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Hydration Structure of L-Hydrogenglutamate Ion in Concentrated Aqueous Solutions

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Neutron diffraction measurements were carried out on $^{14}N/^{15}N$ isotopically substituted aqueous 5 mol % sodium L-hydrogenglutamate solutions in D_2O in order to obtain direct information concerning the structure of the first hydration shell around the amino-group of the L-hydrogenglutamate ion. Hydration parameters were determined through the least-squares fitting analysis of the observed intermolecular difference function, $\Delta_N^{inter}(Q)$. It was shown that, on average, 3.1(1) D_2O molecules were hydrogen-bonded to the amino-hydrogen atoms of the hydrogenglutamate ion with interatomic distances of $r_{NO_W} = 2.92(2)$ and $r_{ND_W} = 3.47(1)$ Å, respectively.

Hydration structure of the amino acid molecule has received much attention, because it is important in several fields of chemical and biological sciences. Since the amino acid molecule involves several functional groups with different hydration natures, it is necessary to obtain the hydration structure of individual functional groups in the partial structure function level.[1] Neutron diffraction in conjunction with an isotopic substitution technique is considered to be one of the best experimental methods to obtain direct information on the environmental structure around the substituted atom.[2,3]

Structure of the first hydration shell around the amino-group has been examined for glycine[4–6] and alanine[7,8] molecules by means of a $^{14}N/^{15}N$ isotopic substitution method. The hydrogen-bonded structure between the amino-group and the nearest neighbor water molecule has been shown to depend strongly on the pH value of the solution and also on the ionization state of amino acid molecule. In a neutral aqueous 5 mol % glycine solution, the amino-group of the glycine molecule in the zwitterionic form ($H_3N^+CH_2COO^-$) forms hydrogen bonds of $N–H\cdots OH_2$ type with 3.0(6) nearest neighbor water molecules.[4] The nearest neighbor $N\cdots O_W$ and $N\cdots H_W$ (O_W and H_W denote water-oxygen and water-hydrogen atoms, respectively) distances have been determined to be 2.85(5) and 3.25(5) Å, respectively.[4] Similar hydration structure of the amino-group was reported for the zwitterionic alanine molecule in an aqueous 3 mol % alanine solution.[7] The nearest neighbor $N\cdots O_W$ distance has been determined to be 2.88(2) Å with a coordination number of 2.4(1),[7] which is considerably smaller value than that found for a glycine molecule. These results imply that the hydration structure around the amino-nitrogen atom is affected by the structure and hydration nature of the side-chain group within the amino acid molecule. Since the glycine and alanine molecules have both apolar side-chain groups with weak hydration shell,[7–9] the hydration number of the amino-group would be affected by the bulkiness of the apolar side-chain group. It is of considerable interest to investigate the effect of a charged side-chain group on the hydration structure of the amino acid molecule. Recently, the structure of aqueous alkaline 2 M (1 M = 1 mol dm^{-3}) L-glutamic acid solutions has been examined by neutron diffraction with H/D isotopic substitution method.[10] From EPSR data analysis[11] of the observed diffraction data, it is reported that each amino-hydrogen atom of the glutamic acid molecule forms a single hydrogen bond with the nearest neighbor water molecule;[10] however, interatomic distances for the nearest neighbor $N\cdots O_W$ and $N\cdots H_W$ interactions are not presented probably due to uncertainties in estimating the $N\cdots O_W$ and $N\cdots H_W$ partial structure factors that contribute ca. 1% of the observed total interference term.

In the present paper, we describe the results of TOF neutron diffraction measurements on aqueous 5 mol % sodium L-hydrogenglutamate heavy water solutions. $^{14}N/^{15}N$ isotopically substituted samples were employed in order to obtain detailed structural information on interaction between the amino-nitrogen atom and the nearest neighbor water molecules. Structural parameters concerning the first hydration shell of the amino-group were determined from a least-squares fitting analysis of the observed intermolecular difference function ($\Delta_N^{inter}(Q)$).

