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Difference in the hydration water mobility around F-actin and myosin subfragment-1 studied by quasielastic neutron scattering

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ABSTRACT

Hydration water is essential for a protein to perform its biological function properly. In this study, the dynamics of hydration water around F-actin and myosin subfragment-1 (S1), which are the partner proteins playing a major role in various cellular functions related to cell motility including muscle contraction, was characterized by incoherent quasielastic neutron scattering (QENS). The QENS measurements on the D_2O- and H_2O-solution samples of F-actin and S1 provided the spectra of hydration water, from which the translational diffusion coefficient (D_T), the residence time (τ_T), and the rotational correlation time (τ_R) were evaluated. The D_T value of the hydration water of S1 was found to be much smaller than that of the hydration water of F-actin while the τ_T values were similar between S1 and F-actin. On the other hand, the τ_R values of the hydration water of S1 was found to be larger than that of the hydration water of F-actin. It was also found that the D_T and τ_R values of the hydration water of F-actin are similar to those of bulk water. These results suggest a significant difference in mobility of the hydration water between S1 and F-actin: S1 has the typical hydration water, the mobility of which is reduced compared with that of bulk water, while F-actin has the unique hydration water, the mobility of which is close to that of bulk water rather than the typical hydration water around proteins.

1. Introduction

The actomyosin interaction is a fundamental biological process in a variety of cellular functions related to cell motility including cell locomotion and muscle contraction. Two partner proteins, actin and myosin, are responsible for this interaction, where myosin molecules cyclically interact with F-actin (the polymerized form of actin) utilizing the energy released by hydrolysis of adenosine triphosphate. Many studies suggest that flexibility of F-actin and myosin molecules plays an important role in the actomyosin interaction [1–3]. Our recent study using incoherent quasielastic neutron scattering (QENS) [4] showed that the dynamics of F-actin is different from that of myosin subfragment-1 (S1), which is a proteolytic fragment of the myosin molecule containing the actin-binding site and the catalytic site, such that the atoms of F-actin fluctuate more rapidly than those of S1. F-actin appears to utilize this enhanced mobility to interact with various actin-binding proteins. As proteins reside in an aqueous environment, such fluctuations of proteins occur under the influence of the dynamics of surrounding water molecules. Conversely, the water molecules near the protein surfaces have distinct dynamical properties from bulk water because of the interaction with the proteins. This dynamics of hydration water as well as the protein dynamics plays an active role for proper functions of proteins [5]. Full understanding of the mechanisms of the protein functions thus requires elucidating how the protein dynamics is related to the dynamics of hydration water. For the ultimate purpose of understanding the mechanism of the actomyosin interaction, the relationship between the protein dynamics and the hydration water dynamics in F-actin and S1 should therefore be elucidated. For this purpose, the dynamical properties of hydration water around F-actin and S1 are characterized in the present study.

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The dynamical properties of water molecules are to be characterized in terms of the translational and rotational motions. Studies on the rotational mobility of hydration water around F-actin and S1 using microwave dielectric spectroscopy [6,7] showed that the rotational mobility is higher for the water molecules around F-actin than for those around S1. On the other hand, whether the translational mobility of hydration water around these proteins is different has not been elucidated yet. The translational motions are particularly important because the translational motions of hydration water promote the large-amplitude motions of proteins required for their functions [8]. It is thus essential to directly compare the translational motions as well as the rotational motions of hydration water around S1 and F-actin.

Among various techniques to investigate the dynamics of hydration water, QENS provides a powerful tool to probe directly the motions of water molecules at ps – ns timescales. QENS has been widely used to study the dynamics of hydration water in hydrated protein powders [8–11]. The incoherent neutron scattering cross-section of hydrogen atoms is much larger than that of any other atoms found in biological macromolecules and the isotope deuterium. The signals from water molecules thus dominate in the QENS spectra of solution samples in H_2O-solvent, while those from hydrogen atoms in protein molecules dominate in the spectra of solution samples in D_2O-solvent. Information on the dynamics of the hydration water molecules can be extracted by combined analysis of the QENS spectra of the samples in the H_2O- and D_2O-solvents. In the present study, we compare the dynamics of hydration water around S1 and F-actin in solution using QENS. It was found that both the translational and the rotational mobility of hydration water are higher for F-actin than for S1.

