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[9] As reported with the BINOL–Zr catalyst,[2a] the induction falls off with a catalyst prepared with a 1:1 stoichiometry of zirconium to VAPOL (to 60% *ee* for the reaction indicated in entry 3 in Table 1).

[10] A similar observation has been made for the Br_2BINOL catalyst where this imine gave a good yield but only 5% *ee*.[2a]

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Cu^{2+} Inhibits the Aggregation of Amyloid β-Peptide(1–42) in vitro**

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Alzheimer's disease (AD) is the most frequent cause of late-life dementia, with pathological characteristics of extracellular aggregation of amyloid β-peptides (Aβs) with 39–43 amino acids, which are proteolytically derived from the transmembrane amyloid precursor protein (APP).[1] Recent studies indicate that the amyloid β-peptide(1–42) (Aβ(42)) plays a central role in the formation of the β-amyloid fibril (fAβ) in vivo among the different coexisting Aβ species.[2] Further elucidation of the mechanism of Aβ(42) aggregation, and the effect of extrinsic or environmental factors such as pH, metal ions, ionic strength, membrane-like surfaces, and solvent hydrophobicity on the aggregation is useful for our understanding of the pathophysiology and treatment of Alzheimer's disease and other similar neurodegenerative diseases.

Some metal ions such as Zn^{2+}, Cu^{2+}, etc., are essential in trace amounts with important fundamental roles in the biochemistry of human life.[3] It was recently reported that Cu^{2+}, Zn^{2+}, and Fe^{3+} are concentrated in the normal neocortex. The concentrations of these cations are more than doubled in the cerebral amyloid deposits of AD brains compared with the neuropil of normal age-matched brains.[4] However, the role of Cu^{2+} in neurodegenerative diseases such as Alzheimer's disease is still not clear, although the effect of Zn^{2+} on the aggregation of Aβs has been demonstrated by several groups in recent years.[5] Our recent study indicated that the complexation of peptides with Cu^{2+} is responsible for inducing and enhancing the formation of the α-helix conformation of the alanine-based peptides with a Trp/His pair in different geometrical spacings and positions.[6] Herein we describe the aggregation of Aβ(42) and demonstrate for the first time that Cu^{2+} inhibits the aggregation of Aβ(42) with both thioflavin T (ThT) fluorescence assay and atomic force microscopy (AFM) in vitro.

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At first, we examined the concentration dependence of Aβ(42) aggregation by using ThT fluorescence assay. The concentrations of the Aβ(42) solution were changed from 6.25 to 100 μM. The formation of fAβ was monitored with their corresponding ThT fluorescence spectra. The characteristic ThT fluorescence spectra of fAβ with an emission peak at 484 nm were obtained with the excitation wavelength at 435 nm (Figure 1a). The intensity of the ThT fluorescence

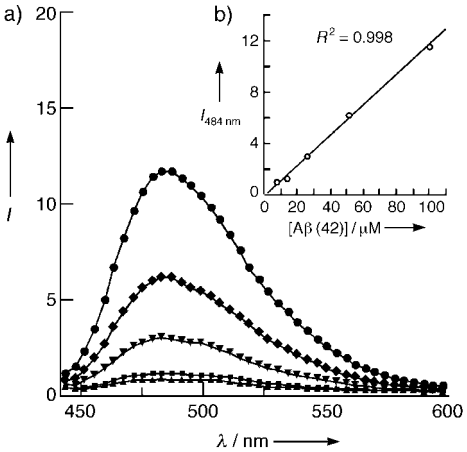

Figure 1. Concentration effect of Aβ(42) on the formation of amyloid fibril. a) ThT fluorescence spectra of Aβ(42) solutions incubated in (●) 100 μM, (◆) 50 μM, (▼) 25 μM, (■) 12.5 μM, and (▲) 6.25 μM. b) ThT fluorescence emission intensity at 484 nm of Aβ(42) solutions incubated in different concentrations.

