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Fine-Bubble-Based Strategy for the Palladium-Catalyzed Hydrogenation of Nitro Groups: Measurement of Ultrafine Bubbles in Organic Solvents

Nobuyuki Mase^{*a,b,c} Yuki Nishina^a Shogo Isomura^a Kohei Sato^a

Tetsuo Narumi^{a,b,c}

Naoharu Watanabe^b

^a Applied Chemistry and Biochemical Engineering Course, Department of Engineering, Graduate School of Integrated Science and Technology, Shizuoka University, 3-5-1 Johoku, Hamamatsu, Shizuoka 432-8561, Japan

^b Graduate School of Science and Technology, Shizuoka University, 432-8561, Japan

^c Green Energy Research Division, Research Institute of Green Science and Technology, Shizuoka University, 432-8561, Japan mase.nobuyuki@shizuoka.ac.jp

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Abstract Fine bubbles of hydrogen were employed as a new reaction medium for the autoclave-free gas-liquid-solid multiphase hydrogenation of nitro groups on a multigram scale. Furthermore, ultrafine bubbles were examined by nanoparticle-tracking analysis in organic solvents.

Key words microbubbles, ultrafine bubbles, hydrogenation, heterogeneous catalysis, green chemistry, nitro compounds

The development of new chemical reactor technologies that permit practical improvements in the efficiencies of gas-liquid multiphase reactions for industrial production or academic research has been a longstanding requirement.¹ In recent years, fine bubbles (FBs)^{2,3} have been used for gas-liquid reactions in the Cu/TEMPO-catalyzed aerobic oxidation of primary alcohols to aldehydes, providing a simple, safe, and user-friendly protocol.⁴ This method has been further applied to gas-liquid-solid multiphase Pd-catalyzed hydrogenations of C-C unsaturated bonds in an autoclave-free environment under atmospheric pressure (Scheme 1, Equation 1).⁵ Although the behavior of FBs in organic solvents still remains unclear,⁶ in principle the FBmediated method can generally be applied to gas-related multiphase reactions.⁷ Here, we report a Pd-catalyzed gasliquid-solid multiphase hydrogenation of nitroarenes (Scheme 1, Equation 2) and we also report that the H_2 -FB method overcomes the drawbacks of the conventional bubbling method. Furthermore, the existence of ultrafine bubbles of H₂ (H₂-UFB) has been confirmed by nanoparticletracking analysis (NTA)⁸ in organic solvents.



Aromatic amines are important intermediates in the industrial production of materials such as urethane monomers, pharmaceuticals, herbicides, dyes, and rubber-processing chemicals. Consequently, many studies on the gasliquid-solid multiphase heterogeneous catalytic hydrogenation of nitroarenes to anilines have been reported.9 However, existing problems need to be addressed to improve the reactivity and chemical yield. The process requires a pressure-resistant reaction vessel operating under high-pressure conditions and/or vigorous bubbling and mechanical stirring, and finely powdered Pd/C is required to obtain a high yield.¹⁰ However, the removal of the Pd/C by filtration often necessitates the adoption of a batch system and entails long operating times; careful monitoring to prevent clogging of the filter is required in continuous-flow systems. These problems can be solved by increasing the concentration of the dissolved gas at atmospheric pressure, without vigorous bubbling and stirring, by using a nonpowdery supported Pd catalyst. We therefore investigated the hydrogenation of nitroarenes under H₂-FB conditions using



Scheme 1 FB-mediated Pd-catalyzed hydrogenations

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Pd on alumina spheres (Pd/Al₂O₃, 0.5% Pd, approx. 2-4 mm), despite the lower reactivity of this catalyst compared with that of Pd/C powder.

