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Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.9b00416 • Publication Date (Web): 04 Dec 2019

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Continuous hydrogenolysis of N-diphenylmethyl groups in a micro-packed bed reactor

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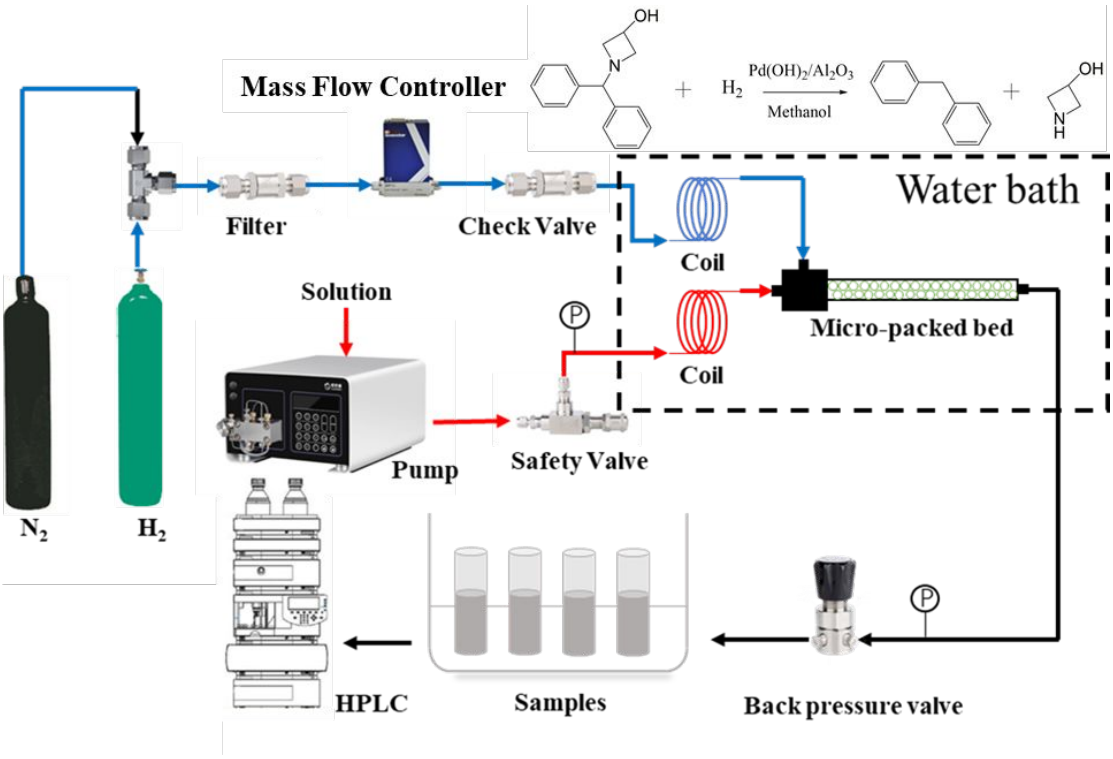


Abstract

In recent years, with the advancements in continuous flow technology and the ever-increasing demand for green processes, continuous flow chemistry has become more and more widely adopted in the pharmaceutical industry. In this work, the continuous hydrogenolysis of N-diphenylmethylazetidin-3-ol to 3-azetidinol in micro-packed bed reactors was demonstrated. The effects of different catalysts, solvent types and the additives on the reaction in a micro-packed bed reactor were investigated. The results indicate that the reaction rate per reactor volume in increased by 100 times due to the larger interfacial area and shorter diffusion distance in micro-packed reactors. To further study the long-term stability of the reaction system, the flow system was successfully operated for 240 h by adjusting the reaction temperature and liquid flowrate. The reaction kinetics model for the hydrogenation of N-diphenylmethylazetidin-3-ol in methanol was studied after the internal and external diffusion limitations were eliminated. In addition, the type of adsorption of the reactants on the catalyst and the rate-determining step of the reaction were investigated.

Keywords: Hydrogenation; Debenzylation; Kinetics; Micro-packed bed reactors

Introduction

The hydrogenation reactions are ubiquitous chemical transformations in petrochemical industry, food industry and pharmaceutical industry. About 9% of all chemical transformations in the pharmaceutical synthesis are hydrogenation reactions [1]. In addition to the common hydrogenations of unsaturated bonds, deprotection reactions with H_2 (hydrogenolysis) are also widely used in organic synthesis, accounting for about 3 % of total pharmaceutical synthesis [1].

In the production of pharmaceuticals and fine chemicals, protection and deprotection of functional groups such as alcohols and amines are often necessary to avoid possible side reactions [2]. In particular, formation and cleavage of benzyl-type ethers and benzyl-type amines represent a common strategy in organic synthesis [3]. The benzyl group is easily installed, by substitution of benzyl halide [4] or condensation of benzaldehyde [5], and is stable to mild aqueous acid/base solutions, metal hydrides and mild oxidants [3a]. Later, it can be removed through direct hydrogenation with the gas of H_2, transfer hydrogenation with $NaBH_4$ or using Lewis acids such as $AlCl_3$ or triflic acid [6]. Among these methods, precious metal catalyzed hydrogenolysis with high pressure gas of H_2 is one of the green and efficient options, in accordance with “atom economy”, “reduce derivative” and “catalysis” described in the green chemistry principles [7].