emission at 484 nm varied from 0.84 at 6.25 μM (▲) to 11.73 at 100 μM (●) and was a linear function ($R^2 = 0.998$) of the concentration of Aβ(42) (Figure 1b). It is known that ThT specifically binds to fAβ, and this binding results in a fluorescent signal proportional to the mass of the formed fibril.[7] Therefore, the linear dependence of the ThT fluorescence intensity at 484 nm with the Aβ(42) concentration indicated that the formation of fAβ is directly proportional to the concentration of Aβ(42) in the range of 6.25 to 100 μM. On the contrary, the characteristic ThT fluorescence spectrum of fAβ was not observed in a solution of 100 μM Aβ(42) that was stored for 6 h at 2 °C (data not shown).

It is known that ThT characteristically stains amyloid-like deposits under a number of pathophysiological conditions.[7–9] They are believed to interact specifically with the crossed-β-sheet structure common to amyloid structures comprised of different materials, although the mechanism is not fully known. This paper examined the interaction between ThT and fAβ of Aβ(42) with a series of ThT concentration dependence experiments. The fluorescence intensity at 484 nm was related to the ThT concentration and reached a saturation state at a high concentration (above 5 μM; Figure 2a). It is known that the Scatchard plot is useful for identifying the noncovalent binding of one or more ligands to a single macromolecule. The Scatchard plot was performed to evaluate the interaction between ThT and fAβ (Figure 2b). The concentration of fAβ bound with ThT was recorded with the ThT fluorescence intensities at different ThT concentrations and the bound/free ratio was calculated approximately

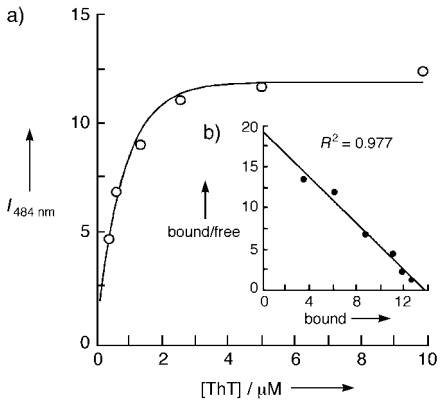

Figure 2. Concentration effect of ThT on the fluorescence assay. a) ThT fluorescence intensities at 484 nm with different ThT concentrations. b) The Scatchard plot of ThT binding to amyloid fibril.

by dividing the ThT fluorescence intensities by the corresponding total ThT concentrations.[8] A single population of binding sites with a dissociation constant of $K_d = (7.1 \pm 0.6) \times 10^{-7}$ M ($R^2 = 0.977$) was obtained with the characteristic Scatchard plot of ThT binding to fAβ. It was revealed that ThT molecules bind fAβ of Aβ(42) in the identical and independent weak binding sites of fAβ. A similar linear dependence of the ThT fluorescence intensity was also observed and the Scatchard plot was performed by other researchers. LeVine reported that the K_d values of the ThT binding with fAβs of Aβ(40) and Aβ(28) at pH 6.0 were 2×10^{-6} M and 5.4×10^{-7} M, respectively.[7] Recently, Naiki and Nakakuki described in detail the interaction of ThT binding with fAβ of Aβ(40).[8] The disassociation constant, $K_d = 8.6 \times 10^{-7}$ M, of the interaction between ThT and fAβ was obtained with the corresponding Scatchard plot (pH 8.5). These results, together with the data herein, confirm that the binding of ThT with various fAβs is of lower affinity. The ThT fluorescence assay is useful for monitoring the assembly process of fAβs, especially in Alzheimer's disease and other similar neurodegenerative diseases, as well as for testing agents that might modulate the assembly and disassembly.