2. Materials and methods

2.1. Sample preparation

S1 and F-actin were purified as described previously [4]. The H_2O-solution samples of these proteins were prepared in the buffer containing 5 mM Tris–HCl (pH 8.0), 0.2 mM ATP, 0.1 mM $CaCl_2$, 1 mM $MgCl_2$, 1 mM NaN_3, and 0.5 mM dithiothreitol (for F-actin), or the buffer containing 20 mM Tris–HCl (pH 8.0), 150 mM KCl, 1 mM NaN_3, and 0.5 mM dithiothreitol (for S1), in H_2O. The concentrations of F-actin and S1 were 151 mg/ml and 75 mg/ml, respectively, determined spectrophotometrically by using the extinction coefficients $E_{280}^{1\%}$ of 11.1 (F-actin) and 7.5 (S1). Each solution sample was put in an aluminum flat cell of 0.2 mm thickness and sealed with indium wire for the QENS experiments. The D_2O-solution samples of F-actin and S1 were prepared in the D_2O-buffer, which contains the same components to those of the H_2O-buffer, except that DCl was used for pD adjustment. The concentrations of F-actin and S1 in the D_2O-buffers were 150 mg/ml and 80 mg/ml, respectively. Note that analysis of the QENS spectra of these D_2O-solution samples was already reported in the previous paper [4].

2.2. Quasielastic neutron scattering experiments

The QENS measurements were carried out using the cold-neutron disk-chopper spectrometer AMATERAS in J-PARC/MLF (Ibaraki, Japan) [12]. Simultaneous measurements of the spectra at the energy resolutions of 90.5, 26.6, and 11.5 μeV (full width at half maximum) were carried out. These energy resolutions correspond to the accessible motions faster than 7, 25, and 57 ps, respectively. The energy resolution thus serves as a motion filter (an instrumental time window) such that the fast motions outside the instrumental time window contribute to a flat background, while the slow motions outside this window are hidden within the instrumental resolution function. Note that the analysis of the QENS spectra at 90.5 and 26.6 μeV energy resolutions are described here. It is because the spectra at 11.5 μeV had poor statistics and the smaller Q-range than those at other energy resolutions (Q is the momentum transfer defined as $4\pi\sin\theta/\lambda$, where 2θ denotes the scattering angle and λ denotes the incident wavelength), and thus were difficult to obtain reliable results by the analysis. A vanadium sample was measured for intensity corrections and for determination of the instrumental resolution functions. The measurement of an empty cell was also carried out, the QENS spectra of which was subtracted from those of all the samples measured. Fitting of the measured QENS spectra was done in the range of $-2.0\ \text{meV} \le \Delta E \le 2.0\ \text{meV}$ using IGOR Pro software (WaveMetrics, Lake Oswego, OR, USA).

2.3. Analysis of the QENS spectra

The QENS spectra of the H_2O-solution samples are dominated by water scattering (bulk and hydration water). To extract the spectra of water, the small but non-negligible contribution from the protein scattering must be subtracted from these spectra. The fractions of the contributions from the proteins and water in these spectra are thus required to be estimated. These fractions can be estimated from the incoherent scattering cross-section σ_{inc}. The values of σ_{inc} per molecule of S1 and water are, for example, calculated from their chemical compositions ($C_{4836}H_{7550}N_{1284}O_{1448}S_{41}$ and H_2O, respectively) to be $603{,}879 \times 10^{-24}\ \text{cm}^2$ and $159.8 \times 10^{-24}\ \text{cm}^2$, respectively. The molar concentration of S1 is calculated from the weight concentration (75 mg/ml) and the molecular weight (108,162) to be $6.93 \times 10^{-7}\ \text{mol/cm}^3$, and that of water is calculated to be $5.08 \times 10^{-2}\ \text{mol/cm}^3$, assuming the partial specific volume of S1 as $0.73\ \text{cm}^3\text{/g}$. Thus, the values of σ_{inc} of S1 and water per unit volume of the sample are $0.25\ \text{cm}^{-1}$ and $5.05\ \text{cm}^{-1}$, respectively, and thereby the fractions of their contributions being 0.05 and 0.95, respectively. Similar calculations provide the fractions of the contributions of F-actin ($C_{1854}H_{2907}N_{493}O_{565}S_{21}$ for a monomer) and water as 0.10 and 0.90, respectively. The fractions of the contributions of the proteins and (heavy) water in the D_2O-solution samples are similarly evaluated, with taking account of the H-D exchange. Assuming that all the exchangeable H atoms are replaced with the D atoms, the chemical compositions of S1 and the actin molecule in D_2O are $C_{4836}H_{5868}D_{1682}N_{1284}O_{1448}S_{41}$ and $C_{1854}H_{2277}D_{630}N_{493}O_{565}S_{21}$, respectively. The fractions of the contributions of the proteins and D_2O were then calculated to be 0.62 and 0.38 for S1, and 0.76 and 0.24 for F-actin, respectively. Using these values as the scaling factors, the QENS spectra of the proteins can be obtained by subtracting the spectra of the D_2O-buffer from those of the D_2O-solution samples [4], and then the QENS spectra of water can be obtained by subtracting these protein spectra from the spectra of the H_2O-solution samples.