The batch reactor is widely used for hydrogenation in the pharmaceutical industry and fine chemical industry because the reactor structure is simple. However, there are still several problems limiting its application. First, the heterogeneous hydrogenation is usually thought to be a fast reaction [8]. Due to the severe gas-liquid mass transfer limitation for hydrogenation in batch reactors, a long reaction time (3~24 h) and a large reactor volume (1000~5000 L) are required in the industry production. Second, multiple gas replacement operations and separation of the catalysts are needed for one batch production, which is troublesome and labor-intensive. Third, safety issue is concerned

for the hydrogenation process because of the store of a great amount pressurized hydrogen and frequent operation of palladium carbon catalyst [9]. As a result, it is highly desired to develop a safe and efficient hydrogenation method for pharmaceutical industry and fine chemical industry.

The continuous flow technology has been identified as the number one research area for the advancement of green pharmaceutics by the ACS GCI Pharmaceutical Roundtable [10]. Continuous flow processes have many inherent advantages including the effective suppression of side reactions by precise control of reaction conditions, reduced cost of the separation/purification process, increased production, reduced energy consumption, reduced equipment volume, and excellent safety [11]. Among them, the continuous hydrogenation in micro-packed bed reactors (μPBRs) is promising for the challenges of hydrogenation. In μPBRs, the pressurized hydrogen and liquid reactants flow concurrently through packed beds of catalyst particles with diameters usually smaller than 500 μm. Due to the microscale dimension, it has the advantages of good gas-liquid-solid mass transfer, excellent heat transfer and improved safety while maintain the plug flow characteristics and fixed bed catalyst immobilization [12]. Bimbisar Desai et al. achieved the selective debenzylation of substrate containing acylamide and carbon-carbon double-bond structure in the H-Cube packed bed reactors [13]. This reaction was performed with Pd/C catalysts under 1 bar, 40 ℃ and a low liquid rate of 1.0 ml/min with the yield of 95%. Marie-Christine Matos et al. successfully achieved simultaneous removal of multiple benzyl groups in μPBRs with the yield of 89 % under 80 bar and 60 ℃ with Pd/C catalysts [14]. These results demonstrate the efficiency and safety of μPBRs in debenzylation than that of the batch reactor.

In this paper, a flow system based on μPBRs was developed to perform the H_2-based hydrogenolysis. The hydrogenolysis of N-diphenylmethylazetidin-3-ol (DMAOL) to 3-azetidinol (Figure 1) was employed as the model reaction, which is an organic pharmaceutical intermediate for the synthesis of antibiotics and antibacterial agents[15].

The catalysts and solvents suitable for this kind of reaction were first screened and then the reaction performance and kinetics were investigated.

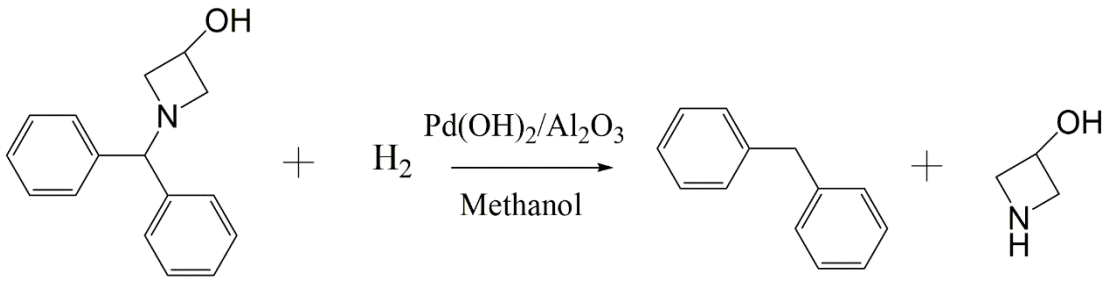


Figure 1. Hydrogenolysis of N-diphenylmethylazetidin-3-ol to 3-zaetidinol

Material and methods

Chemicals. N-diphenylmethylazetidin-3-ol ($C_{16}H_{17}NO$) was acquired from PharmaBlock Sciences Ltd. (Nanjing); Methanol (CH_3OH, 99.9 %) and Acetonitrile (C_2H_3N, 99.9 %) were purchased from J&K Scientific Ltd. (Beijing); Tetrahydrofuran (C_4H_8O, AR), Ethyl acetate ($C_4H_8O_2$, AR), Toluene (C_7H_8, AR) and Triethylamine ($C_6H_{15}N$, AR) were purchased from Beijing Tongguang Fine Chemicals Company; 2-Methyltetrahydrofuran ($C_5H_{10}O$, 99 %) was purchased from Energy Chemical; Diphenylmethane ($C_{13}H_{12}$, 99 %) was purchased from Nuobeiwei Technology Co. Ltd. (Beijing); Acetic acid (CH_3COOH, 99.5 %) was purchased from Beijing Chemical Factory. Hydrogen (H_2, 99.999%) was purchased from Beijing Beiwen Gas Manufacturing Plant. Nitrogen (N_2) was purchased from Air Liquide (Tianjin). The Palladium hydroxide/Alumina particle catalyst ($Pd(OH)_2/Al_2O_3$, 7 wt%) with an average size of 500 μm and palladium/alumina particle catalyst (Pd/Al_2O_3, 5 wt%) with an average size of 500 μm were acquired from Dalian Institute of Chemical Physics The Palladium/Carbon powder catalyst (Pd/C, 5 wt%, 55 % water content) and Palladium hydroxide/ Carbon powder catalyst ($Pd/(OH)_2/C$, 5 wt%, 55 % water content) were acquired from HEOWNS Biochem Technology LLC (Tianjin) and Macklin Biochemical Co. Ltd. (Shanghai), respectively.

