

Precise Size-control of Silica Nanoparticles *via* Alkoxy Exchange Equilibrium of Tetraethyl Orthosilicate (TEOS) in the Mixed Alcohol Solution[†]

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Silica nanoparticles (SNPs) are one of the most interesting materials with regard to their easy preparation, nontoxicity, and simple surface modification. Based on their various advantages, SNPs have been widely studied and used in various fields such as solid support materials in the column chromatography,¹ insulating layer and silica-polymer composite² in engineering fields, and bio-imaging and drug/gene delivery systems in nano-biotechnology.³⁻⁵ To make SNP work effectively in all these applications, it is necessary to synthesize size-controllable and mono-dispersed silica particles. Since Stöber showed that spherical silica particles having narrow size distribution could be prepared from tetraethyl orthosilicate (TEOS) as silica source in alcohol solvent with water and aqueous ammonia as catalyst,⁶ his method has been used and modified to prepare mono-dispersed and regular sized SNPs.⁷ The size control of SNPs was possible by varying the concentration of reactants, the chain length of alkyl group in alcohol solvents and silica sources, base catalysts to primary amine instead of ammonia solution.⁸ It was also reported that the usage of amino acids and the control of the mixing ratio of their optical isomers could change the size of SNPs.⁹

Although it is known that the basic formation mechanism of SNPs is the hydrolysis-and-condensation of TEOS, interestingly, the role of solvent during the formation of SNPs has not been systematically investigated yet. When alcohols with long alkyl chains were used as solvent, the size of SNPs was increased due to the different hydrolysis-and-condensation rate to generate seeds. As an example, it was reported that the different sized SNPs were synthesized in methanol (4 nm) and ethanol (8 nm) because the supersaturation ratio of the hydrolyzed silica sources in methanol was higher than that in ethanol.¹⁰ In other words, many smaller seeds were generated in fast reaction environment in methanol and could grow to produce many smaller SNPs compared to those produced in ethanol. The reason of different reaction rates in different solvents was mainly described as the consequence of the changes of polarity, degree of hydrogen bond, and viscosity;¹¹ the solvent having

a low polarity, low hydrogen bonding ability, and high viscosity could retard the formation of seed leading to increase the final size of SNPs. It was also reported that silica sources with the long or bulky alkoxy groups resulted to generate the large sized SNPs due to the steric effect which decrease the rate of hydrolysis.¹¹ On the other hand, it was well known in silicon chemistry that the alkoxy groups of silicon compounds could be exchanged in alcohol solution, especially in the presence of acid or base catalysts, and the rate of hydrolysis and condensation reactions were also affected by the character of alkoxy groups.¹²⁻¹⁴ Therefore, we investigated the alkoxy exchange reactions in the conditions where SNPs were usually synthesized and found a new factor to give simpler and more precise control over their size than conventional methods.

We synthesized SNPs by the modified Stöber method; 0.6 mL of TEOS was hydrolysed and condensed to give SNPs in various mixed alcohol solutions with a basic catalyst of ammonia solution (1 mL of water and 3 mL of 30% NH₄OH in 50 mL of total alcoholic solution). When the relative volume ratio of methanol:ethanol was varied as 10:0, 8:1, 4:1, 2:1, 1:1, and 0:10 while all the other factors were fixed, the size of produced SNPs increased from 20 to 300 nm as shown in Figure 1. The changes of the size of SNPs in the mixed alcohol solvent might come from the average effect of polarity, hydrogen bonding and viscosity of two alcohols as suggested in earlier reports, but the trend was not lineally related with the mixing ratios of two alcohols. Therefore we speculated the effect of alkoxy exchange of silica sources and deliberately designed the reactions of TEOS in the mixed alcohol solvents; it was important to analyse the early state of silica sources because the generation of seeds or nuclei was expected to be the key event to become nanoparticles.¹⁵

First, the early stage of the reaction was monitored by GC to understand the change of TEOS in a mild basic condition (20 μ L of 30% NH₄OH in 50 mL of total methanol solution); a small amount (1/150 times) of the base catalyst compared to the normal synthetic condition of SNPs was used to slow down the hydrolysis-and-condensation reaction. After treating with the diluted ammonia solution for 4 hours, TEOS in methanol changed to other compounds and these generated compounds were confirmed by GC (Fig. 2). Based on the results of GC-MS analyses (see Supporting

[†]This paper is to commemorate Professor Kook Joe Shin's honourable retirement.

