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**Graphical abstract**

We have successfully demonstrated that W/O nanoemulsion prepared by the tandem acoustic emulsification is extremely useful medium for enhancing the rate of phase-transfer catalytic reactions.
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Phase-transfer catalysis (PTC) has been recognized as a heterogeneous catalysis and known as a practical methodology for organic synthesis. In 1971, C. M. Starks proposed a concept of PTC. This methodology is a convenient and powerful tool in organic synthesis because it offers several advantages for practical organic synthesis, such as easy handling, mild reaction conditions in aqueous media, environmental benefits, and suitability for large-scale reactions. A phase transfer catalyst facilitates the transfer of a reactant in a heterogeneous system from one phase into other phase where reaction can take place. This means PTC is an alternative solution to overcome the heterogeneity problem in a reaction which the interaction between two substrates. Therefore, PTC is applicable to a great variety of reactions.

Since phase transfer catalytic reaction occurs generally at interface between organic phase and aqueous phase, the reaction rate definitely depends on interfacial area. To enhance the reaction rate, increase of interfacial area is the simplest and straightforward way and it can be easily applied for wide range of PTC system. Therefore, the mixing and emulsifying operations for obtaining a large interfacial area are crucial processes.

Ultrasonic irradiation provides stable emulsions without the need for surfactants, simply by the use of mechanical forces generated from acoustic cavitation at the liquid/liquid phase boundaries. This has been termed as acoustic emulsification and is regarded as a powerful method for the rapid production of green emulsions. Emulsion droplets prepared with general-use ultrasonic devices having frequencies ranging from 20 kHz to 1.0 MHz are typically between 100 and 1000 nm in diameter. Hence, they are most commonly milky white compositions, due to the scattering of visible light.

On the other hand, we recently reported that nanoemulsion is easily prepared by using the tandem acoustic emulsification. This method consists of sequential ultrasonifications (kHz range sonication → MHz range sonication) and provides highly clear and transparent nanoemulsion with diameters of a few tens of nanometers. These small emulsion droplets should have a large interfacial area, and hence the use of nanoemulsion would increase in the reaction rate of PTC system. The aim of this work is to investigate the PTC reaction rate in tandem acoustic emulsified solutions. Herein, we wish to demonstrate that the use of nanoemulsion prepared by the tandem acoustic emulsification as a reaction medium for PTC enables to accelerate the reaction rate.

2.0 mL of 50 wt% potassium carbonate aqueous solution was added to 18.0 mL of chloroform in glass beaker cell. The 20 kHz ultrasonication to the water/oil mixture was conducted with an ultrasonic stepped horn connected with a 20 kHz oscillator for 10 min. By this operation, a milky white solution was obtained as shown in Fig. 1a. Then, the sequential ultrasonifications (1.6 MHz, 10 min and 2.4 MHz, 10 min) were conducted after 20 kHz treatment. These sonicating operations yielded an almost clear emulsified solution as shown in Fig. 1b. Finally, this procedure was carried out one more time (two cycles of tandem operation: 20 kHz → 1.6 MHz → 2.4 MHz → 20 kHz → 1.6 MHz → 2.4 MHz). As a result, a perfect clear and transparent solution was obtained (see Fig. 1c). This emulsified solution was so stable that the clear and transparent appearance was maintained for at least 6 months, even under surfactant-free conditions.
To estimate the droplets size quantitatively, we measured the size distributions of the water droplets after the acoustic emulsification treatments by dynamic light scattering (DLS) (Figure 2). After 20 kHz ultrasonication, we could not estimate water droplets size due to their sizes exceeding a measuring limit (measuring limit is over 6 µm). The sequential processing with 2.4 MHz after 20 kHz and 1.6 MHz could break up the larger droplets to form smaller droplets, a single peak in the number-mode was observed at 436 nm. Finally, the ultrasonication with two cycles of tandem ultrasonic treatment enabled a further reduction in droplet size, and the peak shift to 112 nm. Therefore, it can be stated that the size of water droplets is controlled intentionally by selecting the number of ultrasonication steps in the tandem operation.

Subsequently, we used these emulsified solutions as reaction media for PTC. In this demonstration, the catalytic α-benzylation of 2-cyanopropionic acid ethyl ester by tetraethylammonium bromide was employed as a model PTC process (Scheme 1). The PTC was conducted by adding 2-cyanopropionic acid ethyl ester (1 mmol), benzylbromide (1.2 mmol), and tetrabutylammonium bromide (0.01 mmol) to 20 mL of the emulsified solution. During the PTC, the solution was not sonicated but stirred by a rotating magnet bar. The speed of stirring was 1000 rpm, unless stated otherwise. The progress of the reaction was monitored by gas chromatography analysis.

Figure 3 shows yield of the benzylated product in the time course of the model PTC in an untreated two phase solution and W/O emulsions prepared by the single ultrasonication with 20 kHz and two cycles of tandem ultrasonication. In all cases, the yield of the reaction was increased with an increasing the reaction time and saturated at around 60%. However, the reaction rate in the two cycles of tandem treated solution was apparently higher than that in the single sonicated (20 kHz) and untreated solutions. This can be ascribed to smaller size of emulsion droplets prepared by the tandem acoustic emulsification. In other words, the smaller size droplets prepared by the tandem operation created the larger interfacial area between oil and water boundary, and hence the reaction was accelerated in this case.

It is well known that the agitation (stirring) speed is an important parameter for the PTC reaction. We then investigated an influence of the agitation (stirring) speed on the reaction rate for the model PTC process (Table 1). As shown in Table 1, the rate constant increased greatly with an increasing the agitation speed in the single sonicated (20 kHz) and untreated solutions. In sharp contrast, the constant was little influenced by the agitation speed in the two cycles of tandem treated solution. In addition, the constants obtained in the tandem treated solution were significantly higher than those obtained in the other solutions. Small emulsion droplets in the submicrometer range are known to be influenced significantly by the Brownian motion. Therefore, for the case in the tandem treated solution, the mass transfer of droplets might be sufficient even without
mechanical stirring, and consequently the use of tandem treated solutions could provide higher reaction rates for the PTC process.

In conclusion, a highly clear and transparent W/O nanoemulsion containing water droplets with a size of approximately 100 nm was successfully prepared by the tandem acoustic emulsification. In addition, the nanoemulsion was found to be extremely useful media for enhancing the rate of phase-transfer catalytic reactions. This can be ascribed to smaller size of the prepared emulsion droplets with a larger interfacial area between oil and water boundary. These small emulsion droplets had a large interfacial area, and hence the use of nanoemulsion could increase in the reaction rate of PTC system. We believe that the present methodology will be applied to various the PTC processes.

Notes and references