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Structural Studies of the Low-Valent Titanium "Solution": What Goes on in the Pinacol Coupling Reaction?

Yuko Hashimoto, Utako Mizuno,† Hideki Matsuoka,†
Takafumi Miyahara,‡ Masahiro Takakura,‡
Mamoru Yoshimoto,‡ Koichiro Oshima, Kiitiro Utimoto, and
Seijiro Matsubara*,§

Department of Material Chemistry
and Department of Polymer Chemistry
Graduate School of Engineering, Kyoto University
Yoshida, Sakyo, Kyoto 606-8501, Japan
Materials and Structures Laboratory
Tokyo Institute of Technology, 4259 Nagatsuta
Midori-ku, Yokohama 226-8503, Japan

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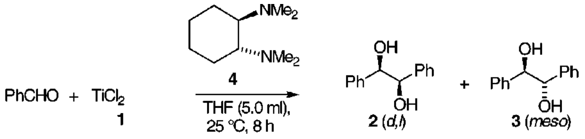
Low-valent metal salts have been widely used for organic syntheses.[1] Their potential as electron donor and Lewis acid is suitable for reactions using a carbonyl compound as a substrate: i.e., Grignard, Barbier, Reformatsky, and pinacol coupling. The low-valent metal salts are used either as a homogeneous solution or heterogeneous dispersion depending on the solvent and ligand. The homogeneous solution often promotes the efficiency of the reaction, including control of the stereochemistry. For example, in the low-valent titanium salt-mediated pinacol coupling reactions,[2] the homogeneous reaction gave higher diastereoselectivity.[3]

Recently, we reported an enantioselective pinacol coupling reaction using titanium(II) chloride ($TiCl_2$)−chiral amine (Scheme 1).[4] In the procedure of this reaction, $TiCl_2$ was dissolved into a mixture of THF and amine and used for the reaction as a solution that seemed to be homogeneous. However, a solution that is judged to be homogeneous merely from its appearance cannot in fact be identified as such.[5] To control the reaction pathway, more detailed information about the solution is necessary. Methods to analyze the structure of the metal salt in a solution are limited. EXAFS (Extended X-ray Absorption Fine Structure), which is a common method, shows mainly the distance between atoms and its coordination number.[6] As we wished obtain more macroscopic information regarding the metal salt (for example, the aggregation situation and cluster size), we tried to apply SAXS (Small-Angle X-ray Scattering) to the structural analysis of our titanium reagent solution.

The low-valent titanium which we used in Scheme 1 was titanium(II) chloride (**1**), prepared by treatment of titanium(IV) chloride with hexamethyldisilane according to the reported procedure (Scheme 2).[7] The method affords titanium(II) chloride and chlorotrimethylsilane, so titanium(II) chloride could be isolated after the removal of volatile compounds. In our reaction (Scheme 1), an addition of THF (5.0 mL) and amine (**4**) (4.0 mmol) to titanium(II) chloride (**1**) gave a solution that realized the pinacol coupling of benzaldehyde in 40% ee. First, we measure SAXS of this THF solution containing $TiCl_2$ (**1**) and amine **4**.

Scheme 1



PhCHO	**1**	**4**	**2** (*d,l*)	**3** (*meso*)
1.0 mmol	1.0 mmol	2.0 mmol	34% (40%ee)	3.0%
1.0	2.0	4.0	82% (41%ee)	5.7%

Scheme 2

$$TiCl_4 + Me_3SiSiMe_3 \xrightarrow[110\ ^\circ C]{} TiCl_2 + 2\ Me_3SiCl$$

The details of the SAXS apparatus are fully described elsewhere.[8] The sample solution was introduced into a glass capillary (2 mmϕ, Mark) and the top of the capillary was completely sealed by silicon adhesive. These procedures were performed in a glove box filled with Ar gas. Figure 1 shows the SAXS curve thus obtained in double logarithmic scale. Obviously, the scattering curve consisted of two components, which means that there are two particles in the "homogeneous" solution. To estimate the size, shape, and number of each particle component, a fitting of the experimental curve by the calculated theoretical curve was performed. We assumed that both of these particles are spherical. Excellent agreement was obtained as shown in Figure 1 (solid line) with $R_1 = 7.7$ Å, $R_2 = 85.0$ Å, $A_1 = 9.6$, and $A_2 = 23.0$, where R_i is the sphere radius and A_i is the amplitude of each component in the scattering curve. According to the basic scattering theory, the scattering intensity is proportional to (1) the square of electron density difference between particle and solvent, (2) the square of particle volume, and (3) the number of particles. Since it is fair to assume that both of these particles have the same electron density, and we already know the size of each spherical particle, we can calculate the number of each particle by using A_i values. By simple calculation, the number ratio of R_1/R_2 particles was found to be 561/1. An apparent large contribution of the larger R_2 particle to the SAXS curve is simply due to the larger volume V_2: We can find only one large particle R_2 in almost 550 smaller particles R_1. Thus, SAXS measurement clearly showed that there are two kinds of particles in the solution, and gave us their sizes and numbers with high accuracy.