Experimental

Materials. Isotopically enriched L-glutamic acid, L-$HO_2CCH_2CH_2CH(^{15}NH_2)CO_2H$ (98.0% ^{15}N, ISOTECH Inc.) and L-$HO_2CCH_2CH_2CH(^{14}NH_2)CO_2H$ (natural abundance, Nacalai Tesque, guaranteed grade) were reacted with NaOH (Nacalai Tesque, guaranteed grade) in aqueous solutions. The product solutions were carefully dehydrated under vacuum to obtain anhydrous sodium L-hydrogenglutamate samples of different $^{14}N/^{15}N$ compositions. Deuteration of exchangeable hydrogen atoms within the hydrogenglutamate ion was achieved by dissolving the anhydrous sodium hydrogenglutamate into 10 times the molar quantity of D_2O (99.9% D, Aldrich Chemical Co.), followed by dehydration under vacuum. This procedure was repeated 4 times. The required amounts of enriched compounds, that is, L-$NaO_2CCH_2CH_2CH(^{15}ND_2)CO_2D$ and L-$NaO_2CCH_2CH_2CH(^{14}ND_2)CO_2D$, were dissolved into D_2O (99.9% D, Aldrich Chemical Co.) to prepare two 5 mol % sodium hydrogenglutamate solutions with different $^{14}N/^{15}N$ ratios, i.e., I [L-$NaO_2CCH_2CH_2CH$-

Published on the web September 13, 2007; doi:10.1246/bcsj.80.1746

Table 1. Isotopic Composition, Average Scattering Length, b_N, of the Nitrogen Atom, Total Cross Section, and Number Density of Sample Solutions Scaled in the Stoichiometric Unit, $[\text{L-NaO}_2\text{CCH}_2\text{CH}_2\text{CH}(^*\text{ND}_2)\text{CO}_2\text{D}]_{0.05}(\text{D}_2\text{O})_{0.95}$, σ_t and ρ, Respectively

Sample	^{14}N/%	^{15}N/%	b_N /10^{-12} cm	σ_t /barns[a)]	ρ/Å^{-3}
$[\text{L-NaO}_2\text{CCH}_2\text{CH}_2\text{CH}(^{14}\text{ND}_2)\text{CO}_2\text{D}]_{0.05}(\text{D}_2\text{O})_{0.95}$	99.6	0.4	0.936	23.937	0.02753
$[\text{L-NaO}_2\text{CCH}_2\text{CH}_2\text{CH}(^{15}\text{ND}_2)\text{CO}_2\text{D}]_{0.05}(\text{D}_2\text{O})_{0.95}$	2.0	98.0	0.650	23.566	

a) For incident neutron wavelength of 1.0 Å.

Table 2. Values of the Coefficients of $a_{ij}(Q)$ in Eq. 1

A/barns	B/barns	C/barns	D/barns	E/barns	F/barns
0.0191	0.0390	0.0048	−0.0027	0.0005	0.0011

$(^{14}\text{ND}_2)\text{CO}_2\text{D}]_{0.05}(\text{D}_2\text{O})_{0.95}$ and II $[\text{L-NaO}_2\text{CCH}_2\text{CH}_2\text{CH}(^{15}\text{ND}_2)\text{CO}_2\text{D}]_{0.05}(\text{D}_2\text{O})_{0.95}$.

The H/D ratio of exchangeable hydrogen atoms within the sample solutions was checked by using attenuated total reflection infrared spectroscopy (ATR-IR), which has been described elsewhere.[7] The sample parameters used in the present study are listed in Table 1.