It should, however, be noted that the degree of the H-D exchange may not be 100%. It has been suggested that a more reasonable assumption is that about 80% of the exchangeable H atoms are replaced [13]. If, as an extreme case, it is assumed that only 50% of the exchangeable H atoms are replaced with D atoms, the numbers of the D atoms are 841 for S1 and 315 for the actin molecule. In this case, the fractions of the contributions of the proteins and D_2O in the QENS spectra are 0.65 and 0.35 for S1, and 0.79 and 0.21 for F-actin, respectively. From comparison of these values with those assuming the 100% exchanges, possible errors in these fractions are estimated to be at most 5%. Since the fractions of the contributions of the proteins in the H_2O-solution samples are 0.05 and 0.1 for S1 and F-actin, respectively, the errors due to

uncertainty in the degree of the H-D exchange are at most 0.5%, which is negligible.

Another possible source of errors is the contribution of hydration water on the QENS spectra of the D_2O-solution samples, which was ignored in extraction of the protein spectra. Assuming the two layers of hydration water (corresponding to the hydration ratio of 1.6 g water/g protein, see "Results and Discussion" below), the molar concentrations of the hydration water in the D_2O-solution samples were calculated from the weight concentrations of the proteins to be 0.64×10^{-2} mol/cm^3 and 1.2×10^{-2} mol/cm^3 for S1 and F-actin, respectively. On the other hand, the molar concentrations of the total water were calculated from the weight concentrations of the proteins, the partial specific volume and the density of D_2O (1.11 g/cm^3) to be 5.2×10^{-2} mol/cm^3 and 4.9×10^{-2} mol/cm^3 for S1 and F-actin, respectively. Thus, 12% and 24% of the water fractions are hydration water for S1 and F-actin, respectively. Since the fractions of the contributions of water on the spectra of the D_2O-solution samples are 0.38 and 0.24 for S1 and F-actin, respectively, subtraction of the water spectra may introduce 4.6% ($=0.12\times0.38$) and 5.8% ($=0.24\times0.24$) errors due to hydration water for S1 ad F-actin, respectively. Considering the fractions of the proteins in the H_2O-solution samples being 0.05 and 0.1 for S1 and F-actin, respectively, the possible errors due to the hydration water in the subtraction of the protein spectra are 0.23% ($=0.046\times0.05$) and 0.58% ($=0.058\times0.1$) for S1 and F-actin, respectively. The effects of these errors on the extracted spectra of water are thus negligible.

The spectra of water, $S_{water}(Q, \omega)$, containing the contributions from both the hydration water and bulk water can be described as,

$$S_{water}(Q,\omega) = DW(Q)\times\exp(-\hbar\omega/2k_BT) \times\left[\left\{A_0(Q)\delta(\omega) + A_1(Q)\left(kS_{hyd}^{theo}(Q,\omega)+(1-k)S_{bulk}^{theo}(Q,\omega)\right)\right\}\otimes S_{res}(Q,\omega)\right] + B(Q), \quad (1)$$

where $\hbar\omega$ is the energy transfer, DW(Q) is a Debye-Waller factor, $\exp(-\hbar\omega/2k_BT)$ is the detailed balance factor, $A_0(Q)$ is the elastic incoherent structure factor of slow hydrogen dynamics that appear immobile for the energy resolution in the present experimental setting, $A_1(Q)$ is the fractional intensity for the spectra of water, k is the fraction of the contribution of the hydration water, $S_{bulk}^{theo}(Q,\omega)$ and $S_{hyd}^{theo}(Q,\omega)$ are the theoretical spectra of bulk water and the hydration water, respectively, $S_{res}(Q,\omega)$ is the resolution function, and B(Q) is the background.