Experimental setup. A schematic overview of the experimental setup is shown in Figure 2. Liquid was delivered by a plunger pump (Beijing Oushisheng Technology Co. Ltd.). N_2 gas and H_2 gas from the regulated cylinder were fed via a mass flow controller (Beijing Sevenstar Electronics Co. Ltd.) The outlet of the pump was connected with a safety valve (Beijing Xiongchuan Technology Co. Ltd.) to automatically release the liquids from the tubing when the pressure exceeded 40 bar. Two pressure gauges were placed in the inlet and outlet of the reactor to monitor the pressure drop across the reactor. The reactor and two coils were immersed in a water bath to control the reaction temperature. The outlet of the packed bed was connected to a back pressure regulator (Beijing Xiongchuan Technology Co. Ltd.) to control the system pressure.

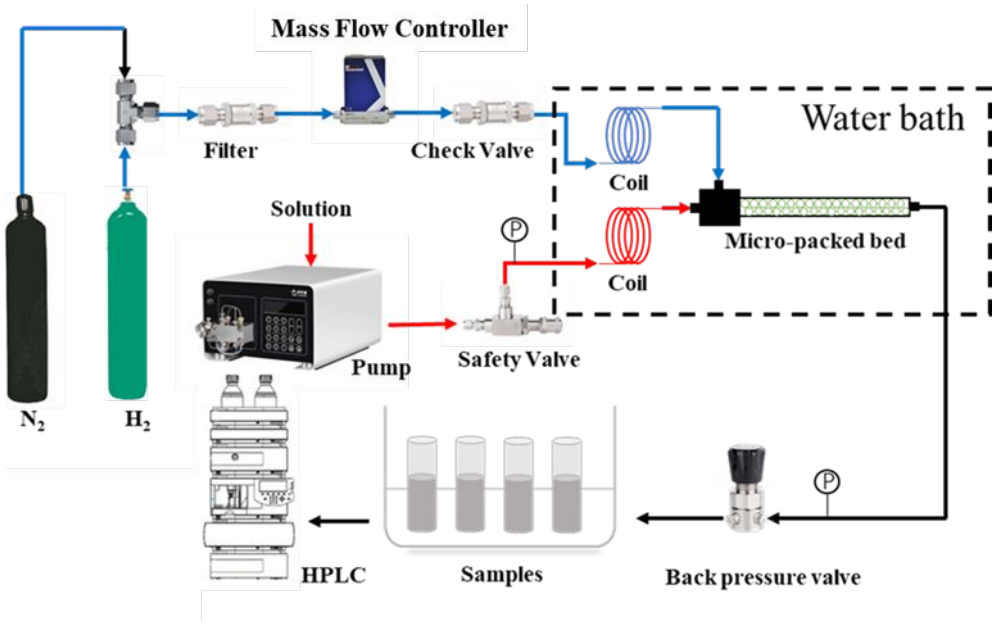


Figure 2. The schematic overview of the flow system for hydrogenation based on the μPBRs.

The mixing of the feeding gas and liquid before the entering the packed bed reactor greatly affects the stability and reproducibility of the system. To minimize the

hydrodynamic instabilities, the reactor structure followed the design which was described in literature [16] and more details about the reactor structure can be found in this paper. The packed tube is made of stainless steel with a length of 20 cm, an outer diameter of 6.35 mm (1/4 inch) and an inner diameter of 4.35 mm.

The reactant DMAOL was prepared as a specific concentration in the solvent. The particulate catalysts were filled into the reactor through a funnel and the catalyst bed was packed as tight as possible. The micro-packed bed packed with a certain mass of catalyst was pre-wetted by the solution, then H_2 was transported into the reactor at a specific flow rate (F_G). Back pressure (P) and liquid flow rate (F_L) were then set to the required values while simultaneously raising system temperature (T). After waiting for the reaction time, which was at least three times of the liquid residence time (τ), the system achieved steady state and a sample was collected. When the desired samples were acquired, water bath was turned off and system pressure was reduced to atmospheric pressure. After the system was depressurized, N_2 gas was transported through the micro-packed bed reactor to fully remove the residual gas-liquid mixture and ensure the catalyst was stored in a nitrogen atmosphere.

As hydrogenation in μPBRs involves gas-liquid-solid process, the residence time of liquid τ representing the reaction time should be carefully calculated. According to the definition of liquid holdup in our previous paper [16], τ is calculated by the following equation:

$$\tau = \frac{\pi D^2 L \varepsilon h}{F_L} \quad (1)$$

where, D (cm) and L (cm) are the inner diameter and the length of the packed tubing, respectively; ε is the bed porosity; h is the liquid holdup representing the fraction of interstitial open space filled by liquid. From this equation, we can find that the residence time is only determined by the liquid holdup, which can be calculated with the equations reported in literature [16].

Sample analysis. The samples were collected directly from the outlet of the hydrogenation system. The samples were diluted and measured by HPLC (Agilent 1260 Infinity II) with a UV detector under the following conditions: the column temperature, 30 °C; the injection volume, 5 μL; the ultraviolet wavelength, 220 nm; the mobile phase composition, Acetonitrile: water (70:30, v/v), 1.0 mL/min; the column, Agilent Eclipse plus C18 (4.6 × 250mm, 5μm). No side reaction was observed when performing hydrogenolysis of DMAOL in the μPBRs. Hence the selectivity of the reaction is assumed to be 100 %. The product of 3-zaetidinol cannot be measured by HPLC because it has no UV absorption. Only the concentrations of DMAOL and diphenylmethane are measured to calculate the conversion (X) of DMAOL as follows.

$$X = \frac{C_B}{C_A + C_B} \times 100\% \quad (2)$$

where, C_A (mol/L) and C_B (mol/L) are the concentration of DMAOL and diphenylmethane in the sample, respectively.

Results and discussion

Screening reaction conditions. As we know that the catalyst and solvent have a great influence on the hydrogenation. To develop a most efficient continuous hydrogenolysis in μPBRs, the screening of catalyst and solvent was first performed.