Neutron Diffraction Measurements. Sample solutions were sealed into cylindrical Ti–Zr null alloy cells (8.0 mm in inner diameter and 0.3 mm in thickness). TOF neutron diffraction measurements were carried out at 25 °C using a HIT-II spectrometer[12] installed at the spallation neutron source (KENS) in the High Energy Accelerator Organization (KEK), Tsukuba, Japan. Scattered neutrons were detected by 104 ^{3}He proportional counters covering a scattering angle of $10 \leq 2\theta \leq 157°$. The data accumulation time was ca. 12 h for each sample solution. Measurements were made in advance for an empty cell, instrumental background, and a vanadium rod of 8 mm in diameter.

Data Reduction. Observed scattering intensities for the sample were corrected for instrumental background, absorption of sample and cell,[13] multiple,[14] and incoherent scatterings. The coherent scattering lengths as well as the scattering and absorption cross sections for the constituent nuclei were referred to those tabulated by Sears.[15] The wavelength dependence of the total cross sections for H and D nuclei was estimated from the observed total cross sections for H_2O and D_2O, respectively.[16] The corrected intensities were converted to an absolute scale using the corrected scattering intensities from the vanadium rod.

The first-order difference function $(\Delta_N(Q))$[2,3] was derived from the numerical difference between scattering cross sections observed for solutions I and II. $\Delta_N(Q)$, scaled to the stoichiometric unit, $[\text{L-NaO}_2\text{CCH}_2\text{CH}_2\text{CH}(^*\text{ND}_2)\text{CO}_2\text{D}]_x(\text{D}_2\text{O})_{1-x}$, can be written as a linear combination of partial structure factors, $a_{Nj}(Q)$, involving contribution from the N···j pair:

$$\begin{aligned}\Delta_N(Q) = {} & A[a_{NO}(Q)-1] + B[a_{ND}(Q)-1] \\ & + C[a_{NC}(Q)-1] + D[a_{NH}(Q)-1] \\ & + E[a_{NNa}(Q)-1] + F[a_{NN}(Q)-1], \end{aligned} \tag{1}$$

where

$$\begin{aligned} & A = 2x(3x+1)\Delta b_N b_O,\ B = 2x(x+2)\Delta b_N b_D, \\ & C = 10x^2 \Delta b_N b_C,\ D = 10x^2 \Delta b_N b_H, \\ & E = 2x^2 \Delta b_N b_{Na},\ \text{and}\ F = x^2({b_{^{nat}N}}^2 - {b_{^{15}N}}^2), \end{aligned}$$

and $\Delta b_N = b_{^{nat}N} - b_{^{15}N}$. The weighting factors $A - F$ are listed in Table 2.

The intramolecular contribution, $I_N^{intra}(Q)$ from the N···α pairs within the hydrogenglutamate ion is estimated by

$$I_N^{intra}(Q) = \Sigma 2x\Delta b_N b_\alpha \exp(-{l_{N\alpha}}^2 Q^2/2)\sin(Qr_{N\alpha})/(Qr_{N\alpha}), \tag{2}$$

where $l_{N\alpha}$ and $r_{N\alpha}$ denote the root-mean-square (r.m.s.) displacement and internuclear distance for the N···α pair, respectively. Values of $r_{N\alpha}$ and $l_{N\alpha}$ used for the present analysis were taken from the literature determined by single crystal X-ray[17,18] and neutron[19] diffraction works and from values calculated for related molecules,[20–22] respectively. On the basis to a single-crystal neutron diffraction study for the β-form of L-glutamic acid, the torsion angle involving carbon atoms, C_α–C_β–C_γ–C_δ (C_α: α-carbon atom, C_β, C_γ, and C_δ: carbon atoms within the side-chain group of the glutamic acid molecule) was determined to be −73.1(2)°.[19] On the other hand, the result of the EPSR analysis for the intramolecular conformation of the zwitterionic glutamic acid molecule indicated that the torsion angle exhibits an extremely broadened distribution in an aqueous solution.[10] In the present analysis, the molecular conformation of the L-hydrogenglutamate ion was assumed to be identical to that for the L-glutamic acid molecule in the crystalline state. The calculated $I_N^{intra}(Q)$ was then subtracted from the observed $\Delta_N(Q)$ to obtain $\Delta_N^{inter}(Q)$,