$S_{bulk}^{theo}(Q,\omega)$ and $S_{hyd}^{theo}(Q,\omega)$ can be approximated as the sum of two Lorentzian functions [14]:

$$S_{bulk}^{theo}(Q,\omega)\ (\text{or } S_{hyd}^{theo}(Q,\omega)) = C_1(Q) \times(\Gamma_T(Q)/(\omega^2+\Gamma_T(Q)^2)) + C_2(Q)\times((\Gamma_T(Q) + \Gamma_R(Q))/(\omega^2+(\Gamma_T(Q)+\Gamma_R(Q))^2)). \quad (2)$$

The first Lorentzian function represents translational diffusion, and the second Lorentzian function combines translational and rotational diffusion with the half-widths at half-maximum (HWHM) $\Gamma_T(Q)$ and $\Gamma_R(Q)$, respectively. $C_1(Q)$ and $C_2(Q)$ denote the fractional intensities for the first and the second Lorentzian

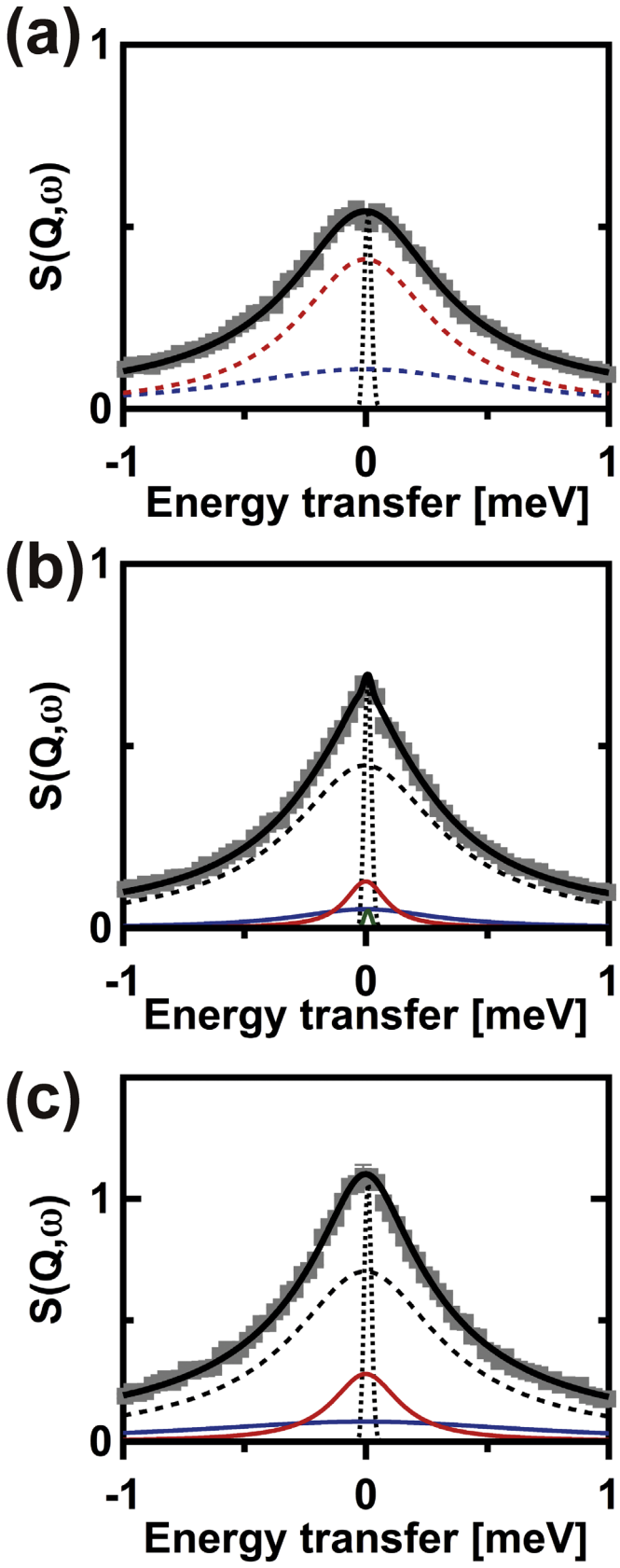

Fig. 1. Examples of the quasielastic neutron scattering spectra of (a) H_2O-buffer, (b) water (containing bulk water and hydration water) of S1, and (c) water of F-actin. The spectra at Q=1.7 Å^{-1} at 26.6 μeV energy resolution are shown. Gray filled squares denote the experimental data (error bars are within symbols if not shown), and black lines denote the total fits. In (a), red and blue broken lines denote the two Lorentzian functions fit to the data. In (b) and (c), broken lines denote the contribution of bulk water, which are the total fits to the data of the H_2O-buffer as shown in (a) with appropriate scaling factors (see Section 2). Green, red, and blue lines denote the elastic component, narrow and wide Lorentzian functions describing the motions of the hydration water, respectively. Dotted lines denote the resolution functions. Note that the elastic component represented by a green line is observed only in the spectra of water of S1 (b): This component is not expected to be observed in the spectra of bulk water (a), and the amplitude of this component is too small to be observed in the spectra of water around F-actin (c). This difference between S1 and F-actin implies the different distributions of motions of hydration water between S1 and F-actin. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