Hydrogenation of nitrobenzene (1a; 10 mmol, 1.2 g) on a gram scale was chosen as a model reaction for the evaluation of the efficiency of the reaction (Table 1). To identify an appropriate solvent for the FB-mediated hydrogenation, we carried out solvent screening. Water and DMF were less effective solvents (Table 1, entries 1 and 2), whereas N-methylaniline was obtained as a byproduct in methanol, which is often used as a solvent for hydrogenation reactions (entry 3).¹¹ In frequently used solvents such as ethanol. THF. acetic acid, or ethyl acetate, the desired aniline (2a) was obtained in yields of over 90% (entries 4-7). Ethyl acetate was chosen as the optimal solvent, due to its low miscibility with water and the lack of byproduct formation during hydrogenation. The superiority of the FB method was examined by comparison with conventional methods. The use of a balloon (1 atm) or bubbling of H₂ through the solution from a conventional gas-dispersion tube, fitted with a porous fritted-glass tip, at the same H₂ flow rate as used in the FB method resulted in low yields (entries 8 and 9). The yield was not improved even when a pressure-resistant reaction vessel at high pressure (0.3 MPa) was used (entry 10). Although it is possible to forcibly improve the yield by vigorous stirring, it is not possible to reuse the catalyst under these conditions due to the resulting damage. Since three hydrogen molecules are involved in the hydrogenation of the nitro group,¹² the concentration of dissolved hydrogen markedly influ-

Table 1	Comparison of Hydrogenation Conditions ^a									
	NO ₂ 1a	Pd/Al ₂ O ₃ (3 mol 30 °C, 5 ł	I%), H₂ ►	NH ₂						
Entry	Conditions	H_2 (mL/min)	Solvent	Yield ^b (%)						
1	FB	5	H ₂ O	69.0						
2	FB	5	DMF	41.0						
3	FB	5	MeOH	68.6°						
4	FB	5	EtOH	93.0						
5	FB	5	THF	96.1						
6	FB	5	AcOH	>99.9						
7	FB	5	AcOEt	>99.9						
8	balloon	-	AcOEt	1.6						
9	bubbling	5	AcOEt	5.2						
10	autoclave ^d	-	AcOEt	1.0						

^a Reaction conditions: aniline (**1a**, 10 mmol), Pd/Al₂O₃ (3 mol%), solvent (80 mL, 0.125 M), H₂-FB or bubbling (5 mL/min) or balloon, 30 °C, 5 h. ^b Determined by GC analyses (column: GL Sciences TC-17).

^c *N*-Methylaniline was formed as a byproduct in 20% yield.

^d This reaction was carried out at 0.3 MPa.

Next, we examined the scope of the substrate in the FB method¹³ in comparison with the conventional bubbling method (Table 2). In the case of electron-donating substituents, such as methyl or methoxy, the corresponding aniline derivatives 2 were produced in quantitative yields (entries 2 and 3). Similarly, hydrogenation of unprotected hydroxyor amino-substituted nitroarenes proceeded smoothly (entries 4 and 5). In the case of (4-nitrophenyl)amine (1e), the difference in reactivity between conventional bubbling and FB conditions was remarkable (91 times faster; entry 5). During the hydrogenation of the nitro group, the aniline product is adsorbed onto the catalyst and might decrease its catalytic activity.¹⁴ However, the exchange of the product with hydrogen at the catalytically active site is considered to be rapid under FB conditions in which hydrogen is dissolved at high concentrations. As a result, deactivation of the catalyst is suppressed, even in the case of benzene-1,4diamine (2e), which is easily adsorbed onto the catalyst. Although nitroarenes substituted with electron-withdrawing groups were readily hydrogenated in high yields, simultaneous partial dehalogenation of 1-chloro-4-nitrobenzene (1g) proceeded in 13% yield (entries 6-8). The heterocyclic 5-nitroquinoline (1i) was efficiently hydrogenated under FB conditions (entry 9).

Because FB-mediated hydrogenations can efficiently and easily be performed at atmospheric pressure, this method is expected to be suitable for the industrial production of 3-(4-aminophenoxy)aniline (**2j**), a monomer used in the preparation of a manmade high-performance aramid fiber. Monomer **2j** has been prepared on an industrial scale by the hydrogenation of [3-(4-aminophenoxy)phenyl]amine (**1j**) in DMF under high-temperature and highpressure conditions.¹⁵ When the amount of catalyst was increased to 4 mol% to compensate for the low hydrogenation reactivity in DMF (Table 1, entry 2), the desired diamine monomer **2j** was obtained twice as efficiently when compared to conventional bubbling conditions (entry 10).