$$\Delta_N^{inter}(Q) = \Delta_N(Q) - I_N^{intra}(Q). \tag{3}$$

The distribution function $(G_N(r))$ around the amino-nitrogen atom was obtained by the Fourier transform of the observed $\Delta_N(Q)$,

$$\begin{aligned} G_N(r) & = 1 + (A+B+C+D+E+F)^{-1}(2\pi^2\rho r)^{-1} \\ & \quad \times \int_0^{Q_{max}} Q\Delta_N(Q)\sin(Qr)\,dQ \\ & = [Ag_{NO}(r) + Bg_{ND}(r) + Cg_{NC}(r) \\ & \quad + Dg_{NH}(r) + Eg_{NNa}(r) + Fg_{NN}(r)] \\ & \quad \times (A+B+C+D+E+F)^{-1}. \end{aligned} \tag{4}$$

The upper limit of the integral, Q_{max}, was set to be 20 Å^{-1}. The intermolecular distribution function, $G_N^{inter}(r)$, was evaluated by the Fourier transform of the $\Delta_N^{inter}(Q)$.

Structural parameters concerning the first hydration shell around the amino-group were determined through a least-squares fitting procedure for the observed $\Delta_N^{inter}(Q)$, employing the model function $\Delta_N^{model}(Q)$ involving both short- and long-range contributions:[23–25]

$$\begin{aligned} \Delta_N^{model}(Q) = {} & \Sigma 2x n_{N\alpha} \Delta b_N \\ & \times \exp(-{l_{N\alpha}}^2 Q^2/2)\sin(Qr_{N\alpha})/(Qr_{N\alpha}) \end{aligned}$$

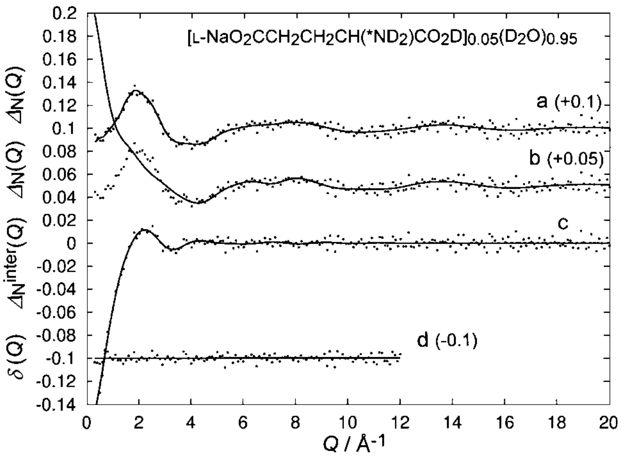

Fig. 1. a) Observed difference function, $\Delta_{\mathrm{N}}(Q)$, for aqueous 5 mol % sodium L-hydrogenglutamate heavy water solutions (dots). Back Fourier transform of $G_{\mathrm{N}}(r)$ denoted by the solid line in Fig. 2a (solid line). b) Observed $\Delta_{\mathrm{N}}(Q)$ (dots), and the intramolecular interference term within the hydrogenglutamate ion, $I_{\mathrm{N}}{}^{\mathrm{intra}}(Q)$ (solid line). c) Intermolecular difference function, $\Delta_{\mathrm{N}}{}^{\mathrm{inter}}(Q)$ (dots). The best-fit of the calculated $\Delta_{\mathrm{N}}{}^{\mathrm{model}}(Q)$ is shown by the solid line. d) The residual function, $\delta(Q)$ (dots).