Furthermore, we tried to observe these particles contained in the solution by the AFM (Atomic Force Microscopy) technique using our ultraflat sapphire (single-crystal Al_2O_3) stages.[9] For AFM observation of molecules or clusters in air, a solution containing molecules should be spread on a stage and dried. During drying of the titanium salt-containing solution, $TiCl_2$−amine particles would be partly oxidized, aggregated, and adhered to the flat sapphire stage. During the manipulation, the sizes of the particles would be changed mainly by aggregation. So, the following procedure was conducted to suppress the change of the sizes: under Ar atmosphere, a solution of **1** and **4** in THF was diluted 3000-fold with benzene, and spread on the ultraflat sapphire stage. The dilution was expected to prevent cohesion of salts. Figure 2 shows the AFM image (1 × 1 μm^2) of the particles deposited on the atomically flat sapphire terraces, indicating the existence of two types of particles. In Figure 3, histograms of the particles on the AFM image are shown. The height of the bigger particle on the stage was measured to be 102 ± 13 Å and the smaller one was 9 ± 2 Å high.

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* To whom correspondence should be addressed. Fax: +81(75)7534863. E-mail: matsubar@mc.kyoto-u.ac.jp.

† Department of Polymer Chemistry, Kyoto University.

‡ Tokyo Institute of Technology.

§ Department of Material Chemistry, Kyoto University.

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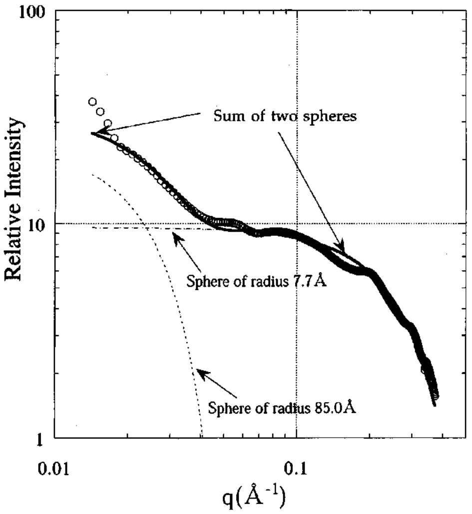


Figure 1. SAXS curve of a solution containing $TiCl_2$ (2.0 mmol) and amine **4** (4.0 mmol) in THF (5 mL). SAXS curve of a solution **1** (2.0 mmol) and **4** (4.0 mmol) in THF (5 mL). The ordinate in the relative intensity of scattered X-rays and the abscissa is the scattering vector q where $q = 4\pi \sin(\theta)/\lambda$ with λ the wavelength of X-ray and 2θ the scattering angle. The dots are experimental data. Clearly, the curve consisted of two components, which means that there are two kinds of particles in the system. The dotted lines are the calculated scattering curves for spheres by the equation $I(q)=\{3(\sin x - x\cos x)/x^3\}^2$, where $x = qR$, R is the radius of sphere, $R_1 = 7.7$ Å and $R_2 = 85.0$ Å. The solid line is the sum of these calculated scattering curves with the amplitude $A_1 = 9.6$ for the R_1 sphere and $A_2 = 23.0$ for the R_2 sphere, i.e. $I(q) = 9.6\{3(\sin(7.7q) - (7.7q)\cos(7.7q))/(7.7q)^3\}^2 + 23.0\{3(\sin(85.0q) - (85.0q)\cos(85.0q))/(85.0q)^3\}^2$. The whole scattering profile is excellently reproduced by this composite curve, which means that there are two kinds of spherical particles in the system in the "homogeneous" solution. The experimental curve shown is the scattering only from solute: the solvent scattering was subtracted from the solution scattering with the transmission coefficient 0.8115, which was determined by the ratio of the direct beam intensities from the solution and solvent.

