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Effect of the Side Chain of *N*-Acyl Amino Acid Surfactants on Micelle Formation: An Isothermal Titration Calorimetry Study

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Abstract

The enthalpy of micelle formation, critical micelle concentration (CMC), and aggregation number of micelles for seven amino acid type surfactants, sodium *N*-dodecanoyl-glycinate (C12Gly), -L-alaninate (C12Ala), -L-valinate (C12Val), -L-leucinate (C12Leu), -L-phenylalaninate (C12Phe), -L-glutamine (C12Gln), and -L-threoninate (C12Thr), were obtained at three temperatures ranging from 288.15 to 308.15 K by isothermal titration calorimetry. The enthalpies of micelle formation for these surfactants were positive at 288.15 K and decreased with increasing temperature to ultimately become negative above 308.15 K. The CMC of the amino acid surfactants decreased monotonously with increasing hydrophobicity of the amino acid residue without exception, while with the exception of the C12Phe system, the enthalpy of micelle formation increased. The micellization behavior of C12Phe also deviated from that of other amino acid systems in terms of the heat capacity and the aggregation number. These results suggest the presence of a strong intra-micelle interaction between the side chains of phenylalanine.

Key-words: Isothermal titration calorimetry; enthalpy of micelle formation; *N*-acyl amino acid surfactant; Side chain of amino acid; Hydrophobicity of amino acid residue

Introduction

Self-assembling amphiphiles form various aggregates such as vesicles and micelles in aqueous solution. To explain the structural formation of the

aggregates, it has been proposed by Israelachvili et al. that a geometric concept called the packing parameter is a significant factor [1,2]. The packing parameter is defined by the length and volume of the hydrophobic tail and the size of the hydrophilic head of amphiphilic molecules. According to the packing parameter theory, a single-tailed surfactant tends to form spherical micelles, while a double-tailed surfactant leads to a bilayer structure in aqueous solution. Generally, a systematical examination of the effect of the surfactant head group on the molecular aggregates has some difficulties compared with that of the hydrophobic tail group, except for some nonionic surfactants with polyethylene or polysaccharide units [3-14]. Another exception is the amino acid-type surfactant system [15-19]. One can systematically control a head group, because surfactants derived from a different amino acid have a different head group. *N*-Acyl amino acid surfactants, which are anionic amino acid-type surfactants, are useful both from industrial and domestic viewpoints, because of their biodegradability and low toxicity. Further, concern over the effect of the residues on aggregation has been growing since it was reported that some amphiphiles containing peptide groups like *N*-acyl amino acid, self-assembled to form various highly-organized nanometer-scale structures [20-23]. Since micelle formation is one of the most basic of aggregation behavior, it is useful to investigate the effect of amino acid residues for the purpose of understanding the higher self-assembly behavior, including that of polypeptides [24-27].

Calorimetry is a powerful technique for acquiring information on the molecular interactions in molecular aggregates by surfactant rather directly. Especially, isothermal titration calorimetry (ITC) has been widely employed for the investigations of micelle formation [28-37]. From a thermodynamic

point of view, one of the main advantages of titration calorimetry is considered to be that the partial molar enthalpy change of the solute, which can be approximately and directly evaluated from the experimental results obtained by dividing the titration heat by the number of moles of injected solute. Furthermore, it is considered that not only the enthalpy of micelle formation, but also the critical micelle concentration (CMC) and aggregation number of micelles can be obtained from a single experiment by employing appropriate thermodynamic analysis.

In this study, therefore, we have examined the effect of the side chain of *N*-acyl amino acid surfactants on the micelle formation using ITC. We chose seven amino acids and synthesized the corresponding *N*-acyl amino acid surfactants. In addition to the partial molar enthalpy change accompanied by micelle formation, the CMC and aggregation number of the micelle were estimated simultaneously. These parameters were discussed from the view points of both the size and hydrophobicity of the amino acid residue.

Experimental

Materials

Glycine (Gly), L-alanine (Ala), L-valine (Val), L-leucine (Leu), L-phenylalanine (Phe), L-glutamine (Gln), and L-threonine (Thr) were purchased from the Peptide Institute, Inc., and used without further purification. *N*-Dodecanoylamino acid (C12-amino acid) was synthesized by the reaction of an amino acid (except for C12-Gln and C12-Thr) with dodecanoyl chloride, as described previously [38]. Both C12-Gln and C12-Thr were synthesized using

the *N*-hydroxysuccinimide ester of dodecanoic acid [39]. All the above substances were purified by recrystallization from ethanol solution. Their purities were checked by HPLC and DSC and by observing no minimum on the surface tension vs concentration curves at 298.15 K. These sodium salts were prepared by the addition of an equivalent amount of sodium hydroxide. As a solvent, 0.1 M tris(hydroxymethyl)aminomethane (tris)-HCl buffer at pH = 7.4 was employed. Although, the *N*-acyl amino acid salts needed to be dissolved in alkali solution in order to prevent their precipitation, they were completely dissolved even in neutral aqueous medium by use of tris-HCl buffer. Since the ionic strength of the solvent is sufficiently high in this study, the dissociation of the surfactant was neglected for the following thermodynamic treatment.

Calorimetry

The enthalpy of mixing the buffers and buffer solutions of the surfactants was measured by isothermal titration microcalorimetry (VP-ITC, MicroCal, Northampton, MA) at 288.15, 298.15, and 308.15 K. Ten microliters of the micellar solutions of surfactant at ca. 15 times the concentration of their CMC was injected by using a computer-controlled syringe pump to 1.5 ml of buffer in the cell. The amounts of titrant and buffer in the cell were converted into weight using their density values.