$$+ 4\pi\rho(A + B + C + D + E + F)$$
$$\times \exp(-l_0{}^2Q^2/2)[Qr_0\cos(Qr_0) - \sin(Qr_0)]Q^{-3}, \qquad (5)$$

where $n_{\mathrm{N}\alpha}$ denotes the coordination number of α atom around the amino-nitrogen atom. l_0 is the long-range parameter describes the sharpness of the boundary at r_0. The structural parameters, $n_{\mathrm{N}\alpha}$, $l_{\mathrm{N}\alpha}$, $r_{\mathrm{N}\alpha}$, l_0, and r_0, were determined from a least-squares fit of the observed $\Delta_{\mathrm{N}}{}^{\mathrm{inter}}(Q)$. The fitting procedure was performed in the range of $0.3 \leq Q \leq 12.0\,\text{Å}^{-1}$ with the SALS program,[26] assuming that the statistical uncertainties distribute uniformly.

Results and Discussion

The observed $\Delta_{\mathrm{N}}(Q)$ is shown in Fig. 1a. The first diffraction peak at $Q \approx 2\,\text{Å}^{-1}$ and the oscillational feature of the $\Delta_{\mathrm{N}}(Q)$ extending to the higher-Q region were clearly observed. The calculated $I_{\mathrm{N}}{}^{\mathrm{intra}}(Q)$ (Fig. 1b) was subtracted from the observed $\Delta_{\mathrm{N}}(Q)$. The normalization factor, γ, defined by $I_{\mathrm{N}}{}^{\mathrm{intra}}(Q) = \gamma \times \Delta_{\mathrm{N}}(Q)$ (in sufficiently high-Q region), was determined to be $\gamma = 0.99(4)$ from a least-squares fit in the range of $7 \leq Q \leq 20\,\text{Å}^{-1}$, implying that the overall normalization error in the present $\Delta_{\mathrm{N}}(Q)$ is roughly within 4%. $\Delta_{\mathrm{N}}{}^{\mathrm{inter}}(Q)$ (Fig. 1c) was characterized by the first peak at $Q \approx 2\,\text{Å}^{-1}$.

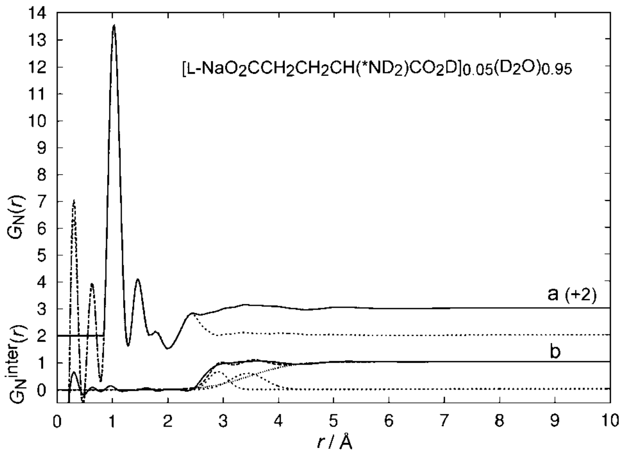

Fig. 2. a) Total distribution function around the amino-nitrogen atom, $G_{\mathrm{N}}(r)$, observed for aqueous 5 mol % sodium L-hydrogenglutamate heavy water solutions (solid line). Fourier transform of the intramolecular interference term, $I_{\mathrm{N}}{}^{\mathrm{intra}}(Q)$, is shown by the dotted line. b) Observed intermolecular distribution function, $G_{\mathrm{N}}{}^{\mathrm{inter}}(r)$ (solid line). Fourier transform of the calculated $\Delta_{\mathrm{N}}{}^{\mathrm{model}}(Q)$ is shown by a broken line. The contribution from the short- and long-range interactions are denoted by the thick and thin dotted lines, respectively.

