20.4 kg mol<sup>-1</sup>, 49.4 mol % styrene, and 50.6 mol % FOA; 3.7<sup>k</sup>-*b*-39.8<sup>k</sup> diblock copolymer:  $\langle M_n \rangle = 43.5$  kg mol<sup>-1</sup>, 28.9 mol % styrene, and 71.1 mol % FOA; 3.7<sup>k</sup>-*b*-61.2<sup>k</sup> diblock copolymer:  $\langle M_n \rangle = 64.9$  kg mol<sup>-1</sup>, 20.9 mol % styrene, and 79.1 mol % FOA. Telechelic PS:  $\langle M_n \rangle = 4.5$  kg mol<sup>-1</sup>, PDI = 1.7, functionality = 1.6; 4.5<sup>k</sup>-*b*-24.5<sup>k</sup> diblock copolymer:  $\langle M_n \rangle = 28.9$  kg mol<sup>-1</sup>, 44.5 mol % styrene, and 55.5 mol % FOA. Telechelic PS:  $\langle M_n \rangle = 6.6$  kg mol<sup>-1</sup>, PDI = 1.8, functionality = 2.3; 4.5<sup>k</sup>-*b*-34.9<sup>k</sup> diblock copolymer:  $\langle M_n \rangle = 41.5$  kg mol<sup>-1</sup>, 45.1 mol % styrene, and 54.9 mol % FOA.

- 21. L. J. Magid, Colloid Surf. Sci. 19, 129 (1986).
- 22. W. C. Koehler, *Physica (Utrecht)* B **137**, 320 (1986). 23. R. J. Nelmes *et al.*, *Acta Crystallogr.* **A49**, 427
- (1993). 24. S. Janssen, D. Schwahn, K. Mortensen, T. Springer,
- Macromolecules **26**, 5587 (1993). 25. G. D. Wignall, in *The Physical Properties of Polymers*,
- J. E. Mark, Ed. (American Chemical Society, Washington, DC, 1993), pp. 313–378.
- 26. \_\_\_\_\_ and F. S. Bates, *J. Appl. Crystallogr.* **20**, 28 (1986).
- 27. Experiments were performed under equilibrium conditions, justified by an approximately 1-hour delay between the mixing of the system and the taking of data and by the observation that there was no change in the scattering curve during 3 to 8 hours of data acquisition.
- E. Caponetti and R. Triolo, Adv. Colloid Interface Sci. 32, 235 (1990); see also R. Triolo and E. Caponetti, in Industrial and Technical Applications of Neutrons, F. Rustichelli, M. Fontana, R. Coppola, Eds. (North-

Holland, Amsterdam, 1992), pp. 403-424.

 A. Halperin, M. Tirrell, T. P. Lodge, *Adv. Polym. Sci.* 100, 31 (1992).

- 30. T. M. Birshtein and E. B. Zhulina, *Polymer* **30**, 171 (1989).
- 31. Y. Hsiao et al., Macromolecules 28, 8159 (1995).
- J. F. Ely, CO<sub>2</sub>PAC: A Computer Program to Calculate Physical Properties of Pure CO<sub>2</sub> (National Bureau of Standards, Boulder, CO, 1986).
- 33. The model CO<sub>2</sub>-insoluble oligomers were PS (500 g mol<sup>-1</sup>) made by living anionic polymerization. Also, to simplify the experimental system and to ensure minimal free oligomer dissolved in CO<sub>2</sub> under the experimental conditions, we extracted oligomer samples in advance with CO<sub>2</sub> at 50°C and 400 bar.
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## Grain Growth Rates of MgSiO<sub>3</sub> Perovskite and Periclase Under Lower Mantle Conditions

Daisuke Yamazaki,\* Takumi Kato, Eiji Ohtani, Mitsuhiro Toriumi

The grain growth rates of MgSiO<sub>3</sub> perovskite and periclase in aggregates have been determined at 25 gigapascals and 1573 to 2173 kelvin. The average grain size (G) was fitted to the rate equation, and the grain growth rates of perovskite and periclase were  $G^{10.6} = 1 \times 10^{-57.4} t \exp(-320.8/RT)$  and  $G^{10.8} = 1 \times 10^{-62.3} t \exp(-247.0/RT)$ , respectively, where *t* is the time, *R* is the gas constant, and *T* is the absolute temperature. These growth rates provide insight into the mechanism for grain growth in minerals relevant to the Earth's lower mantle that will ultimately help define the rheology of the lower mantle.