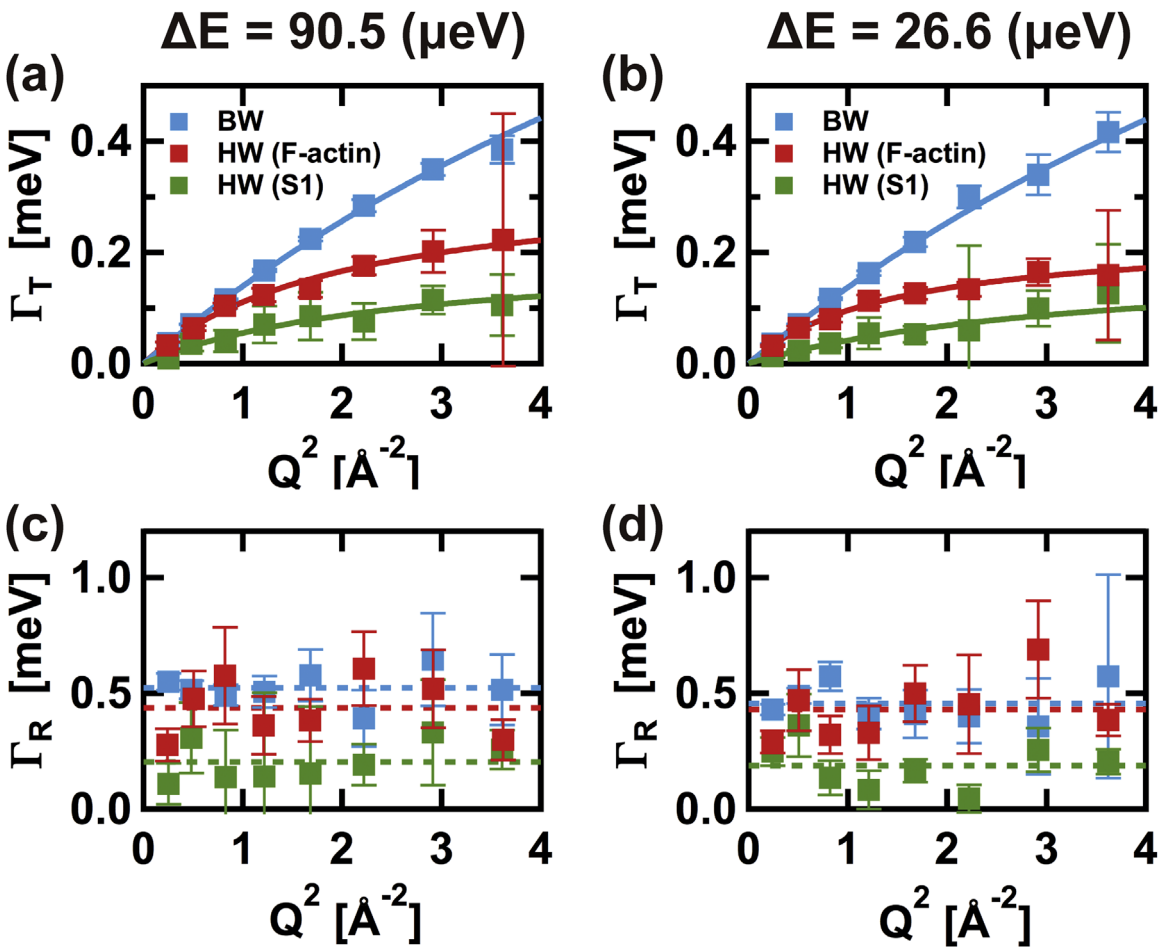

Fig. 2. Q^2-dependence of the half widths at half-maximum, $\Gamma_T(Q)$, of the translational diffusion process, and, $\Gamma_R(Q)$, of the rotational diffusion process of the water molecules. The variations of $\Gamma_T(Q)$ and $\Gamma_R(Q)$ obtained from the spectra at 90.5 μeV are shown in (a) and (c), respectively. Those at 26.6 μeV are shown in (b) and (d). Filled squares in cyan, red, and green are the data for bulk water (BW), the hydration water (HW) of F-actin, and that of S1, respectively. Solid lines in (a) and (b) denote the fits with Eq. (3). Dotted lines in (c) and (d) denote the averaged values over the all Q-range. Error bars are within symbols if not shown. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Summary of the parameters on the translational and rotational diffusion of bulk water, and the hydration water of S1 and F-actin.

		D_T ($\times 10^{-5}$ cm^2/s)	τ_T (ps)	τ_R (ps)
90.5 μeV				
	Bulk water	2.30 (0.02)	0.42 (0.04)	1.2 (0.1)
	Hydration water (S1)	1.1 (0.5)	3.2 (2.0)	3.2 (1.2)
	Hydration water (F-actin)	2.5 (0.2)	2.0 (0.4)	1.5 (0.2)
26.6 μeV				
	Bulk water	2.26 (0.02)	0.40 (0.06)	1.4 (0.2)
	Hydration water (S1)	0.8 (0.1)	3.5 (2.4)	3.5 (0.5)
	Hydration water (F-actin)	2.4 (0.2)	2.8 (0.3)	1.5 (0.3)

Values in parenthesis are the standard deviations.

functions, respectively. The parameters for the theoretical spectra of bulk water were determined from the spectra of the H_2O-buffer because the scattering cross-section per unit volume of the chemical components in the buffer (for example, 0.01 cm^{-1} for the H_2O-buffer of S1) is negligible compared to that of the