The total and intermolecular distribution functions, $G_{\mathrm{N}}(r)$ and $G_{\mathrm{N}}{}^{\mathrm{inter}}(r)$, are represented in Figs. 2a and 2b, respectively. The Fourier transform of $I_{\mathrm{N}}{}^{\mathrm{intra}}(Q)$ is also shown by a dotted line in Fig. 2a. The dominant first peak located at $r = 1.03\,\text{Å}$ and the second peak at $r = 1.45\,\text{Å}$ in the present $G_{\mathrm{N}}(r)$ were assigned to the intramolecular N–D and N–C$_\alpha$ interactions within the hydrogenglutamate ion, respectively. A small negative peak appearing at around $r = 2.0\,\text{Å}$ was attributed to intramolecular non-bonding interaction between the amino-nitrogen atom and the α-carbon-bonded hydrogen atom, which has a negative scattering length. A sum of the contributions from intramolecular non-bonding N$\cdots$C(carboxyl) and N$\cdots$C(methylene) interactions contribute to the partially resolved peak at $r = 2.5\,\text{Å}$. The intramolecular N$\cdots\alpha$ contribution extends to the range of $r \leq 5\,\text{Å}$, considering the molecular structure of the hydrogenglutamate ion; however, the contribution from the intramolecular N$\cdots\alpha$ contribution seems considerably small for $r \leq 2.8\,\text{Å}$ as shown in Fig. 2a, where the intermolecular interaction between the amino-nitrogen atom and the nearest neighbor D_2O molecule should fall. This smaller intramolecular contribution for $r \leq 2.8\,\text{Å}$ can be explained by relatively larger value of the r.m.s. displacements for the non-bonding N$\cdots\alpha$ interactions as well as the partial cancellation of the N$\cdots$C or O (positive contribution in $G_{\mathrm{N}}(r)$) and N$\cdots$H (negative contribution in $G_{\mathrm{N}}(r)$) terms arising from the interactions between the amino-nitrogen atom and atoms involved in the side-chain group. The result implies that the intramolecular conformation employed in the evaluation of $I_{\mathrm{N}}{}^{\mathrm{intra}}(Q)$ term does not significantly affect the intermolecular structure functions in the present study.

The observed $G_{\mathrm{N}}{}^{\mathrm{inter}}(r)$ is shown in Fig. 2b. The present $G_{\mathrm{N}}{}^{\mathrm{inter}}(r)$ looks very similar to that observed for an aqueous 5 mol % glycine solution.[4] Although $G_{\mathrm{N}}{}^{\mathrm{inter}}(r)$ seems rather featureless, contributions from the nearest neighbor N$\cdots$O$_{\mathrm{W}}$ and N$\cdots$D$_{\mathrm{W}}$ interactions should be involved in the range of $2.5 \leq r \leq 4\,\text{Å}$. In order to obtain structural parameters concerning the first hydration shell around the amino-group, a least-squares fitting analysis was applied to the observed $\Delta_{\mathrm{N}}{}^{\mathrm{inter}}(Q)$. The following assumptions were adopted in evaluating the theoretical interference term. a) Parameters for the first nearest neighbor N$\cdots$D$_2$O interaction, $r_{\mathrm{NO_W}}$, $l_{\mathrm{NO_W}}$, $n_{\mathrm{NO_W}}$, $r_{\mathrm{ND_W}}$, and $l_{\mathrm{ND_W}}$, were treated as independent parameters. The coordination number, $n_{\mathrm{ND_W}}$, was fixed to the value $2n_{\mathrm{NO_W}}$ in the fitting procedure. In the present analysis, N$\cdots$O$_{\mathrm{W}}$ and N$\cdots$D$_{\mathrm{W}}$ distances and corresponding r.m.s. displacements for the neatest neighbor N$\cdots$D$_2$O interaction were assumed to be the same values for all N$\cdots$D$_2$O interactions within the first

Table 3. Results of the Least-Squares Refinement for the Intermolecular Difference Function, $\Delta_{\mathrm{N}}^{\mathrm{inter}}(Q)$, Observed for Aqueous 5 mol % Sodium L-Hydrogenglutamate Solutions in D_2O[a)]