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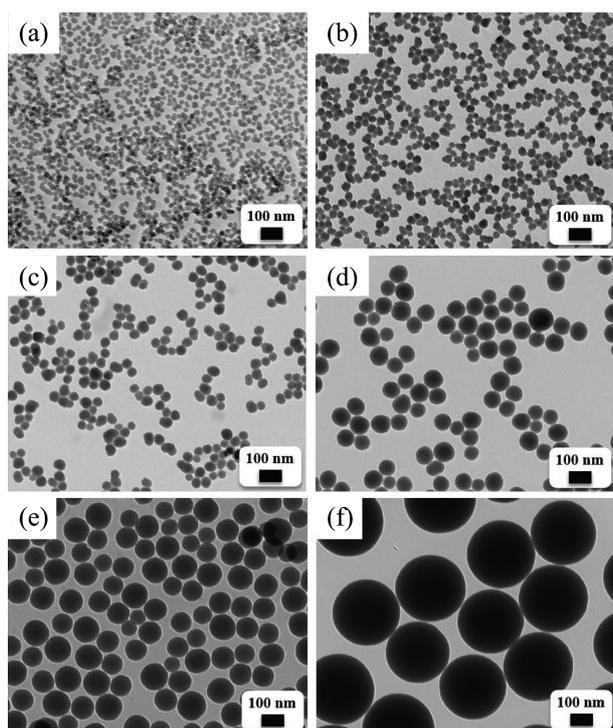


Figure 1. TEM images of SNPs prepared in the mixtures of methanol:ethanol(v/v); (a) 10:0, (b) 8:1, (c) 4:1, (d) 2:1, (e) 1:1, and (f) 0:10.

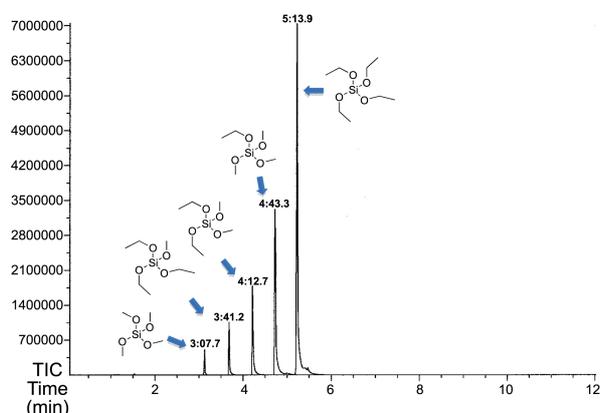


Figure 2. GC analysis of TEOS in methanol after stirring in the mild basic condition for 4 hours.

Information Fig. S1 and S2), these compounds were assigned as the methoxy exchanged TEOS with different numbers of the methoxy group from 0 to 4; $\text{Si}(\text{OEt})_{4-n}(\text{OMe})_n$. In order to trace the behavior of TEOS in more detail with time, further GC analyses at various times were tried and the change of TEOS was detected (see Supporting Information Fig. S3). However the exchange rate to generate $\text{Si}(\text{OEt})_{4-n}(\text{OMe})_n$ did not show any significant changes and quantitative analysis was very complicated due to the characteristic reactivity of TEOS in basic condition; alkoxy exchange reaction always competed with hydrolysis reaction which went further to burst condensation. It was known that, with acidic catalyst, the hydrolysis rate of TEOS was relatively fast but the condensation rate was relatively slow,

and the ultimately generated product was not in a particle shape but generally in amorphous gel because a dense condensation could not occur.^{12,16} Therefore, when an acid catalyst was employed, the fast alkoxy exchange and retarded hydrolysis-and-condensation could make it possible to monitor silicon species at the early stage of the reaction in the mixed alcohol solvent systems. Even though acidic catalyst condition is not the real reaction condition for preparing SNPs, we expect that it is possible to monitor the relative amounts of alkoxy exchanged products with time and to explain the size control of SNPs in different mixed alcohol solvent systems.