**M**antle dynamics depends on the rheology of the constituent materials and the transition from spinel,  $(Mg,Fe)_2SiO_4$ , to perovskite,  $(Mg,Fe)SiO_3$ , plus magnesiowustite, (Mg,Fe)O, that is believed to be responsible for the 660 km discontinuity, which separates the upper and lower mantle (1). Some tomographic studies suggest that high-velocity anomalies may correspond to a cold, subducted slab penetrating into the lower mantle (2). Grain growth rates and the intergranular texture of perovskite plus magnesiowustite are important factors for

understanding the rheology of the lower mantle, because grain size and orientation should affect flow dynamics (3). Karato et al. (3) suggested that the dominant deformation mechanism in perovskite is volume diffusion creep at lower mantle conditions when the average grain size is less than 1 mm. In this case, the effective viscosity is proportional to the square of the grain size. The evidence for a lack of seismic anisotropy in the lower mantle is consistent with deformation by diffusion creep (4). However, grain growth rates of lower mantle minerals have not been determined, and direct experimental determination of the rate laws is needed.

We conducted annealing experiments at pressures up to 25 GPa to determine the grain growth rates of aggregates of perovskite (MgSiO<sub>3</sub>) and periclase (MgO), using a multianvil apparatus (5). A fine powder

(<1-µm grain size) of synthetic forsterite was loaded in the apparatus at room temperature and the pressure was increased to 25 GPa, which corresponds to about 700 km depth in the mantle (6). Then the sample was heated at a constant rate of 100°C per minute to the run temperature which ranged from 1573 to 2173 K (7). Run durations at constant temperature ranged from a few seconds to 1897 min (8). The run products were investigated using a scanning electron microscope (SEM) to measure grain sizes, an electron microprobe to determine the composition of each phase, and an x-ray diffractometer to determine the structure of each phase. The grain boundaries were traced on backscattered electron images (BSE) of thin sections, using computerized image-processing. The grain sizes were estimated from the area of each grain, assuming the irregular grain boundary outlines could be approximated by a circle. Schwartz-Saltykovs method (9) was used to estimate the three-dimensional average grain size from the estimated grain areas (Table 1).

At low temperature (1573 K) and short duration (6 min), aggregates of perovskite and periclase formed eutectoid-like grains with equigranular spinel grains (Fig. 1A) (10). The eutectoid texture may be due to the growth of nuclei, controlled by atomic diffusion toward the interface between the host grain that contains the nuclei and the high-pressure phases already created in the

**Table 1.** Experimental conditions and calculated average grain size (9) for perovskite (Pv) and periclase (Pc). For each experiment, the forsterite (Fo) powder was held at 25 GPa at constant temperature (*T*) for the given duration. The Fo was transformed to a mixture of equigranular Pv and Pc in all the runs except PV13 (only equigranular spinel was observed) and PV20 (spinel, perovskite, and periclase were observed in a eutectoid texture). Numbers in parentheses are the standard deviations (1 $\sigma$ ) for the grain size distributions; f.s., run duration is a few seconds (8); n.d., not determined because the grain size was less than 0.5  $\mu$ m and could not be measured.