Because *N*-methylaniline was obtained as a byproduct during nitro-group reduction in methanol (Table 1, entry 3),¹¹ reductive amination reactions were expected to occur in the presence of ketones or aldehydes. Indeed, the secondary and tertiary amines **3** and **4**, in the presence of acetone and butyraldehyde, respectively, were produced in one-pot operations in yields of over 90% (Scheme 2, Equations 1 and 2). Not only are nitro and imino groups smoothly reduced in the FB method, but also carbonyl groups are efficiently reduced in a synthetically useful manner; for example benzaldehyde was quantitatively reduced by using 3 mol% Pd/Al₂O₃ and H₂-FB (5 mL/min) to give benzyl alcohol (see Supporting Information).

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Entry	Substrate	R	Time (h)	Product	Yield A ^b (%)	Yield B ^c (%)	Ratio ^d
1	1a	Н	5	2a	>99.9	5.2	19
2	1b	4-Me	12	2b	>99.9	8.7	11
3	1c	4-OMe	5	2c	>99.9	4.2	24
4	1d	4-OH	9	2d	91.6	14.0	7
5	1e	4-NH ₂	6	2e	91.0	<1.0	91
6	1f	4-F	7	2f	>99.9	6.1	16
7	1g	4-Cl	7	2g	86.7	3.1 ^e	28
8	1h	4-CO ₂ Me	12	2h	90.4	3.7	24
9			10	2i	97.0	3.4	29
10 ^f	1j H ₂ N	-0 NO ₂	7	2j	>99.9	48.0	2

^a Reaction conditions: nitroarene **1** (10 mmol), Pd/Al₂O₃ (3 mol%), solvent (80 mL, 0.125 M), H₂-FB (A) or bubbling (B) (5 mL/min), 30 °C (see also Reference 13). ^b Yield under FB conditions, determined by GC (column: GL Sciences TC-17).

^c Yield under bubbling conditions, determined by GC (column: GL Sciences TC-17).

^c Ratio = Yield A/Yield B.

^d The dehalogenation product **2b** was obtained in 13% yield.

^e The reaction was carried out in DMF.



UFBs are too small to be observed by visual inspection or optical microscopy; consequently the solutions appear to be clear because of the extremely small size of the dispersed bubbles. However, it has recently become possible to examine UFBs through technological innovations in nanoparticle-analysis equipment. Consequently, the behavior of UFBs in water is gradually being revealed. On the other hand, the analysis of UFBs in organic solvents has hardly been studied. We reported preliminary analytical results for UFBs in methanol. The USBs were produced by using an FB generator (MA3-FS), and the H₂-UFB number (2.7×10^7) particles/mL) and the average size of the bubbles (158 nm) were determined by using a NanoSight LM10-HS nanoparticle-tracking analysis (NTA) instrument, fitted with a red (638 nm) laser.⁵ To understand the behavior of UFBs in more detail, we chose to use a NanoSight LM10-VHST instrument, which has a purple (405 nm) laser that increases the intensity of the light scattered by the UFBs. H₂-UFBs were observed in the 50-200 nm size range in water, with an average of 148.5 ± 6.4 nm (Figure 1, left). The number of UFBs per milliliter was determined to be $(1.35 \pm 0.17) \times 10^8$; therefore, purple lasers can visualize more UFBs than can red lasers. Despite the small numbers of visually observable microscale bubbles in the ethyl acetate used during the hydrogenation of nitroarenes, the number and sizes of the H₂-UFBs in this solvent were confirmed to be similar to those in H₂O [average size: 134.1 ± 10.8 nm, number of H₂-UFBs/mL: (2.17 ± 0.38) × 10⁷, Figure 1, right].¹⁶