water molecules (5.34 cm^{-1}). Fitting the spectra of water with Eq. (1) thus provides information on the diffusive motions of hydration water. We carried out the fits at various values of k in Eq. (1) corresponding to the range of the hydration ratio between 1.6 g H_2O/g protein and 3.6 g H_2O/g protein. The value of $h=1.6$ corresponds to the value of k=0.13 for S1 and 0.28 for F-actin, and the value of $h=3.6$ corresponds to the value of k=0.29 for S1 and 0.64 for F-actin. The different corresponding k values arise from the different concentrations of the proteins in the samples. Note that the fits at the k values below this range did not converge because the fraction of bulk water scattering in Eq. (1) becomes so large that the remaining spectra suffer significant noises and cannot be described by the sum of the Lorentzian functions.

3. Results and discussion

Fig. 1(a) shows an example of the QENS spectra of the H_2O-buffer, which can be regarded as those of bulk water. These spectra were well fit with Eq. (2) with the Debye-Waller factor and the detailed balance factor included. The parameters determined from these fits were used to fit the spectra of water of S1 and F-actin. Fig. 1(b) and (c) show examples of the QENS spectra of water of S1 and F-actin. These spectra were fit with Eq. (1), using the parameter values of bulk water, determined from the H_2O-buffer spectra. Solid lines in Fig. 1(b) and (c) are the results of the fits for the case of the hydration ratio $h=1.6$, which are described below.

Fig. 2 shows the Q^2-dependences of the HWHM for the translational diffusion, Γ_T, and that for the rotational diffusion, Γ_R, of