Effect of catalyst. It is well known that catalytic activity can be influenced by the catalyst type and support. It has been reported that Pd on activated carbon is more effective for debenzylation than Pd on oxide supports such as SiO_2, Al_2O_3, TiO_2 [17]. In addition, Pearlman's catalyst—$Pd(OH)_2/C$ [18] was commonly used in debenzylation reaction, which demonstrated the best catalytic activity [19]. In this study, the catalysts of Pd and $Pd(OH)_2$ on the supports of activated carbon and alumina were tested under the same conditions. The reaction performances and the catalytic activities using different catalysts are given in Table 1. Here the mass of the substrate converted per unit time

and unit mass catalyst [g(raw material)*g(catalyst)$^{-1}$*min^{-1}] was used to evaluate the catalyst activity.

Table 1 . The comparison of the catalytic activities of several catalysts on the hydrogenolysis of DMAOL

Catalyst	Conversion	Catalyst activity [g(raw material)*g(catalyst)$^{-1}$*min^{-1}]
Pd/C (5wt. %, 55% H_2O content)	36.9%	0.31
Pd/Al_2O_3 (5wt. %)	28.3%	0.11
$Pd(OH)_2$/C (5wt. %, 55% H_2O content)	86.3%	0.73
$Pd(OH)_2$/Al_2O_3 (7wt. %)	86.4%	0.23

Experimental conditions: flow rate of DMAOL (3.8 wt.% in methanol) solution: 0.3 ml/min; P= 21 bar; T= 313.15 K; F_G= 40 sccm (the molar ratio of H_2 to DMAOL: 43); the amount of catalyst (diluted with 4.5 g alumina sphere): 0.5 g.

From Table 1, it can be concluded that the catalytic activity of $Pd(OH)_2$ catalyst is about two times of that of Pd catalyst for the hydrogenolysis reaction. At the same time, it also proves that Pd or $Pd(OH)_2$ catalyst on activated carbon is more efficient than Pd or $Pd(OH)_2$ on oxide supports of Al_2O_3. But the carbon support used here was at powder state, which would cause a large pressure drop and even clogging in μPBRs. For the oxide supports of Al_2O_3, no significant pressure drop was observed, which means that values of the pressure transducers before and after the packed bed reactor were almost the same. As a result, $Pd(OH)_2$/Al_2O_3 catalyst was adopted for the following research in this paper.

Effect of solvent. In hydrogenation, the solvent frequently plays an important role [20], which would affect the solubility of hydrogen, adsorption mechanism of solvent molecules on the active sites of the catalyst, agglomeration of catalyst particles and nonbonding interactions between reactant or product molecules with the solvent [21]. The choice of a suitable solvent can effectively increase the reaction rate, and conversely, it will inhibit the reaction rate and even poison the catalyst. Here, the effect of some common organic solvents was explored. To ensure the catalyst has the same catalytic activity, the reaction using the solvent of methanol was performed for a catalyst activity test every time before the solvents were changed.

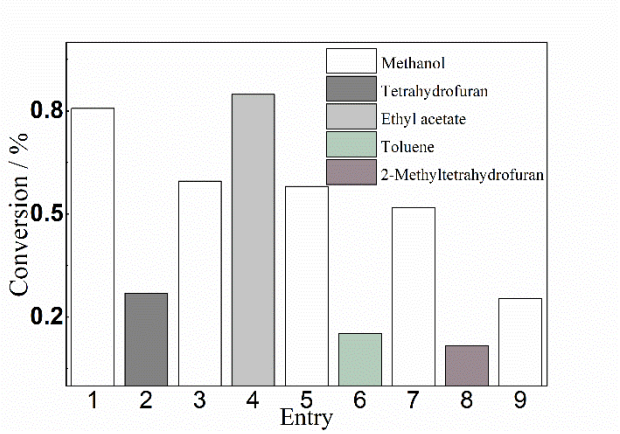


Figure 3. Conversion of DMAOL in different solvents

Experimental conditions: flow rate of DMAOL (3.8 wt.% in methanol) solution: 0.5 ml/min; P= 21 bar; T= 313.15 K ; F_G = 40 sccm (the molar ratio of H_2 to DMAOL: 26); the amount of 7 wt. % $Pd(OH)_2/Al_2O_3$ catalyst (diluted with 4.0 g alumina sphere): 1.0 g.

Figure 3 shows the effect of several organic solvents on the conversion of DMAOL at the same experimental conditions. When the solvents are methanol and ethyl acetate, X can reach about 81% and 85% at the residence time of 2.1 min in the micro-packed bed, indicating the beneficial effect on the catalytic activity. Compared with the two

solvents, the reaction rates in the other three solvents are much slower. In addition, it is found that the *X* is abruptly decreased after the use of the tetrahydrofuran (Entry 2) and 2-methyltetrahydrofuran (Entry 8). It indicates that tetrahydrofuran substances have a certain toxic effect on the catalyst which should be avoided in the reaction. But the reason for this toxic effect is still unclear and we didn't find any reports about the toxic effect of tetrahydrofuran for the hydrogenolysis with $Pd(OH)_2$ catalysts. Further research are required to find the exact mechanism of catalyst deactivation. As a result, both methanol and ethyl acetate are excellent solvents for hydrogenation of DMAOL. Considering the low price and easy recyclability of methanol (low boiling point), methanol is chosen as the solvent for this reaction.

Effect of additive. It is known that N-benzyl is the acid-labile protecting group. Acidic conditions favor N-debenzylation, while basic conditions inhibit N-debenzylation [22]. In order to investigate whether the effect of acidic or basic additives on the removal of the diphenylmethyl group was similar to that of the debenzylation, an experiment was carried out by adding acetic acid and triethylamine to the solution. The conversions with different additives are given in Table 2.