The exchange reaction of TEOS in methanol with a diluted hydrochloric acid as a catalyst was monitored and the generated silicon compounds were confirmed as exactly same as those from the basic condition (see Supporting Information Fig. S4). This experiment was carried out with a very small amount of acid (1/100 times) and within a short period of time (few minutes) compared to the case of basic condition shown in Figure 2. Therefore the detailed GC analyses of TEOS in methanol with the acid catalyst could be performed with time intervals and same peaks were observed as those from the basic condition in Figure 2 with slight differences of peak intensities (Fig. 3). When TEOS in methanol was characterized by GC, only two peaks of methanol solvent (1.3 min) and TEOS itself (6.0 min) were observed without the acid catalyst. With the acid catalyst, however, the intensity of TEOS peak was reduced and other new peaks appeared with time. Just after the addition of the acid catalyst, a new peak at 5.4 min at the left side of TEOS was detected, that was confirmed to have one methoxy group and three ethoxy groups by separated GC-MS experiment. With time, ethoxy groups in TEOS were sequentially changed to methoxy groups to show new peaks at 4.9, 4.3, and 3.6 min. All five peaks were clearly observed from the sample after 5 min of acid treatment, and the relative intensities were shifted towards the tetramethyl orthosilicate (TMOS) peak at 3.6 as time passed. Unlike to the case with

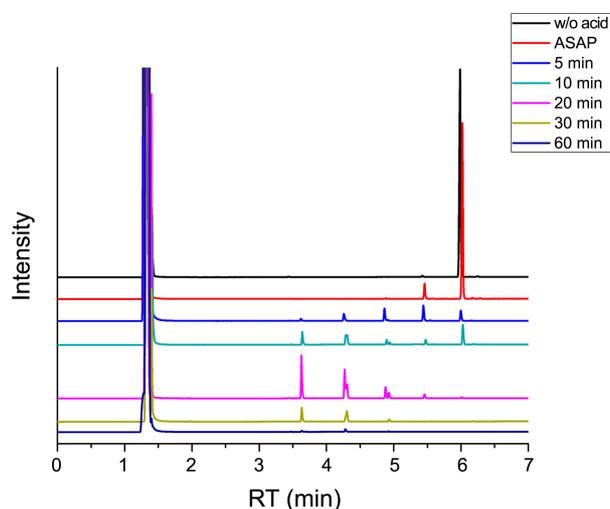
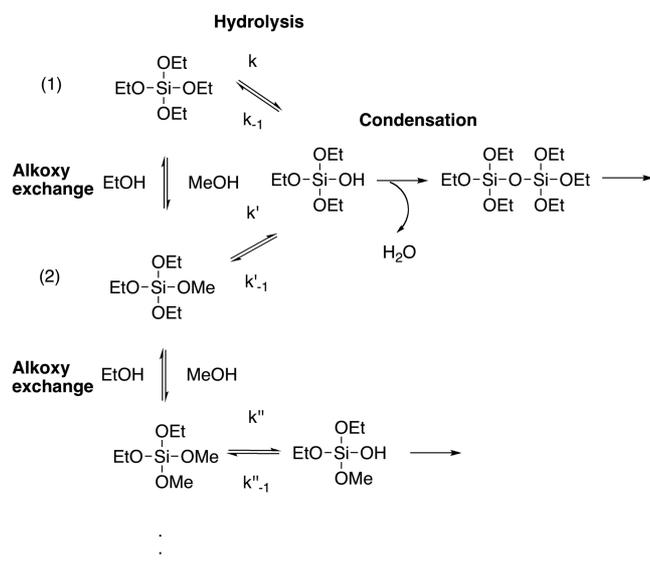


Figure 3. GC analysis of TEOS in methanol; before and after the addition of the acid catalyst.

the base catalyst, owing to the decreased speed of the hydrolysis-and-condensation reaction to generate Si-O-Si siloxane linkage, those mixed alkoxy silicon compounds, $\text{Si}(\text{OEt})_{4-n}(\text{OMe})_n$, generated by fast alkoxy exchange reaction could have a reasonable stability showing the accumulated species during the reaction. However, all those silicon species eventually reacted with water to form silica and no significant amounts of them were left after 60 min. Most of the hydrolysed compounds and condensed oligomeric products were not observed in GC experiments probably due to the adsorption in the column because of their strong interaction through the polar Si-OH bonds. During the alkoxy exchange reaction from TEOS to TMOS, ethanol was generated but its retention time was so close to that of methanol in GC condition that these peaks were hard to be clearly distinguished.