To evaluate the effect of Cu^{2+} on the aggregation of Aβ(42), the incubation of 100 μM Aβ(42) for 6 h was performed in the absence and presence of Cu^{2+} with Aβ(42)/Cu^{2+} 1:5 (molar) at 37 °C. The intensities of the ThT fluorescence emission at 484 nm of Aβ(42) solutions were incubated at different pH values (Figure 3). It is apparent that the aggregation of Aβ(42) is dependent on the pH of the Aβ(42) solution. A high potential of the Aβ(42) aggregation was observed at neutral and basic pH values in the absence of Cu^{2+}. However, it decreased in the acidic solution. On the contrary, the characteristic ThT fluorescence spectra of fAβ with an emission peak at 484 nm disappeared in the Aβ(42) solutions that were incubated at different pH values in the presence of Cu^{2+}. The corresponding intensities of the ThT fluorescence emission at 484 nm are also shown in Figure 3. Comparing the intensities of the ThT fluorescence emission at 484 nm between the absence and presence of Cu^{2+}, it is demonstrated that Cu^{2+} inhibits the aggregation of Aβ(42) in vitro.

AFM was also used to evaluate the aggregation of Aβ(42) and the effect of Cu^{2+} inhibition on the process. The Aβ(42)

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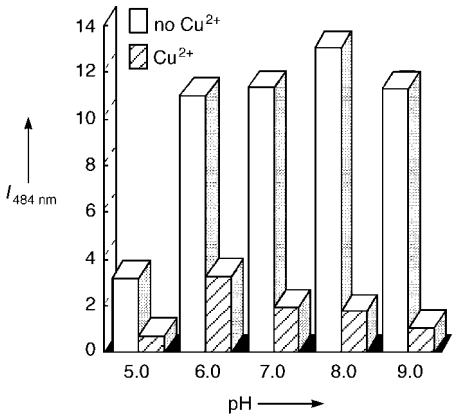

Figure 3. pH effect on the aggregation of Aβ(42) in the absence and presence of Cu^{2+}. Fluorescence intensities at 484 nm were used to monitor the aggregation of Aβ(42).

solutions incubated under different conditions were adsorbed on freshly cleaved mica surfaces and imaged in the tapping mode. The advantage of the tapping mode over the contact mode is that the damage to biological samples (protein) is evidently reduced owing to the decrease in the tip–sample forces. The images were simultaneously collected in the height mode, in which increasing brightness corresponded to the increasing height feature. The amyloid fibril was not observed in the sample stored for 6 h at 2 °C in the absence of Cu^{2+}, although some small particles were revealed in the figure (Figure 4a). Longer fibrous strands and larger globular particles are evident in the sample incubated for 6 h at 37 °C in the absence of Cu^{2+} (Figure 4b). On the contrary, it is novel that the longer fibrous strands disappeared and that the small particles were reduced in the sample incubated for 6 h at 37 °C in the presence of Cu^{2+} (Figure 4c). The results of the AFM