Table 2 . The effect of additive on conversion of DMAOL

Entry	Pressure/bar	Additive	Conversion/%
1	21	No additive	79.7
2	21	Acetic acid	91.9
3	21	Triethylamine	67.6
4	21	Water	73.5

Experimental conditions: flow rate of DMAOL (3.8 wt.% in methanol) solution: 0.5 ml/min; T= 313.15 K ; F_G= 40 sccm (the molar ratio of H_2 to DMAOL: 26); the amount of 7 wt. % $Pd(OH)_2/Al_2O_3$ catalyst (diluted with 4.0 g alumina sphere): 1.0 g; the concentration of additive is 8.8 wt. % in entry 2, 3 and 4.

It is found that the conversion of entry 2 is higher than that of entry 1 while the conversion of entry 3 is lower than that of entry 1. The results indicate that acidic conditions favor the removal of the diphenylmethyl group, while basic conditions inhibit the removal of the diphenylmethyl group. The results indicate that the debenzylation with hydrogenolysis can be enhanced by addition of acetic acid into the solution and the addition of basic additive should be avoided. The conversions of entry 4 is also slightly lower, indicating that the existence of water would have an adverse effect on the reaction. The exact reason for the adverse effect of water on the reaction is still unclear, which required further investigation.

Reaction performance test. In this part, we compared the reaction performance of traditional batch reactor (250 mL volume) with that of micro-packed bed reactor. Here the mass of the substrate converted per unit time of the unit reactor volume [g(raw material)*mL(reactor volume)$^{-1}$*min^{-1}] was used to evaluate the reactor performance. As shown in Table 3, the reaction rate in batch reactor was very slow with a low conversion of 18.5% after 3h and 38.1% after 5h. The main reason is the limited gas-liquid mass transfer rate in batch reactor. In contrast, due to the larger interfacial area and shorter diffusion distance in micro-packed reactors, a high conversion of 63% can be obtained with only a short residence time of 1.9 min. In addition, the value of conversion per unit volume per unit time of the micro-packed bed reactor is 100 times of that of the batch. As a result, the micro-packed bed reactor is more efficient for the hydrogenation of DMAOL than the traditional batch reactor.

Table 3 . The comparison of performances of traditional batch and micro-packed bed reactors

Entry	Residence time	Conversion/%	reactor performance [g(raw material)* mL(reactor volume)$^{-1}$*min^{-1}]
1	3.0 h	18.5	2.5×10^{-5}
2	5.0 h	38.1	3.1×10^{-5}
3	1.9 min	63.0	3.1×10^{-3}

Experimental conditions: initial concentration of DMAOL in methanol: 3.8 wt.%; T= 333.15 K; P= 21 bar; the amount of $Pd(OH)_2/Al_2O_3$ catalyst (7 wt. %): 0.5 g; the entry 1 and 2 were carried out in traditional batch: stirring speed was 200 rpm to avoid the damage of catalysts; raw material volume was 200 mL; the entry 3 was carried out in micro-packed bed reactor: F_L = 0.5mL/min, F_G= 40 sccm (the molar ratio of H_2 to DMAOL: 26).

To further study the long-term stability of the reaction system and catalyst life of $Pd(OH)_2/Al_2O_3$, the reaction performance was investigated in the micro-packed bed reactor for 240 h as shown in Figure 4. In order to achieve the maximum reaction conversion, the catalyst bed was not diluted with alumina sphere filler (4.3 g $Pd(OH)_2/Al_2O_3$) and the concentration of the substrate was further improved to 10 wt.% in this experiment. As first, the fresh catalyst had a high catalytic activity and the conversion could reach 100% for 70 h. After 70 h, the conversion began to decrease because of the deactivation of the catalyst. The reason of deactivation and following regeneration method are still unclear and we are still working on them. The most possible reason for the deactivation is the adsorption of substances on the precise metal catalyst due to the strong interaction between amine and precise metal. To increase the reaction rate, the reaction temperature was gradually increased to maintain the high conversion. After 116 h, the liquid flow rate was decreased from 0.4 ml/min to 0.3 m/min to increase the residence time to ensure the conversion. By increasing the

temperature and decreasing the flow rate, the conversion of the substrate could stay above 99.5% for 190 h. After that, the conversion decreased rapidly indicating a severe catalyst deactivation occurred and the catalyst was required to be replaced or regenerated. From the results in Fig. 4, it demonstrates that about 90 g DMAOL can be efficiently converted to the product for one gram $Pd(OH)_2/Al_2O_3$ catalyst in the micro-packed bed and the continuous flow system can achieve an efficient production of 3-azetidinol for 190 h (the temperature and liquid flowrate were changed after 70h). However, more issues such as heat transfer, gas-liquid mixing and pressure drop across the packed bed should be carefully considered in the scaling up of this continuous system.

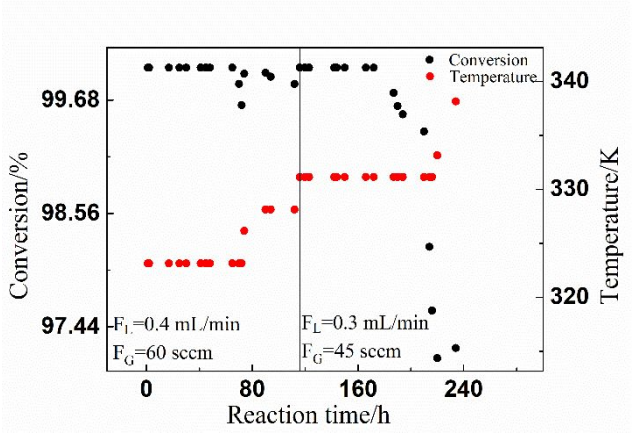


Figure 4. The stability of reaction system in the micro-packed bed reactor

Experimental conditions: initial concentration of 1-(diphenylmethyl)-3-hydroxyazetidine: 10 wt.%; P= 25 bar ; the amount of $Pd(OH)_2/Al_2O_3$ catalyst (7 wt. %): 4.3 g. When the reaction time is less than 116 h, F_L= 0.4 mL/min, F_G= 60 sccm; when the reaction time is more than 116 h, F_L= 0.3 mL/min, F_G = 45 sccm.