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Next, air-UFBs were examined in ten conventional organic solvents (Figure 2); UFBs were observed in all the organic solvents examined except hexane. The microbubble (MB) rising speed depends on the viscosity (η) of the liquid, in accordance with the Stokes equation, and the surface zeta potential of the MB depends on the permittivity (ε) of the liquid, in accordance with the Smoluchowski equation.² Consequently, the viscosity and permittivity of the liquid should not only affect the stability of MBs, but also that of UFBs. We observed no clear correlation between the viscosity or permittivity and the UFB number (the number of UFBs per milliliter). In contrast, the calculated value (CV) obtained by multiplying the normalized viscosity and permittivity, based on the values for water, correlates linearly with the UFB number (Figure 2). In hexane, which has a low viscosity (0.3 mPa·s) and low permittivity (1.9 ε), UFBs are hardly observed under our measurement conditions. When the calculated value is larger than 0.01, the UFB number can be determined. As the viscosity and/or permittivity increases, more UFBs are detected. For example, propan-2-ol $(n = 2.0, \epsilon = 19.9, CV = 0.58)$ produces an air-UFB number of 6.2×10^7 . Water ($\eta = 0.9$, $\varepsilon = 78.5$, CV = 1.00) and DMSO ($\eta =$ 2.0, $\varepsilon = 46.5$, CV = 1.32) contain more than 10⁸ UFBs per milliliter of liquid.



permittivity × viscosity (normalization based on H_2O)

In principle, FBs can be generated from various gases; indeed, UFBs of various gases were observed not only in water, but also in ethyl acetate (Figure 3). The UFB number in water ranged from 1×10^8 to 1.6×10^8 and that in AcOEt ranged from 2×10^7 to 2.6×10^7 . Interestingly, the UFB number depends on the solvent, but is largely independent of the gas.



For example, when less water-soluble nitrogen gas was used, 1.08×10^6 UFBs per milliliter were observed, whereas for highly soluble ammonia gas in water, 1.13×10^6 UFBs per milliliter were observed. It is apparent that the average UFB size does not depend on the kind of gas or the solvent under any conditions. The average UFB sizes of various gases in H₂O or AcOEt lie in the 100–200 nm range (Figure S1 in Supporting Information). With our current level of understanding, the reason why the numbers of UFBs and their average sizes are largely independent of the gas or solvent remains unclear. However, the rate of gas dissolution into the liquid and the saturation depend on the type of gas and liquid, but UFB numbers and sizes are about the same in their gas–liquid-saturated equilibrium states.

In conclusion, H_2 -FBs were used as a new reaction medium for gas–liquid–solid multiphase reactions in autoclavefree multigram-scale hydrogenations of nitro groups. In addition, several kinds of UFB were examined by NTA in organic solvents. FBs were generated by using various gases and liquids; therefore, the FB method is widely applicable. This environmentally friendly FB-mediated gas-related reaction system has the potential to contribute to the synthesis of various fine chemicals, as well as bulk chemicals.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588869.

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The hydrogenation was carried out in a 100 mL vial equipped with an FB generator, without additional stirring. Nitroarene **1** (10 mmol) was dissolved in AcOEt (80 mL) and the solution was warmed to 30 °C. By using the FB generator (MA3-FS), H₂-FB were introduced into the reactor in the presence of Pd on alumina spheres (0.5% Pd, 2–4 mm, 0.3 mmol, 3 mol%) at a H₂ flow rate of 5 mL/min. Samples of the reaction mixture were removed periodically to permit monitoring of the progress of the reaction by GC analysis. When the hydrogenation reaction was complete, the AcOEt was evaporated in vacuo to afford the desired aniline **2** with good to excellent purity.

GC analyses: SHIMADZU GC-2010, capillary column: GL Sciences TC-17; He = 0.80 MPa, H₂ = 0.50 MPa, air = 0.50 MPa, flow rate: 1.4 mL/min, T_{inj} = 250 °C, T_{det} = 250 °C, T_i = 100 °C, T_f = 250 °C, rate = 10 °C/min; Nitrobenzene (**1a**, CAS Reg. No.: 98-95-3; t_R = 5.3 min), aniline (**2a**, CAS Reg. No: 62-53-3; t_R = 5.5 min) (see Supporting Information).

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