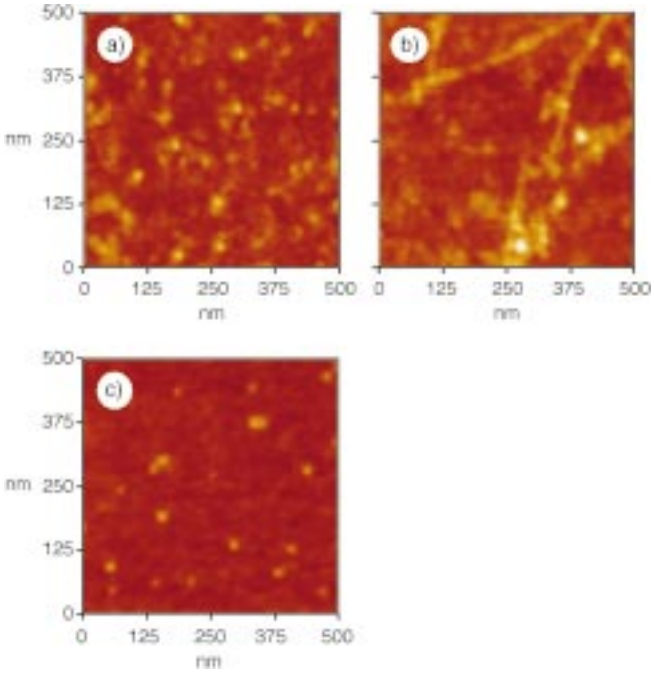

Figure 4. AFM images of Aβ(42) incubated under different conditions. The images were 500 × 500 nm and were collected simultaneously in the height mode; a) at 2 °C in the absence of Cu^{2+}, b) at 37 °C in the absence of Cu^{2+}, and c) at 37 °C in the presence of Cu^{2+}.

imaging confirmed that Cu^{2+} was able to inhibit the aggregation of Aβ(42) in vitro.

As described above, both the ThT fluorescence assay and AFM revealed that Cu^{2+} is an inhibitor in the aggregation of Aβ(42) in vitro. This corresponds well to our recent results that Cu^{2+} is able to induce and enhance the α-helix conformation in short alanine-based peptides.[6] The formation of Cu^{2+}–Aβ(42) complex is responsible for the inhibition of Cu^{2+} because it is useful to stabilize the soluble form of Aβ(42) and to control the conformational transition from the random coil to the β-sheet. The possible mechanism of the inhibition by Cu^{2+} of the aggregation of Aβ(42) will be proposed in our next paper. The distinct biochemical role of Cu^{2+} was not only observed in the aggregation of Aβ(42) as described above, but also in some other bioprocesses. For example, the importance of Cu^{2+} was indicated in the conformational transition of the prion protein (PrP) found in bovine spongiform encephalopathy (BSE).[10] Finally, it should be mentioned that the biochemical role of Cu^{2+} is still a challenging task. It is not clear in which oxidation–reduction state the involved copper ions are present in vivo or to what extent and in which way copper creates conformational changes of the protein portion. Further work has to be performed to answer these questions.

Experimental Section

Aβ(42) used in this study was purchased from the Peptide Institute, Inc. (Lot No. 491120). The other substances used in this study were purchased from Wako Pure Chemical Industries, Ltd. Aβ(42) was dissolved in dimethyl sulfoxide (DMSO) as a stock solution (1.0 mM) and stored at −30 °C before the aggregation assay. The aggregation solution of Aβ(42) (100 μM) was prepared by diluting the stock solution with the appropriate buffers containing sodium citrate (1 mM), sodium phosphate (1 mM), sodium borate (1 mM), and sodium chloride (10 mM) in an ice-water bath of 2 °C, which were adjusted by HCl or NaOH to different pH values.[6, 11] Unless otherwise noted, all the incubations for the aggregation of Aβ(42) were performed at 37 °C for 6 h in a B1-515 Block Incubator (ASTEC). The chloride salt of Cu^{2+} was used with Aβ(42)/Cu^{2+} 1:5 (molar) to observe its effect on the aggregation of Aβ(42). The solutions were not agitated during the incubation.

The formation of fAβ was monitored with the ThT fluorescence assay by using a F-3010 Fluorescence Spectrophotometer (Hitachi Co., Ltd.) with a quartz cell (1.0 cm path length) at 2 °C. The fluorescence intensity is shown in arbitrary units. After incubation, an aliquot of the Aβ(42) solution (25 μL) was added to glycine buffer (pH 9.0, 50 mM), containing ThT (5 μM) with a final volume of 1.2 mL in an ice-water bath of 2 °C. Its fluorescence spectrum from 440 to 600 nm was immediately measured at the excitation wavelength of 435 nm. The concentration dependence of Aβ(42) aggregation was monitored by incubating Aβ(42) in different concentrations and examining the corresponding ThT fluorescence intensities at 484 nm with the excitation wavelength of 435 nm. A curve-fitting procedure was performed by MacCurveFit version 1.4 of Kevin Raner Software.[6]