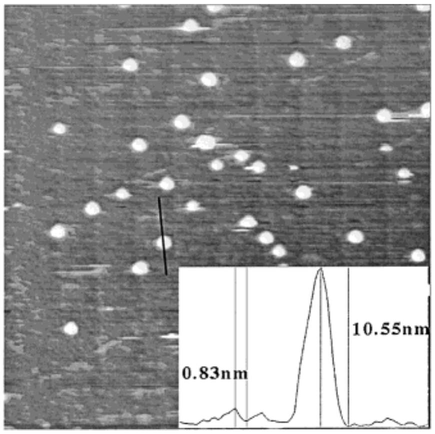


Figure 2. AFM image (1 × 1 μm^2) of particles prepared from a solution containing $TiCl_2$ (2.0 mmol) and amine **4** (4.0 mmol) in THF. [10]

Interestingly, two sizes of particles (the supposed radius: 4.5 and 51 Å)[11] observed from the AFM image are comparable to the values estimated from the SAXS measurements ($R1 = 7.7$ Å and $R2 = 85.0$ Å). Although the AFM results do not show the particle size of $TiCl_2$ species in solution precisely owing to oxidation and drying manipulation,[12] the results after our high dilution procedure showed the particle sizes in solution with relatively high accuracy. Thus, it may be possible through AFM measurements of the metal salt-containing solution to get some supporting information for particles in solution on an atomic scale.

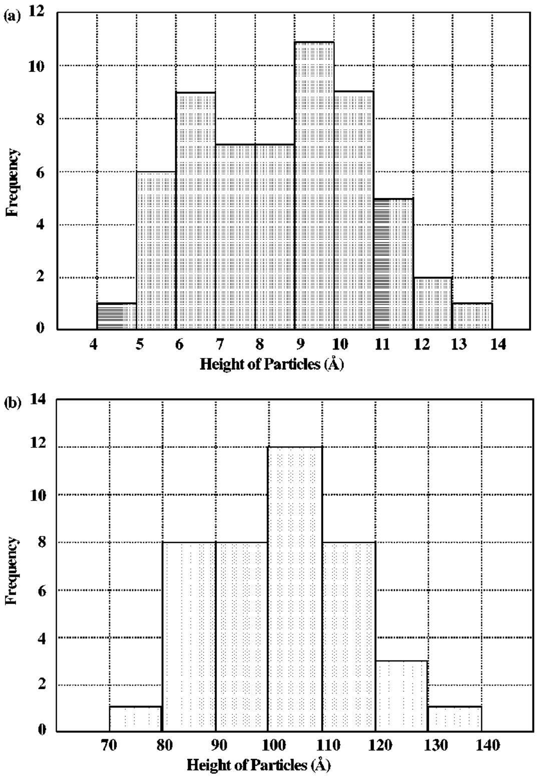
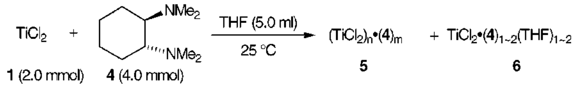


Figure 3. Histograms of particles in the AFM image in Figure 2: (a) the average of the height for 58 smaller paticles, 9 ± 2 Å, and (b) the average of the height for 39 bigger paticles, 102 ± 13 Å.

Scheme 3



The large particle (R_2) in the SAXS was considered to be a cluster (**5** in Scheme 3); the smaller one (R_1) might be a monomeric amine−titanium−THF complex (**6** in Scheme 3) considering the single-crystal X-ray data of the titaminum−amine complex.[13] The existence of two kinds of particles, which are supposed to be a cluster (large) and a monatomic titanium−amine complex (small), will cause a decrease in enantioselectivity. Addition of another solvent will allow the collapse of the cluster. Work toward improvement of the enantioselective pinacol coupling is underway.[14] The present structural studies of the active metal solution by SAXS as well as AFM measurements will give us useful information to show the actual situation in solution, which will lead to the precise control of the pinacol coupling reaction.

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[10] The AFM images were obtained in air, at room temperature using an AFM (Seiko Instruments SPI 3700). The sapphire stage used in this measurement has an ultra-smooth surface with atomic steps (2 Å in height) and atomically flat terraces. The inset shows the height profile along the solid line (180 nm long) in the AFM image. The contact mode AFM image was taken using a 100 μm long microfabricated V-shape Si_3N_4 cantilever with a spring constant of 0.09 N/m. The curvature radius of the AFM Si_3N_4 tip was about 20 nm.

[11] The AFM data showed the heights of the adhered titanium complexes. The radius was estimated simply by supposing those are spheres.

[12] The oxidation and drying procedure changes the size of the particle more or less. Especially, the drying procedure is supposed to cause the shrinking of the particles.

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[14] With the addition of tetrahydrothiophene to the reaction in Scheme 1, the product was obtained in 58% ee: Hashimoto, Y.; Matsubara. S. Unpublished result.