Run no.	T (K)	Duration (min)	Grain size	
			Pv (μm)	Pc (µm)
PV13 PV20 PV10 PV17 PV15 PV22 PV11 PV21 PV21 PV18 PV23 PV16 PV12 PV19	1573 1573 1573 1873 1873 1873 1873 1873 1873 1873 2173 2173 2173	f.s. 6 600 f.s. 19 600 1897 f.s. 60 600	n.d. 0.75 (0.26) 0.92 (0.26) 0.88 (0.22) 1.03 (0.28) 1.29 (0.34) 1.27 (0.38) 1.30 (0.36) 1.69 (0.46) 1.10 (0.31) 1.61 (0.43) 1.72 (0.48)	n.d. n.d. 0.67 (0.16) 0.67 (0.17) 0.80 (0.18) 1.07 (0.24) 1.03 (0.26) 1.07 (0.30) 0.15 (0.33) 0.82 (0.22) 1.12 (0.29) 1.29 (0.36)

D. Yamazaki and M. Toriumi, Geological Institute, Faculty of Science, University of Tokyo, Bunkyo, Tokyo 113, Japan.

T. Kato, Institute of Geoscience, University of Tsukuba, Tsukuba, Ibaragi 305, Japan.

E. Ohtani, Institute of Mineralogy, Petrology and Economic Geology, Tohoku University, Sendai 980-77, Japan.

<sup>\*</sup>To whom corresponce should be addressed. E-mail: daisuke@geol.s.u-tokyo.ac.jp





Fig. 1 (left). BSE images of run products. Aggregates of perovskite (Pv, light gray) and periclase (Pc, dark gray) show a homogeneous, interlocking texture. (A) Sample from run no. PV20. The coarse grains show  $\gamma$ -spinel (Sp, gray portion). (B) Sample from run no. PV17. (C) Sample from run no. PV16. (D) Sample from run no. PV19. Fig. 2 (right). Experimental results for the change of grain size of perovskite (A) and periclase (B) with time. Open, solid, and double circles represent the grain size at 1573 K, 1873 K, and 2173 K (Table 1), respectively. The solid line is the grain growth rate inferred by least squares fit to the grain growth rate equation (13).

experimental run (11). For longer duration (Fig. 1B) and higher temperature (Fig. 1C) runs, the textures became more uniform and most of the grains were equigranular. This variation of textures is consistent with observations of the high-pressure transition of  $\gamma$ -spinel to perovskite and periclase (12), suggesting that the transformation starts as a eutectoid texture and becomes more equigranular during grain growth. The grain sizes of perovskite and periclase increased with increasing duration and temperature (Fig. 2 and Table 1). We applied the rate equation for normal grain growth (13),  $G^n$  $-G_0^n = G^n \{1 - (G_0/G)^n\} = kt$ , where  $G_0$ is the initial average grain size, n (>2) is the grain growth exponent, and k is the growth rate constant,  $k = k_0 \exp(-Q/RT)$ , where  $k_0$  is the pre-exponential factor and Q is the activation energy of grain growth. For G<sub>0</sub>  $\ll$  G, the law may be written as  $G^n = kt$ .

At 25 GPa, only  $\gamma$ -spinel was formed at temperatures less than 1573 K. The grain size of  $\gamma$ -spinel was several micrometers. The  $\gamma$ -spinel partially transformed (about 80% by volume) into perovskite (about 55% by volume) plus periclase (about 25% by volume) at 1573 K after 6 min. From these observations, we assumed that the grain growth of perovskite and periclase started at time,  $t_0 = 6$  min, at 1573 K and that perovskite and periclase in contact with  $\gamma$ -spinel was the initial texture (Fig. 1A). If the thickness and spacing of these perovskite and periclase grains represents  $G_0$ , then  $G_0$  is always less than about 0.2  $\mu m,$  satisfying the condition,  $G_0 \ll G.~A$ least squares fit to the experimental results (Table 1) gives n,  $k_0$ , and Q to be 10.6 ± 1.0, 1 × 10<sup>-57.4±5.9</sup> m<sup>10.6</sup>/s and 320.8 ± 33.9 kJ/mol for perovskite, respectively, and

 $10.8 \pm 1.9$ ,  $1 \times 10^{-62.3 \pm 11.6}$  m<sup>10.8</sup>/s and 247.0  $\pm$  55.3 kJ/mol for periclase, respectively (Fig. 2).