Kinetic study of hydrogenolysis of DMAOL

Mass transfer considerations. In the three-phase catalytic reaction system, the mass transfer typically includes three steps in series: dissolution of H_2 in liquid, diffusion of dissolved H_2 through liquid to the solid catalyst surface and intra-particle diffusion to the active catalytic sites, which can influence the reaction kinetics [23]. Therefore, it is important to confirm that the mass transfer limitation can be ignored before determining the kinetic parameters.

First, external mass transfer should be carefully evaluated [10a]. Due to the use of pure hydrogen as reactant, the mass transfer resistance occurred in the gas film side of the gas–liquid interface can be ignored, and the mass transfer resistance on the liquid side at gas–liquid interface and the mass transfer resistance at the liquid–solid interface should be considered[24]. Exploring the effect of different liquid superficial velocities (flow rate/cross-sectional area of packed bed) on the reaction rate at the same residence time can be used to determine whether external mass transfer limitation can be ignored.

In the present study, four μPBRs with the same volume (3.0 ml) and different internal diameters (4.35 mm; 4.57 mm; 5.35mm; 5.75mm) were designed for the experiments. These reactors were filled with the same amount of catalyst. This method can successfully achieve different liquid superficial velocities in different reactors under the same flow rate and residence time.

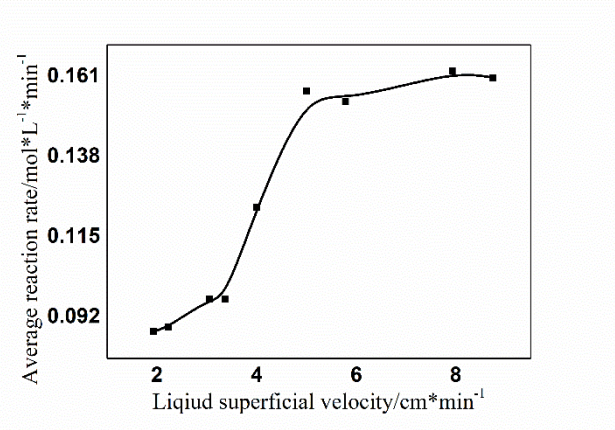


Figure 5. Effect of different liquid superficial velocities on the average reaction rate.

Experimental conditions: initial concentration of DMAOL: 5.7 wt. %; P= 21 bar; T= 313.15 K; F_G= 40 sccm; the amount of 7 wt. % $Pd(OH)_2/Al_2O_3$ catalyst (diluted with 4.0 g alumina sphere): 1.0 g.

Figure 5 shows that when the liquid superficial velocity exceeds 5.0 cm/min, the average reaction rate does not change significantly as the liquid velocity increases. This result indicates that the reaction is independent of external mass transfer when the liquid superficial velocity is greater than 5.0 cm/min. It can be considered that the external mass transfer resistance has been eliminated.

Internal mass transfer limitations within the porous media were evaluated by calculating the Weisz modulus (Mw), which ratios the effective reaction time and the diffusion time within the catalyst particle [25]. The Weisz modulus of substrate and H_2 were calculated as shown in the supporting information. The values of the Weisz modulus were determined to be 0.123 and 0.776, for H_2 and DMAOL, respectively, indicating only minor contributions from intraparticle diffusion and the internal mass transfer resistance can be ignored.

Kinetic model of hydrogenolysis of DMAOL. The reaction kinetic model was studied after the internal and external transfer resistances were eliminated to ensure that the reaction was in the kinetic-control region. Here, the kinetics is presented by a power-law model, which can be described by an empirical kinetic expression:

$$r = k' C_A^{\alpha} P^{\beta} = -\frac{dC_A}{dt} \quad (3)$$

where α and β are the reaction orders of reactants.

First, the value of α was determined by changing the initial concentration of the reactants at the same residence time. During the experiment, it was found that there was no significant pressure drop in the reactor through the pressure gauges at the inlet and outlet of the packed bed reactor, the reaction pressure can be considered to be constant. At first, the temperature and pressure were kept unchanged, the term $k'P^{\beta}$ could be regarded as a constant K, and the following equation is obtained:

$$r = KC_A^{\alpha} = -\frac{dC_A}{dt} \quad (4)$$

After integrating the Equation 4 and considering the boundary conditions [t= 0, C_A= C_{A0}; t= τ, C_A= C_{A0}(1-X)], Equation 5 is obtained.

$$X = 1 - \left[\frac{K\tau(\alpha - 1)}{{C_{A0}}^{1-\alpha}} + 1\right]^{\frac{1}{1-\alpha}} \quad (5)$$

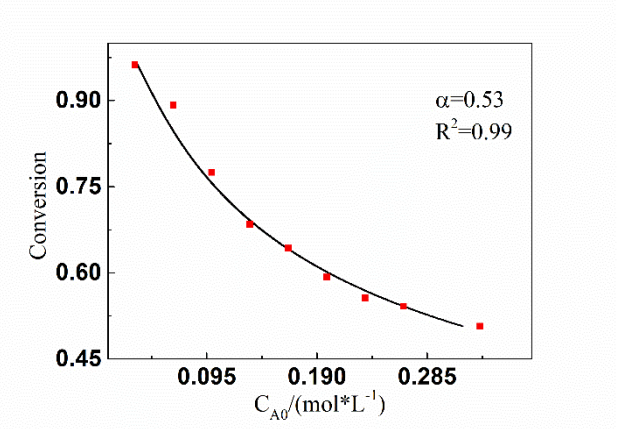


Figure 6. The conversion versus the initial concentration of DMAOL in methanol.