Based on the GC analyses, more than one silica source could exist in the methanol solution of TEOS with a catalyst while only TEOS peak was detected from the solution of TEOS in ethanol (result was not shown), corroborating that the reactivity difference of silica sources could have a relationship with the size of generated SNPs. The relative amounts of mixed alkoxy silicon compounds, $\text{Si}(\text{OEt})_{4-n}(\text{OMe})_n$, generated by a fast alkoxy exchange reaction at the different mixing ratio of methanol:ethanol (1:1 and 1:9) were monitored by GC in the acidic catalyst condition (see Supporting Information Fig. S5). As expected, the methoxy exchange rate of TEOS was decreased when the ratio of ethanol in the mixed alcohol solution was increased. Therefore, the size of SNPs synthesized in the mixed alcohol solvent seemed to be determined by the effect of alkoxy exchange of TEOS and the averaged reactivity of generated silicon species in the early stage of the hydrolysis-and-condensation reaction.

The effect of alkoxy exchange reaction of TEOS in the early stage of the hydrolysis-and-condensation reaction can be simply explained as follows:



For the reaction of TEOS in ethanol, normal hydrolysis

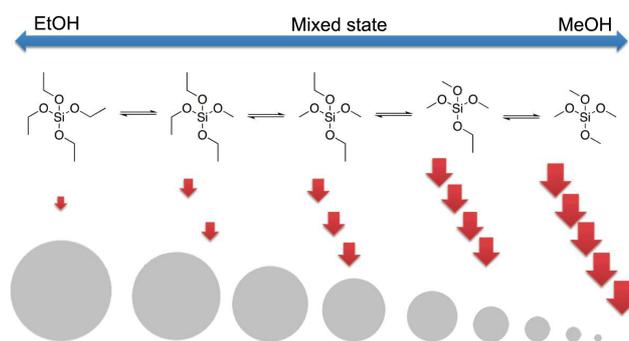


Figure 4. Schematic illustration of the size control of SNPs by generating various silicon compounds by alkoxy exchange equilibrium with different mixing ratios of solvents.

and condensation occurs as a major reaction route. When methanol exists as a cosolvent, the methoxy exchange reaction can compete to hydrolysis so some portion of TEOS is changed to $\text{Si}(\text{OEt})_3(\text{OMe})$. Since the hydrolysis rate constant of TMOS is known to be more than four times faster than TEOS,¹⁷ this methoxy-exchanged silicon compound can also participate in hydrolysis and the hydrolysis rate of $\text{Si}(\text{OEt})_3(\text{OMe})$ should be faster than that of TEOS ($k' > k$). Therefore, the more methoxy groups are exchanged on the Si site, the faster hydrolysis occurs, and the faster supersaturation point is reached starting to form seeds for SNPs; many small seeds are generated at the fast reaction environment in methanol and they can grow to generate many small sized SNPs compared to those from the ethanol solution.

From the sizes of prepared SNPs when the mixed alcohol solvent was used (Fig. 1), the more methanol was mixed, the more reactive silicon compounds were formed, the faster hydrolysis-and-condensation occurred, and ultimately, the smaller SNPs was produced as illustrated in Figure 4. As an extension of the idea to control the size of SNPs by the alkoxy exchange equilibrium, 1-propanol having the longer alkyl chain compared to methanol was mixed with ethanol. However, all the SNPs prepared from ethanol, 1-propanol, and the 1:1 mixture of ethanol and 1-propanol showed almost same sizes and no dependency on the solvent ratio (see Supporting Information Fig. S6). It was pretty similar to the result recently reported by Kang *et al.*; the solvent mixtures of ethanol and 1-butanol with different volume ratios did not actually change the size of SNPs.¹⁸ These result might come from the concentration of TEOS and ammonia, which were already high enough to produce large size SNPs in the presence of ethanol. Therefore another condition to generate smaller size SNPs in ethanol was selected by decreasing the amount of the base catalyst. At this reaction condition, the size of SNPs was precisely controlled by the alkoxy exchange equilibrium. As shown in Figure 5, the size of SNPs was increased from 80 to 100, and finally to 200 nm when the volume ratio of ethanol and 1-propanol was varied from 10:0, 5:5, and 0:10, respectively.