The exponents n = 10.6 and 10.8 for perovskite and periclase, respectively, are larger than those for other silicate minerals and oxides in two phase aggregates (14). The large exponents indicate how difficult grain growth is and the slow growth rate may be attributed to the spatial relationships of the two phases within the aggregates. Here, the presence of two interlocking phases may decrease the grain growth rate of perovskite and periclase due to grain boundary pinning (15). The large grain growth exponents cannot be explained by previous models (16, 17). Nichols' model (16) suggests that grain growth is controlled by a grain boundary drag effect exerted by pores within which the material is transported by surface diffusion to the pore surface. Here, the pore drag mechanism is unlikely to occur since porosity was not detected in our SEM observations. Hanitzch and Kalweit's model (17) describes grain growth controlled by atomic diffusion along dislocation pipes. Grain growth through diffusion along dislocations is not applicable in our experiments since a high dislocation density probably does not exist in the starting material, which was hotpressed at high temperature. On the other hand, Q for periclase (247.0 kJ/mol) is similar to Q (261 kJ/mol) for self-diffusion of oxygen in periclase (18), suggesting that the grain growth of periclase is governed by oxygen diffusion at 25 GPa. It is not possible to compare the Q for perovskite to the Q for oxygen or silicon diffusion in perovskite because the Q for oxygen or silicon diffusion in perovskite is unknown.

## **REFERENCES AND NOTES**

- 1. For example, A. E. Ringwood, Geochim. Cosmochim. Acta 55, 2083 (1991).
- P. G. Silver and W. W. Chan, *J. Geophys. Res.* 91, 13787 (1986); K. M. Fischer, T. H. Jordan, K. C. Creager, *ibid.* 93, 4773 (1988); R. Van der Hilst, R. Engdahl, W. Spakman, G. Nolet, *Nature* 353, 37 (1991).
- S. Karato, J. Geophys. Res. 91, 8151 (1986); S. Karato and P. Li, Science 255, 1238 (1992).
- Based on shear wave splitting, C. Meade, P. G. Silver, and S. Kaneshima [Geophys. Res. Lett. 22, 1293 (1995)] concluded that the lower mantle was effectively isotropic. S. Karato [Phys. Earth Planet. Inter. 51, 107 (1988)] and S. Karato, S. Zhang, and H. R. Wenk [Science 270, 458 (1995)] suggested that lattice-preferred orientation was caused during ductile deformation by dislocation creep rather than diffusional deformation. The measured elastic anisotropy of perovskite [J. D. Bass, Phys. Earth Planet. Inter. 36, 145 (1984); A. Yageneh-Haeri, D. J. Weidner, E. Ito, Science 243, 787 (1989)] suggested that the preferred orientation of perovskite should produce a detectable seismic anisotropy in the lower mantle.
- We used a double-stage multianvil (MA) system consisting of an outer MA6 and an inner MA8 assembly. A graphite capsule and LaCrO<sub>3</sub> heater were used for the furnace assembly.
- A. M. Dziewonski and D. L. Anderson, *Phys. Earth Planet. Inter.* 25, 297 (1981).
- 7. We synthesized the starting material of pure forsterite by heating the stoichiometric mixtures of reagents (MgO: Junsei Chemical Co. Ltd., SiO<sub>2</sub>: Wako Pure Chemical Industries Ltd.) for 45 hours at 1600°C in air. Pressure was calibrated on the basis of the ilmenite-perovskite transition of MgSiO<sub>3</sub> and the spinelpost spinel transition of MgSiO<sub>3</sub> and the spinelpost spinel transition of Mg2SiO<sub>4</sub> [T. Kato *et al.*, *J. Geophys. Res.* **100**, 20475 (1995); E. Ito and E. Takahashi, *ibid.* **94**, 10637 (1989)]. Temperature was monitored with a W3%Re-W25%Re thermocouple located in the furnace. Temperature was kept within 10°C of the desired value.
- The runs with heating duration of a few seconds were terminated when the temperature reached the prescribed value by shutting off the heating power supply.
- S. A. Saltykov, Stereometric Metallography (Metallurgizdat, Moscow, 1958), pp. 446.
- E. Ito and H. Sato [*Nature* **351**, 140 (1991)] reported that spinel [(Mg<sub>0.9</sub>,Fe<sub>0.1</sub>)<sub>2</sub>SiO<sub>4</sub>] transformed to perovskite + magnesiowustite with a eutectoid texture at 24 GPa and 1873 K for 1 hour.