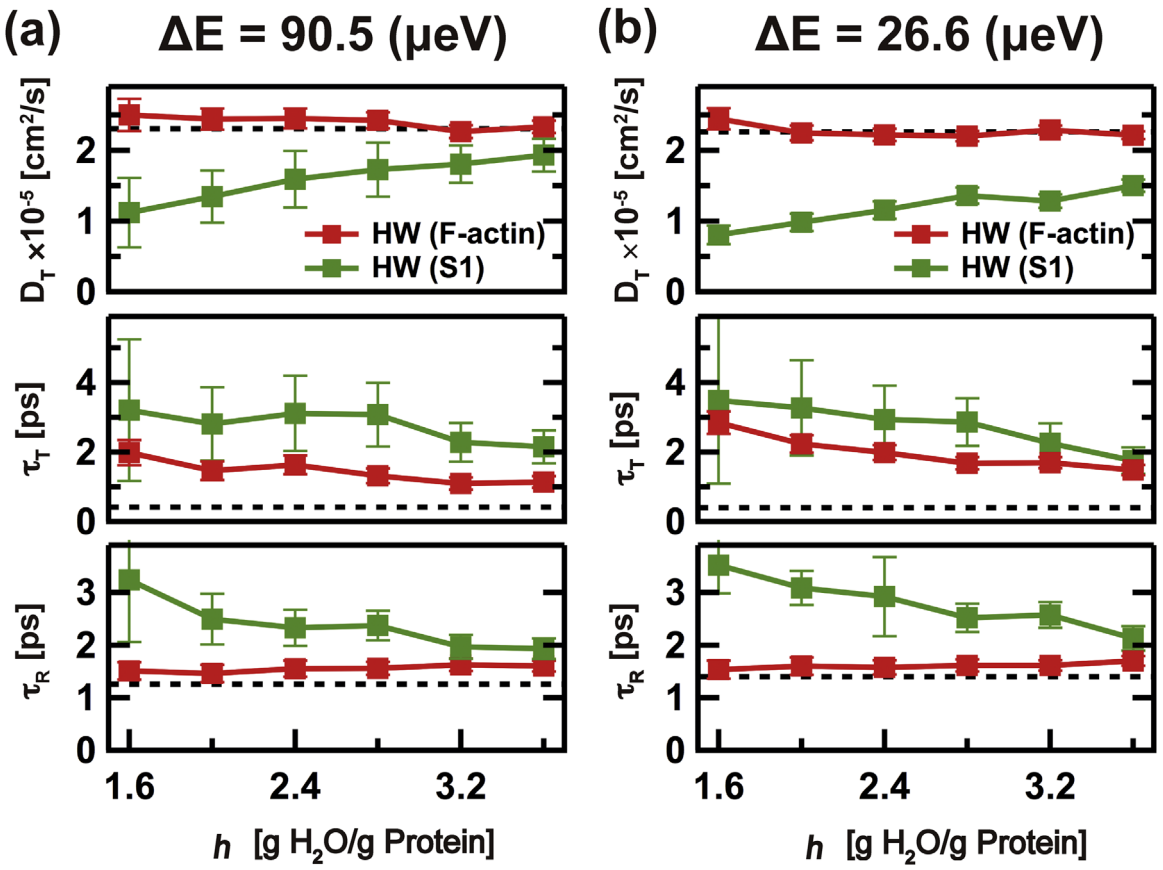

Fig. 3. Dependence of the dynamics parameters for the hydration water on the hydration ratio (h) of the proteins at (a) 90.5 μeV and (b) 26.6 μeV. Filled squares in red and green denote the dynamics parameters (D_T: translational diffusion coefficient, τ_T: residence time, and τ_R: rotational correlation time) of the hydration water (HW) of F-actin, and S1, respectively. The corresponding values of bulk water (BW) are shown as dotted lines for comparison. Error bars are within symbols if not shown. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

bulk water, the hydration water of S1, and the hydration water of F-actin. The Γ_T values approach asymptotically to plateau values for all samples. On the other hand, the Γ_R values for all samples show no appreciable Q^2-dependency over the measured Q-range, which is expected for rotational diffusion. The behavior of Γ_T is characteristic of the jump diffusion [13], and described by the equation,

$$I_T(Q)=D_T Q^2/(1 + D_T Q^2 \tau_T), \quad (3)$$

where D_T denotes the translational diffusion coefficient, and τ_T denotes the residence time. The fits to the data shown in Fig. 2 (a) and (b) with Eq. (3) provide the values of D_T and τ_T. The results of the fits are summarized in Table 1. The rotational correlation times τ_R ($=1/\Gamma_R$), calculated from the average values of Γ_R, are also summarized in Table 1.

As shown in Table 1, the D_T values are similar between the hydration water of F-actin and bulk water, but significantly smaller for the hydration water of S1. This indicates that the translational diffusion of the hydration water of S1 is suppressed compared with bulk water. On the other hand, the residence times, τ_T, are similar between the hydration water of S1 and F-actin, but larger than that of bulk water. The differences in the rotational correlation time, τ_R, indicate that the rotational motions of the hydration water of S1 are reduced while those of F-actin are similar to bulk water. These results suggest that the hydration water of S1 is less mobile than that of F-actin. Note that the differences in the hydration-water dynamics between S1 and F-actin were detected from the spectra at the two energy resolutions. The fact that the independent analysis of the spectra at two energy resolutions detected the similar differences strengthens the reliability of our results.