In conclusion, we investigated the solvent effect on the synthesis of SNPs and concluded that the fast equilibrium of alkoxy exchange at the early stage of the hydrolysis-and-

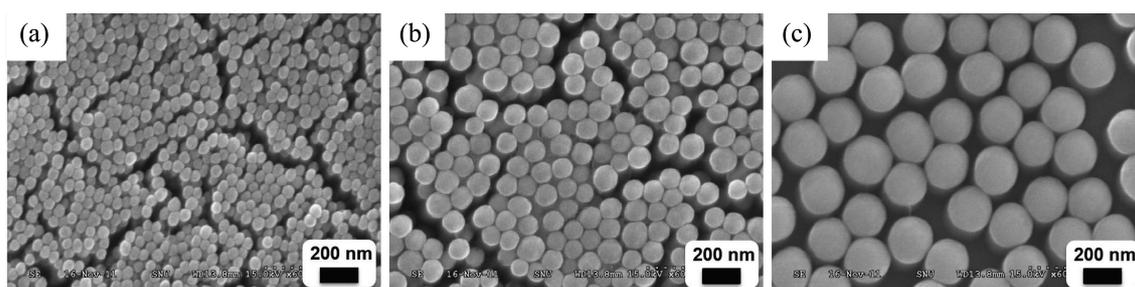


Figure 5. SEM images of SNPs synthesized from (a) ethanol, (b) the 1:1 mixture of ethanol:1-propanol, and (c) 1-propanol.

condensation reaction of TEOS was very critical to determine the size of the resulted SNPs. From the deliberately designed GC and GC-MS experiments, it would be observed that the larger amount of alcohol having a short alkyl chain was employed, the more reactive silicon compound was generated. As the result, the rate of hydrolysis-and-condensation was increased to produce many small sized SNPs. Based on our finding of solvent effect, the size of produced SNPs could be precisely tuned in the ranges from 20 to 300 nm by simply varying the relative volume ratio of methanol: ethanol while all the other factors were fixed.

Experimental Section

Materials. Methanol, ethanol, 1-propanol, ammonia solution, and hydrochloric acid were purchased from Samchun (Korea) and 99% ethanol was purchased from J.T. Baker. TEOS was purchased from TCI and all solvent was used without any purification.

Characterization. Transmission Electron Microscopy (TEM) and Field-Emission Scanning Electron Microscopy (FE-SEM) images were acquired using Hitachi-7600 (Hitachi) and Hitachi S-4300 (Hitachi) instruments, respectively. Gas chromatography (GC) analyses of TEOS in alcohol solvents were carried out by using Acme-3000 (Young Lin) and Gas Chromatography-Mass Spectrometry (GC-MS) used to analyze silicon compounds was JMS-600W (JEOL).

Synthesis of SNPs in the Mixed Alcohol Solutions. SNPs were synthesized from the condition of 0.6 mL of TEOS, 3 mL of ammonia, and 1 mL of water in the mixed alcohol solvent (methanol and ethanol, total volume was maintained to be 50 mL). In case of using ethanol and 1-propanol, SNPs were synthesized from the condition of 0.6 mL of TEOS, 2 mL of ammonia in the mixed alcohol solvent (99% ethanol and 1-propanol, total volume was maintained to be 50 mL). The reaction mixture was stirred at the speed of 400 rpm for 12 h at room temperature. The SNP products were washed three times with ethanol by the centrifugation-redispersion at 15,000 rpm.

GC Analyses. The injection temperature was 200 °C and the detection temperature was 250 °C. The column temperature was programmed as the initial temperature (30 °C) was hold for 1 min., and increased to 75 °C by the speed of 30 °C/min, and finally increased to 150 °C by the speed of 10 °C/min. GC samples in the acid catalyst were prepared by

adding 2.44 μmol of hydrochloric acid to 0.45 mmol of TEOS dissolved in 47 mmol of methanol, and samples in the base catalyst were prepared with the same composition except using 0.29 mmol of ammonia solution.

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