11. R. A. Fournelle and J. B. Clark, *Metall. Trans.* **3**, 2757 (1972).

 J. P. Poirier, J. Peyronneau, M. Madon, F. Guyot, A. Revcolevschi, *Nature* **321**, 603 (1986).

- J. E. Burke, in Grain Control in Industrial Metallurgy, (American Society for Metals, Cleveland, 1949), pp. 1–73; R. J. Brook, in Treatise on Materials Science and Technology, vol. 9, Ceramic Fabrication Process, F. F. Wang, Ed. (Academic Press, New York, 1976), pp. 331–364; M. Hillert, Acta Metall. 13, 227 (1965); A. M. Glaeser, Yogyo Kyokaishi, J. Cer. Soc. Japan 92, 538 (1984).
- J. B. Baldo and R. C. Bradt, J. Am. Ceram. Soc. 71, 720 (1988); T. Senda and R. C. Bradt, *ibid.* 73, 106 (1990); A. Hoshikuma, H. Sato, E. Ito, J. Seismol. Soc. Japan 48, 159 (1995).
- 15. G. C. Nicholson, J. Am. Ceram. Soc. 49, 47 (1966);

T. M. Harkulich, J. Magder, M. S. Vukasovich, R. J. Lockhart, *ibid.*, p. 295;
 T. K. Gupta, *ibid.* 54, 413 (1971);
 J. B. Baldo and R. C. Bradt, *ibid.* 71, 720 (1988);
 I. Chen and L. A. Xue, *ibid.* 73, 2585 (1990).
 F. A. Nichols, J. Appl. Phys. 37, 4599 (1966).

- F. A. Nichols, J. Appl. Phys. 31, 4399 (1900).
  E. Hanitzch and M. Kalweit, Z. Phys. Chem. 57, 145 (1968).
- Y. Oishi and W. D. Kingery, J. Chem. Phys. 33, 905 (1960).
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## Late Complications of Immune Deviation Therapy in a Nonhuman Primate

Claude P. Genain,\* Kristina Abel, Nicole Belmar, François Villinger, Daniel P. Rosenberg, Christopher Linington, Cedric S. Raine, Stephen L. Hauser

The administration of antigens in soluble form can induce antigen-specific immune tolerance and suppress experimental autoimmune diseases. In a marmoset model of multiple sclerosis induced by myelin oligodendrocyte glycoprotein (MOG), marmosets tolerized to MOG were protected against acute disease, but after tolerization treatment a lethal demyelinating disorder emerged. In these animals, MOG-specific T cell proliferative responses were transiently suppressed, cytokine production was shifted from a T helper type 1 ( $T_H$ 1) to a  $T_H$ 2 pattern, and titers of autoantibodies to MOG were enhanced. Thus, immune deviation can increase concentrations of pathogenic autoantibodies and in some circumstances exacerbate autoimmune disease.