The results shown above are for the hydration ratio $h=1.6$. This value corresponds to 9764 water molecules around S1 and 3717 water molecules around an actin monomer in F-actin. The number of water molecules that covers entirely the surface of the protein can be estimated from the solvent accessible surface area (ASA) and the area on the protein surface occupied by one water molecule, which was estimated to be 9.6 $Å^2$ [15]. The ASAs of S1 and F-actin are calculated to be 44,977 $Å^2$ and 18,665 $Å^2$ (the latter value is per monomer in F-actin), respectively, using the software Chimera [16]. The number of water molecules covering the protein is thus 4685 for S1 and 1944 for (an actin monomer in) F-actin. Both of these values correspond to $h=0.8$, taking account of the molecular weights of the proteins. The hydration ratio of 1.6 thus corresponds roughly to two layers of hydration shells. Although the range of the hydration water around the protein in solution is not really known, a molecular dynamics study [17] suggests that in aqueous solution, the water molecules residing within 6 Å from the protein surface, which includes the first and the second hydration shell, behave differently from bulk water. The differences between S1 and F-actin described above should thus reflect the different behavior of hydration water between S1 and F-actin.

We carried out the analysis of the QENS spectra of water at various h. Fig. 3 shows the dependences of the dynamics parameters on h in the range between 1.6 and 3.6. Increase in h corresponds to increase in the effects of bulk water on the parameter evaluation. The parameter values for S1 gradually change with increasing h while those for F-actin show little dependency on h. These results suggest that the dynamics of the hydration

water of S1 is significantly different from that of bulk water while the dynamics of the hydration water of F-actin is similar to that of bulk water. Note, however, that τ_T decreases with increasing h for both S1 and F-actin, indicating that the residence time of the hydration water of both S1 and F-actin is different from that of bulk water. These results at the increasing h thus support that the results at $h=1.6$ indeed arise from the differences in hydration water between S1 and F-actin.

Our results for τ_R of hydration water confirm the results of the microwave dielectric spectroscopic study that the rotational mobility of hydration water is higher for F-actin than for S1 [6]. Furthermore, the results for D_T and τ_T indicate that the translational mobility of hydration water is higher for F-actin than for S1. The present data thus show for the first time that not only the rotational mobility but also the translational mobility is higher for the hydration water of F-actin than that of S1. The reduced dynamics of the hydration water of S1 compared with bulk water is consistent with the dynamics of the hydration water of proteins studied so far [18], suggesting that S1 has the typical hydration water. On the other hand, the hydration water of F-actin shows the dynamical properties that are similar to those of bulk water rather than the typical hydration water.

The major difference in the sample environment, which may affect the dynamics of hydration water, is existence of 150 mM KCl in the S1 buffer. The effect of KCl is, however, to slightly increase the translational diffusion coefficient of water molecules [19]. It is therefore unlikely that the dynamics of the S1 hydration water is lowered by K^+ and/or Cl^- ions in the solution. Another possible factor that affects the dynamics of hydration water is binding of these ions to the protein surface. Binding of these ions to the protein surface might screen the electric field produced by the charged residues, thereby modulating the mobility of water molecules around the protein. A molecular dynamics simulation study, however, shows that elimination of the electrostatic interactions between the protein and solvent molecules leads to enhancement of diffusion of the superficial water molecules, rather than depressing their mobility [20]. Thus, the observed difference in the dynamics of the hydration water between S1 and F-actin should not be an artifact caused by the sample environment but the genuine difference.

In the previous study, we have shown that mobility of the atoms is higher in F-actin than in S1 [4]. The present study shows that both translational and rotational mobility of the hydration water of F-actin are higher than those of the hydration water of S1. Taken together, these results suggest that the differences in the dynamics between F-actin and S1 arise from coupling of the protein dynamics to the dynamics of their hydration water. This coupling should be the origin of multi-functions of F-actin. The hydration water with enhanced mobility around F-actin should lower the viscosity around F-actin [21], and thereby making the atoms of F-actin fluctuate rapidly [4]. This concerted action of F-actin and its hydration water would allow F-actin to explore the conformational space frequently, which facilitates the adjustment of its conformations for the binding of various actin-binding proteins including S1 to F-actin.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.bbrep.2016.04.013.

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