Experimental conditions: P= 21 bar; T= 313.15 K; F_G= 40 sccm; F_L = 0.9 mL/min; τ = 63.6 s; the amount of 7 wt. % $Pd(OH)_2/Al_2O_3$ catalyst (diluted with 4.0 g alumina sphere): 1.0 g.

The hydrogenolysis of DMAOL was performed at nine initial concentrations ranging from 0.033 mol/L to 0.33 mol/L and the conversions at different concentrations were given in Figure 6. The experimental data was fitted with Equation 5. It was found that when α is 0.53, the calculated curve agreed well with the experimental values (R^2=0.99), indicating that the reaction order of DMAOL is 0.53.

The value of β is determined by changing the reaction pressure at the same residence time. The liquid holdup is related to the superficial velocities of the gas and liquid. The change of the reaction pressure will lead to an obvious change for the superficial velocity of the gas and corresponding residence time of liquid. To eliminate the effect of reaction pressure on the residence time, the liquid flowrate was varied from 0.58 to 1.04 mL/min according to the model described in literature [16] to ensure the same residence time. Taking α = 0.53, integrating and deforming the Equation 3, the Equation 6 was obtained.

$$X = 1 - \left[1 - \frac{0.47k'\tau P^{\beta}}{C_{A0}^{0.47}}\right]^{\frac{1}{0.47}} \quad (6)$$

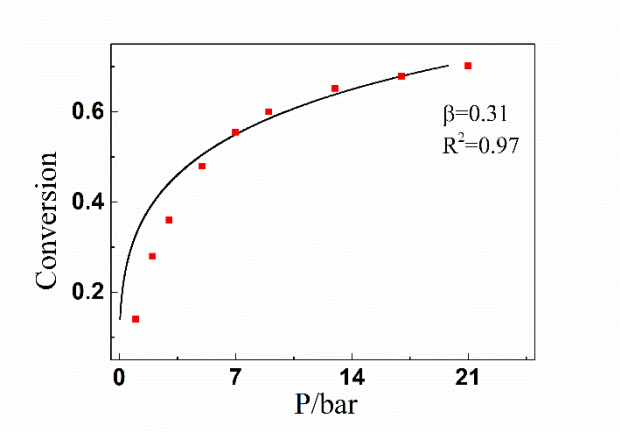


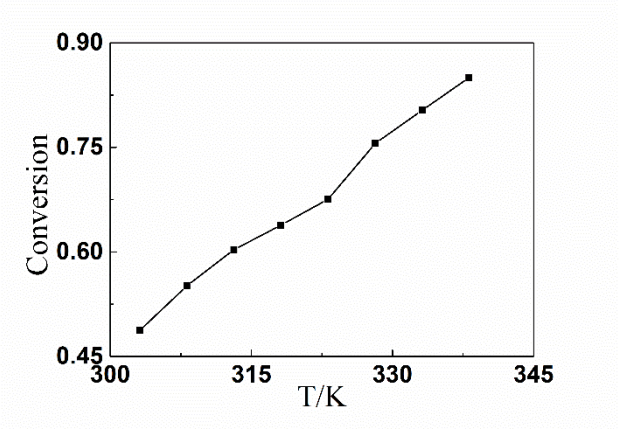
Figure 7. The conversion versus the reaction pressure.

Experimental conditions: C_{A0}= 0.20 mol/L; T= 313.15 K; F_G= 40 sccm; flow velocity = 16.32 cm/min; $\tau =$ 73.5 s; the amount of 7 wt. % $Pd(OH)_2/Al_2O_3$ catalyst (diluted with 4.0 g alumina sphere): 1.0 g.

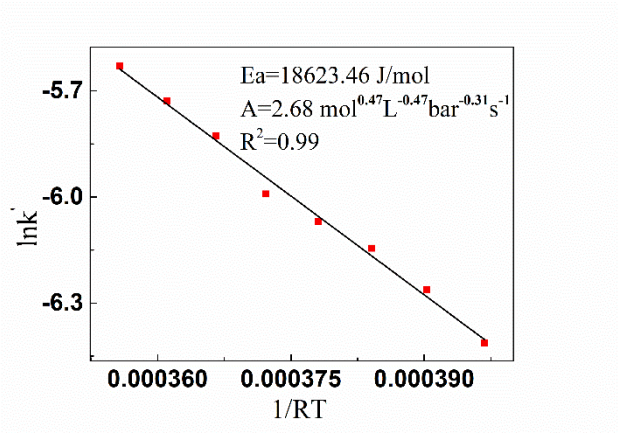
The hydrogenolysis of DMAOL was performed at nine reaction pressures and the obtained experimental results were shown in Figure 7. Then the experimental data was fitted with Equation 6. It shows that when β is 0.31, the calculated curve agreed well with the experimental values (R^2= 0.97), indicating that the reaction order of hydrogen pressure is 0.31.

After determining the values of α and β, the two values were substituted into Equation 3, Equation 7 can be obtained to calculate the value of k'.

$$k' = \frac{C_{A0}^{0.47}[1-(1-X)^{0.47}]}{0.47P^{0.31}\tau} \quad (7)$$



(a)



(b)

Figure 8. (a) The conversion versus the reaction temperatures. (b) Plot of lnk' versus $1/RT$.