Experimental allergic encephalomyelitis (EAE) is an autoimmune disease of the central nervous system (CNS) that serves as a laboratory model for the human demyelinating disease multiple sclerosis (MS) (1, 2). In rodents, EAE is mediated by effector T cells that respond to myelin antigens and secrete proinflammatory (T<sub>H</sub>1) cytokines, primarily interleukin-2 (IL-2), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interferon- $\gamma$ (IFN- $\gamma$ ) (3). The therapeutic administration of myelin antigens in nonimmunogenic form can suppress disease-inducing T cells and protect against EAE (4). This protection may result from enhanced production of anti-inflammatory  $(T_{\mu}2)$  cytokines, notably IL-4, IL-6, and IL-10 (5), an effect known as immune deviation (6). Protection can be conferred by adoptive transfer of antigen-specific  $T_H^2$  cells or administration of  $T_H^2$  cytokines, and is abrogated by antibodies to IL-4 (7).

We have developed a primary demyelinating form of EAE in the common marmoset *Callithrix jacchus* that has a clinical and pathological similarities to human MS (8, 9). In this species, synergistic T cell and B cell responses result in the MS-like lesion. Diverse populations of  $T_{\rm H}$ 1-cells recognizing myelin basic protein (MBP) or myelin oligodendrocyte glycoprotein (MOG) mediate the inflammatory component of the lesion, whereas antibodies to MOG mediate demyelination (9). Thus, MOG, a minor constit-

**Fig. 1.** Clinical course of EAE in placebo-treated and rMOG-treated *C. jacchus* marmosets. Animals were treated from day 7 until day 18 (shaded area) after immunization and received either 300 μg of rMOG dissolved in 0.025M Na-

uent of myelin comprising less than 0.05% of myelin proteins by weight, is a major encephalitogenic antigen capable of inducing pathogenic T cell and B cell responses in C. *jacchus*. Here, we characterize the effects of immune deviation in this model.

Seven C. jacchus marmosets were immunized with a recombinant protein corresponding to the extracellular domain of rat MOG (rMOG) in adjuvant (10). From day 7 to day 18 after immunization, animals received either soluble rMOG (rMOGtolerized) or placebo (control-tolerized). Consistent with previous observations in rMOG-immunized marmosets (9), clinical signs of EAE developed in four controltolerized animals between 9 and 16 days after immunization. In contrast, in the three animals treated with soluble rMOG, signs of EAE were suppressed, indicating that tolerization was successful. However, after cessation of treatment a rapidly progressive, lethal form of hyperacute EAE developed that was clinically more severe than in controls (Fig. 1) or than in any of more than 40 previously studied marmosets with acute EAE.

Neuropathologic findings confirmed the presence of widespread and histologically severe lesions. Lesions in the cerebral hemispheres and spinal cord of rMOG-tolerized animals were visible to the naked eve and were microscopically centered on blood vessels around which there was residual inflammation rich in plasma cells, demyelination, and macrophage activity. In the spinal cord and optic nerve (Fig. 2), lesions consisted of broad bands of subpial and perivascular white matter involvement. In contrast to control-tolerized animals in which lesion activity was limited to perivascular and subpial areas, in rMOG-tolerized animals there was a prominent zone of myelin pallor, sometimes up to 2 mm in width, surrounding a narrow band of demyelination and extending into the adjacent white matter. Within this zone of myelin pathology, cellular infiltration was absent and affected nerve fibers displayed dilated myelin sheaths with the axon either lying to one side of a large myelin vacuole or within a web of



acetate buffer, pH 3.0 (left panel) or placebo [right panel: buffer alone, recombinant glutathione-Stransferase (rGST), or cytochrome c] by intraperitoneal injection every other day for a total of six injections. Clinical signs were graded by blinded observers according to a scale of 1 to 5 as described (19).

C. P. Genain, K. Abel, N. Belmar, D. P. Rosenberg, S. L. Hauser, Department of Neurology, University of California, San Francisco, CA 94143, USA.

F. Villinger, Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA 30322, USA.

C. Linington, Department of Neuroimmunology, Max Planck Institut für Psychiatrie, Martinsried, Germany. C. S. Raine, Department of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461, USA.

<sup>\*</sup>To whom correspondence should be addressed.