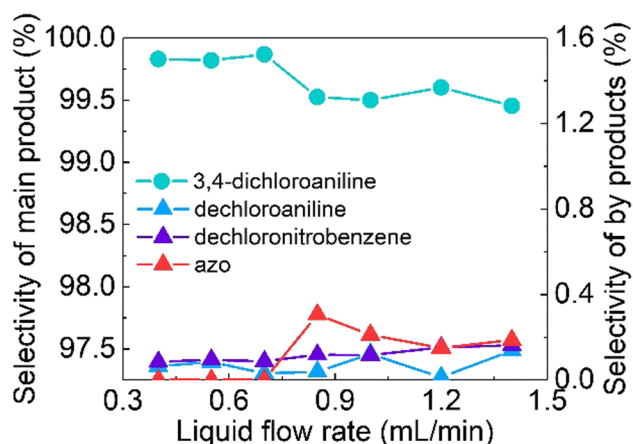


Fig. 5 Product composition for the hydrogenation of 3,4-DCNB with different liquid flow rates with Pt/C catalyst. Reaction condition: system pressure: 2.0 MPa, reactant mass concentration: 10 wt%, gas flow rate: 25 sccm, temperature: 70 °C, solvent: methanol, catalyst loading: 2.53 g

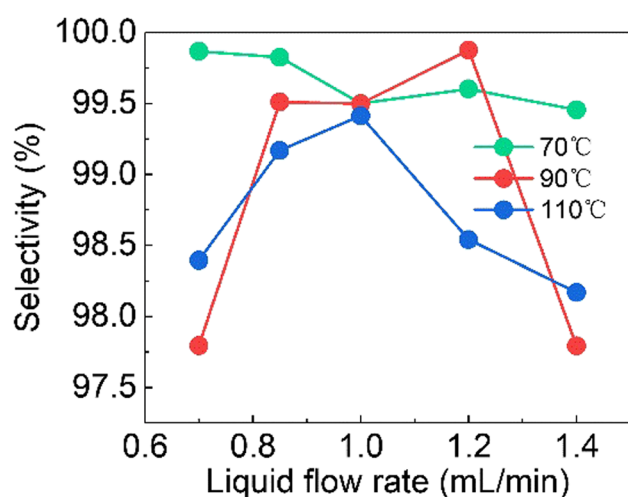


Fig. 6 Product composition for the hydrogenation of 3,4-DCNB in different liquid flow rates with Pt/C catalyst at varied temperatures. Reaction condition: system pressure: 2.0 MPa, reactant mass concentration: 10 wt%, gas flow rate: 25 sccm, solvent: methanol, catalyst loading: 2.53 g

Table 2 The comparison of yield at different temperatures under batch and continuous flow mode

Temperature	Operation mode	Conversion	Selectivity
60 °C	Batch	100	61.8
	Continuous flow	100	99.7

Reaction conditions: reactant mass concentration: 10 wt%, liquid flow rate: 0.7 mL/min, gas pressure: 2 MPa. Stirring speed: 200 r/min, solvent: methanol, catalyst: Pt/C, catalyst loading: 2.54 g.

reaction temperature of 70 °C, pressure of 2.0 MPa and liquid flow rate of 0.7 mL/min.

Comparison between batch and continuous flow

In this part, selective hydrogenation of 3,4-DCNB in a batch reactor (200 mL) was conducted and the reaction results were compared between batch and continuous-flow mode. In the batch experiment, the solution (100 mL) and catalysts were added into the reactor and N₂ was transferred into the batch reactor three times to fully remove the air. Then H₂ was filled into the reactor and released to atmospheric pressure for three times. Finally, the reaction was conducted and the samples were collected. For the continuous flow experiment, the reaction was conducted under the same conditions and the liquid flow rate was set to 0.7 mL/min to ensure the same production capacity.

Based on the data shown in Table 2, the selectivity of 3,4-DCAN was 61.8% and more than 30% CAN was detected by GC in batch reactor. Moreover, the reaction was completed in two hours. In contrast, due to the larger interfacial

area and shorter diffusion distance in the micropacked bed reactor, hydrogenation in the micropacked bed reactor was finished within two minutes. In addition, side reaction such as dechlorination could be perfectly inhibited by the precise control of residence time while in the batch reactor, dichloroaniline would be further hydrogenated to *m*-chloroaniline and *p*-chloroaniline owing to back mixing resulting in huge challenge for the subsequent separation process.

Applications in relevant substrates

While 3,4-DCNB represented a suitable model compound for the screening different catalysts and optimizing the reaction conditions, an efficient H-flow system based on micropacked bed reactor was successfully applied on the selective hydrogenation process and the system was also tested for the hydrogenation of relevant chlorinated nitro compounds which were significant intermediates in fine chemical industry [32, 41, 42].


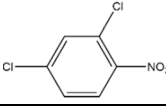
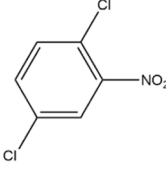
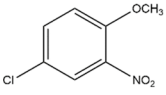
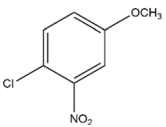
Table 3 presented that the results of other chlorinated nitro compounds reduced in the H-flow system. In comparison with the reduction of 3,4-DCNB, lower pressure was demanded by the 2,4-dichloronitrobenzene and 2,5-dichloronitrobenzene, otherwise, the content of CAN would exceed 2%. This difference may be attributed to the mutual position of Cl atom and nitro group in the benzene ring. While for 4-chloro-2-nitroanisole and 5-chloro-2-nitroanisole, these two substances were more prone to dechlorinate, hence the reaction temperature was adjusted to 50 °C except for the adjustment of pressure. And due to the low solubility of 4-chloro-2-nitroanisole in methanol, the concentration was also altered to 5 wt%.

The yields of corresponding aniline were all at the level of 99.5%, verifying the efficiency and applicability of H-flow system for the selective hydrogenation of chlorinated nitro compounds.

Conclusion

The H-Flow system based on micropacked bed reactor was successfully applied for the selective hydrogenation of 3,4-DCNB. The reaction performance under different pressures, liquid flow rates, temperatures and catalysts were optimized and maximal yield of 99.8% was obtained using Pt/C catalyst under the temperature of 60 °C, the mass concentration of 10 wt%, the pressure of 2.0 MPa and the liquid flow rate of 0.7 mL/min. Additionally, various relevant chlorinated nitro compounds were also applied for the continuous hydrogenation in micropacked reactor and all yields were at the level of 99.5% with full conversion. The H-flow system based on micropacked bed reactor exhibited remarkable selectivity and efficiency for the reduction of halogenated

Table 3 Selective hydrogenation of chlorinated nitro compounds in the H-flow system

Substrate	Mass concentration	<i>T</i>	Pressure/MPa	conversion	Product composition	
					Main product	Dechlorinated product
	10 wt%	60	2.0	100	99.6	0.4
	10 wt%	60	1.5	100	99.4	0.6
	10 wt%	60	1.5	100	99.5	0.5
	5 wt%	50	1.5	100	99.6	0.4
	10 wt%	50	1.5	100	99.4	0.6

Reaction conditions: residence time: 2.2 min, solvent: methanol, H₂ flow rate: 15 sccm

nitroaromatics and side reaction was perfectly suppressed through the precise control of residence time and intensified mass transfer. Further purification for the recovery of the 3,4-DCAN could be achieved by a simple distillation owing to the large difference of the boiling points between methanol (64.7 °C) and 3,4-DCAN (272 °C) at the standard conditions. Nevertheless, considering scale-up and process intensification, optimization toward higher flow rate and substrate concentration will be crucial for further development.

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