Interaction	i···j	r_{ij}/Å	l_{ij}/Å	n_{ij}
N···D_2O	N···O_W	2.92(2)	0.17(2)	3.1(1)
	N···D_W	3.47(1)	0.30(1)	(6.2)[b)]
		r_0/Å	l_0/Å	
Long-range	N···X[c)]	3.60(1)	0.60(1)	

a) Estimated errors are given in parentheses. b) Fixed at the value $2n_{\mathrm{NO_W}}$. c) X: C, O, N, H, D, and Na.

hydration shell of the amino group. The intermolecular distances between the amino-nitrogen atom and the two D atoms belonging to a D_2O molecule in the first hydration shell were assumed to be identical in the fitting procedure. b) Structural parameters for l_0 and r_0 were refined independently.

The best-fit result is compared with the observed $\Delta_{\mathrm{N}}^{\mathrm{inter}}(Q)$ in Fig. 1c. A satisfactory agreement was obtained in the range of $0.3 \leq Q \leq 12\,\text{Å}^{-1}$. The observed and calculated $G_{\mathrm{N}}^{\mathrm{inter}}(r)$ (Fig. 2b) also agreed with each other. The final results of the least-squares fit are summarized in Table 3. The value of $r_{\mathrm{NO_W}}$ (2.92(2) Å) agreed with the average value of the N(–H)···O hydrogen-bond length found in various organic crystals ($r_{\mathrm{NO}} = 2.89$ Å),[27] implying that D_2O molecules within the first hydration shell of the amino-group form hydrogen bonds of N–D···OD_2 type. The present $r_{\mathrm{NO_W}}$ value was slightly larger than that reported for aqueous glycine ($r_{\mathrm{NO_W}} = 2.85(5)$ Å)[4] and alanine ($r_{\mathrm{NO_W}} = 2.88(2)$ Å)[7] solutions. The present $r_{\mathrm{ND_W}}$ value (3.47(1) Å) was also larger than that found for the glycine (3.25(5) Å)[4] and the alanine (3.31(2) Å)[7] zwitterions. The tilt angle θ between the N···O_W axis and the molecular plane of D_2O was calculated to be 44(5)° using the molecular geometry of the D_2O reported for pure heavy water ($r_{\mathrm{OD}} = 0.983$ Å, $r_{\mathrm{DD}} = 1.55$ Å).[28,29] The value was considerably smaller than that reported for the glycine ($\theta = 63(15)°$)[4] and the alanine ($\theta = 60.4(5)°$)[7] solutions, which reflects that there is a difference in the hydrogen-bonded interaction among water molecules in the first and second hydration shell of the amino-group between amino acid molecules involving the apolar side-chain groups and those involving the charged side-chain group, such as $-CH_2CH_2COO^-$. The present value of $n_{\mathrm{NO_W}}$ (3.1(1)) is in consistent with the value (3.0) obtained from the EPSR analysis by McLain et al.[10] On the other hand, n_{NO} (2.4(1)) was reported for an alanine solution,[7] which implies that the hydration structure of the amino-group is affected by the hydration nature of the side-chain group of the amino acid molecule. It is of considerable interest to investigate the hydration structure of the side-chain group of the hydrogenglutamate ion as well as the coordination structure of coexisting sodium ion, which requires additional neutron and X-ray diffraction measurements. This will be a future research subject.

The authors would like to acknowledge Prof. Toshiharu Fukunaga (Kyoto University) and Dr. Keiji Itoh (Kyoto University) for their help during the course of neutron diffraction measurements. All calculations were carried out at the Yamagata University Networking and Computing Service Center. This work was partially supported by Grant-in-Aid for Scientific Research on Priority Area (No. 1641205), Scientific Research (C) (No. 16550049), and Creative Scientific Research (No. 16GS0417), from the Ministry of Education, Culture, Sports, Science and Technology.

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