The formation of fAβ and the effect of Cu^{2+} were also examined by using AFM (JSPM-4200, JEOL). An aliquot of incubated Aβ(42) solution (ca. 5 μL) was transferred to a piece of freshly cleaved mica and dried with nitrogen gas. The buffer salts and loosely bound Aβ(42) were washed from the surface of the mica with distilled water (2 × 10 μL each time) and the mica was dried again with nitrogen gas. The sample was stored in a covered container to protect it from contamination until it was imaged (within 1–2 h). The images shown above were measured in the tapping mode and simultaneously collected in the height mode. All imaging was performed at room temperature (about 25 °C).

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Pure Polymorph C of Zeolite Beta Synthesized by Using Framework Isomorphous Substitution as a Structure-Directing Mechanism**

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Zeolites are crystalline tectoaluminosilicates, whose structure is formed by TO_4 tetrahedra (T = Al, Si) and each apical oxygen atom is shared between two adjacent tetrahedra. The main interest of these materials lies on the fact that the TO_4 tetrahedra are organized in such a way that micropores of regular dimensions are formed giving these materials molecular-sieve properties. The regular and shaped pores and cavities could act as microreactors selecting the transition state that better fits to a given particular structure. However, an important prerequisite for supramolecular inorganic host – guest chemistry will be production of tailor-made host systems with designed topologies and adapted surface properties.[1] Important advances towards this direction have been made by introducing organic cations into the synthesis media. The very relevant work carried out on this field by the groups of Davis and Zones[2–4] have allowed these authors to conclude that while organic cations play an important role as structure directing agents during the synthesis, very seldom they act as true templates, at least in the sense that this term is used in biological systems.[5] Therefore, it is not surprising that only in very few cases it can be claimed that the organic cations act as true templates.[6–8] This implies that, despite the important attempts to carry out "a priori design of zeolites",[9, 10] the synthesis of new zeolitic structures advances by accumulating knowledge on the influence of the different synthesis variables.

A more sophisticated achievement would be to direct the synthesis of zeolites, which are formed by an intergrowth of polymorphs, towards the production of a single, pure polymorph. As far as we know, this has been done in the case of SSZ-33, which corresponds to an intergrowth of two polymorphs, and one pure polymorph could be obtained by choosing the appropriate organic structure-directing agent (SDA).[8, 11, 12]

Zeolite Beta is accepted as a highly faulted intergrowth of two polymorphs, A and B, which are normally found in a 60:40 ratio.[13] However, it has been proposed that a third polymorph (polymorph C) should also exist even if has not been detected experimentally.[13] The structure of the proposed polymorph C of Beta is closely related to those of polymorphs A and B and could be generated from polymorph A simply by the recurrent application to the building layers of a shear operation along both *a* and *b* axes. In this way, the space group of polymorph A ($P4_122$) is transformed into the more symmetrical polymorph C ($P4_2/mmc$).

What is interesting is that the hypothetical structure of polymorph C has a three-dimensional pore topology, in which all three 12-membered-ring channels are linear, while in the case of the other two polymorphs one of the channels is sinusoidal.[13] An additional important structural difference between the different polymorphs is that polymorph C contains double four-membered-ring (D4MR) cages as secondary building units, namely two D4MR cages per unit cell (u.c.), while polymorphs A and B do not contain such secondary building units. If one takes into account that the D4MR cages should be under high tension in this structure, thereby introducing a certain instability, it is not surprising that polymorph C has been elusive under the synthesis conditions of zeolite Beta.

By means of theoretical calculations, we have found (see Supporting Information) that stability is gained in D4MR cages when germanium replaces silicon in the TO_4 tetrahedra.[14] Indeed, the isomorphous substitution of Si by Ge does not introduce any framework charge but allows angles and distances to vary and thereby stabilizing such a secondary

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