Experimental conditions: C_{A0}= 0.20 mol/L; P=21 bar; F_G = 40 sccm; F_L = 0.9mL/min; τ = 63.6 s; the amount of $Pd(OH)_2/Al_2O_3$ catalyst (7 wt. %): 1.0 g.

Figure 8. (a) shows the conversions at varied reaction temperatures ranging from 303.15 K to 343.15 K. The results indicate that the reaction rate increases as the temperature increases. The values of k' at different temperatures were calculated with the Equation 7. According to the Arrhenius formula, $k' = Ae^{\frac{-E_a}{RT}}$, the activation energies (Ea) and Arrhenius constant (A) can be obtained by fitting lnk' and $1/RT$ as shown in Figure 8. (b), which are 18.6 ± 0.7 kJ/mol and 2.68 ± 0.25 $mol^{0.47}/(L^{0.47}bar^{0.31}s)$, respectively ($R^2$=0.99).

After all the parameters were obtained, the kinetic model could be established.

$$r = 2.68\left(\frac{mol^{0.47}}{L^{0.47}\cdot bar\cdot^{0.31}s\cdot g\text{cat}}\right)\times e^{\frac{-1.86\times10^4\,(J/mol)}{8.314\,(J\cdot mol^{-1}\cdot K^{-1})\times T}}C_A^{0.53}P^{0.31} \quad (8)$$

The type of adsorption of the reactant on the catalyst and the rate-determining step of the reaction were studied after the kinetic model was established. The heterogeneous hydrogenation rate is determined by one of the steps of adsorption of the substrate or

hydrogen, desorption of the product, and surface reaction when the reaction is in the kinetics-control zone [26]. In addition, due to the different adsorption mechanisms of the reactants on the porous catalysts, research work on kinetic models has been further complicated. Based on Langmuir equation, many rate expressions were studied in this paper.

Due to the different adsorption mechanisms of the reactants [26], there are up to 16 different theoretical kinetic models. All the possible theoretical models have been fitted with the experimental data. If a mathematical model agrees well with the data, the model can be considered to be the reaction kinetic model.

After excluding the other 15 models, the kinetic model was obtained (R^2=0.99 for C_{A0}, R^2=0.96 for P, the detailed process and fitting results were shown in supporting information):

$$r = \frac{kK_A C_A K_H P}{(1 + K_A C_A + K_B C_B)(1 + \sqrt{K_H P})^2} \quad (9)$$

where, k, K_A, K_B, and K_H are the reaction rate constant, adsorption equilibrium constant of substrate, product and H_2, respectively.

From the kinetic model, we can find that the diphenylmethyl removal rate of DMAOL with $Pd(OH)_2/Al_2O_3$ catalyst was controlled by surface reaction rate and the adsorption type of substrate and H_2 on the catalyst are non-competitive and dissociative adsorption. Hyun Tae Hwang [22b] et al. studied the debenzylation of N-benzyl-4-fluoroaniline, and the obtained rate-determining step and the adsorption type of the reactant on the catalyst were consistent with the conclusions in our study. In addition, compared with the activation energy value (138.4 kJ/mol) obtained by Hyun Tae Hwang, we found that the activation energy value (18.6 kJ/mol) in our study is very small, which indicate that the palladium hydroxide catalyst have better catalytic activity for debenzylation than palladium catalyst. The kinetic model obtained in this study maybe helpful for the reactor design and process optimization for the continuous

deprotection development.

Conclusion

In this study, a micro-packed bed reactor has been successfully applied to the continuous hydrogenation of DMAOL using hydrogen gas. It is demonstrated that the μPBRs is more efficient for the hydrogenation of DMAOL than the traditional batch reactor. The conversion per unit reactor volume per unit time in the micro-packed bed reactor is 100 times of that of the batch. The reaction kinetics model was obtained after the external and internal mass transfer limitations have been eliminated and the reaction is in the kinetics-control region. The reaction rate is found to be 0.53 order with respect to DMAOL concentration and 0.31 order to hydrogen pressure. The activation energy (*E*a) of the rate constant is 18.6 kJ/mol and the Arrhenius constant (A) is 2.68 $mol^{0.47}/(L^{0.47}bar^{0.31}s)$. The experimental results were fitted with several kinetic models to determine the rate-determining step, which indicated that the diphenylmethyl removal rate of DMAOL with $Pd(OH)_2/Al_2O_3$ catalyst was controlled by surface reaction rate and the adsorption type of substrate and H_2 on the catalyst are non-competitive and dissociative adsorption.

Acknowledgements

We gratefully acknowledge the supports of the National Natural Science Foundation of China (21978146), Tsinghua University Initiative Scientific Research Program (2019Z08QCX02) and the State Key Laboratory of Chemical Engineering (SKL-ChE-17T01) on this work.

Nomenclature

F_L	Liquid flow rate	ml/min
F_G	Gas flow rate	sccm

P	Pressure	bar
T	Temperature	K
h	Liquid holdup	–
D	Reactor inner diameter	cm
L	Reactor length	cm
C_{A}	Concentration of DMAOL	mol/L
C_B	Concentration of diphenylmethane	mol/L
C_{A0}	Initial concentration of DMAOL	mol/L
X	conversion of N-diphenylmethylazetidin-3-ol	m/s^2
E_{a}	Activation energy	kJ/mol
A	Arrhenius constant	$\frac{mol^{0.47}}{L^{0.47} \cdot bar \cdot {}^{0.31}s \cdot g\mathrm{cat}}$

Greek letters

τ	Liquid residence time	s
ε	Porosity	–

Subscripts

G	Gas
L	Liquid

Supporting Information

The calculation of Weisz modulus and detailed results on the intrinsic kinetic model fitting are supplied as Supporting Information.

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