Results and discussion

From a thermodynamic point of view, one of the main advantages of ITC is considered to be related to the partial molar enthalpy change of the solute, which can be approximately and directly evaluated from the experimental

results obtained by dividing the titration heat by the number of moles of injected solute. Strictly speaking, this advantage is available only when a pure solute liquid is injected. The obtained enthalpy data needs to be analyzed in an appropriate manner when an aqueous surfactant solution is injected, because the amount of solvent increases simultaneously with titration. It has been proposed that this was carried out by use of the partial derivative of total heat per weight of solvent h^M by molality of solute m_1 [31].

$$h^M = H^M / w_s = \frac{n_s^0 (h_s - h_s^0) + n_s^* (h_s - h_s^*)}{w_s} + m_1^m (h_1^m - h_1^*) + Nm_{\text{mic}} \left(\frac{h_{\text{mic}}}{N} - h_1^* \right) \quad (1)$$

Here, H^M is the total enthalpy of mixing, which was evaluated by integration of each titration heat, w_s is the weight of the solvent, h_i is the partial molar enthalpy of component i in the solution, N is the aggregation number of the micelle, the superscripts 0 and * refer to the solvent initially contained within the cell and the titrant, the superscript m refers to the surfactant monomer, and the subscripts s, 1, and mic refer to the solvent, surfactant, and micelle respectively. The total molality of the surfactant is given by the mass balance relation:

$$m_1 = m_1^m + Nm_{\text{mic}}. \quad (2)$$

In the case of the titration of the micellar solution, the partial derivative $(\partial h^M / \partial m_1)_{T,p}$ was expressed by:

$$\begin{aligned} & (\partial h^M / \partial m_1)_{T,p} \\ &= \frac{1}{m_1^*} \frac{(h_s^* - h_s^0)}{M_s} + (\partial m_1^m / \partial m_1)_{T,p} (h_1^m - h_1^*) + \left[1 - (\partial m_1^m / \partial m_1)_{T,p} \right] \left(\frac{h_{\text{mic}}}{N} - h_1^* \right) \end{aligned} \quad (3)$$

where m_1^* and M_s correspond to the molality of the titrant and the molar mass of the solvent, respectively. Since $(\partial m_1^m / \partial m_1)_{T,p} \approx 0$ at a concentration above the CMC, eq. 3 is reduced to:

$$(\partial h^M / \partial m_1)_{T,p} (m_1 > \text{CMC}) = \frac{1}{m_1^*} \frac{(h_w^* - h_w^0)}{M_w} + \frac{h_{\text{mic}}}{N} - h_1^*. \quad [4]$$

Subtracting eq. 4 from eq. 3 gives us the following expression:

$$\begin{aligned} & (\partial h^M / \partial m_1)_{T,p} (m_1 > \text{CMC}) - (\partial h^M / \partial m_1)_{T,p} \\ &= (\partial m_1^m / \partial m_1)_{T,p} \left(\frac{h_{\text{mic}}}{N} - h_1^m \right) = (\partial m_1^m / \partial m_1)_{T,p} \times \Delta_w^M h, \end{aligned} \quad (5)$$

where $\Delta_w^M h$ is the enthalpy of micelle formation. The value of $\Delta_w^M h$ can be obtained by the following limiting, since $(\partial m_1^m / \partial m_1)_{T,p} = 1$ at $m_1 = 0$.

$$\lim_{m_1 \rightarrow 0} \left[(\partial h^M / \partial m_1)_{T,p} (m_1 > \text{CMC}) - (\partial h^M / \partial m_1)_{T,p} \right] = \Delta_w^M h \quad (6)$$

In order to evaluate the partial molar enthalpy change according to eq. 2, the h^M values obtained from the original ITC data were depicted as a function of m_1 in Fig.1a for the C12Ala system as an example. The difference in the partial derivative defined by the left hand side of eq. 5, where the reference state is taken as the partial molar enthalpy at higher concentration beyond the CMC, was evaluated from the curves in Fig. 1a and plotted against m_1 in Fig.1b. It should be noted in Fig.1b that the partial derivative of enthalpy is not constant but increases slightly with increasing m_1 before the transition region around the CMC. This may reflect a deviation from the ideal solution of surfactant monomer owing to a coulomb interaction. On the other hand, in nonionic surfactant systems, the approximation of the ideal surfactant monomer solution was adequate usually [6, 31]. In this treatment, the term of $\partial m_1^m / \partial m_1$ included

the deviation from ideality, and the standard state of surfactant monomer in the enthalpy of micelle formation was that in infinite dilution as shown in eq.6. Therefore, by use of eq. 6, the $\Delta_w^M h$ values were evaluated and shown in Fig. 2 and Table 1 as a function of temperature for the whole systems.

First, it is noted that the all $\Delta_w^M h$ values are positive at 288.15 K. This shows that micelle formation diminishes the overall molecular interaction between water and the surfactant molecules and, therefore, the dehydration of the surfactant plays an important role in micelle formation especially at lower temperature. Next, we note that the $\Delta_w^M h$ values decrease linearly with increasing temperature, and are even negative at 308.15 K, except for the C12Val system. This suggests that the contribution of dehydration accompanied by micelle formation decreases, while the contribution from the interaction between the surfactant molecules becomes dominant with increasing temperature.

To elucidate the influence of the amino acid residue of the surfactants on the enthalpy of micelle formation, let us consider it from the standpoint of the molecular size of the residue. Therefore, molecular volumes of amino acids were regarded as the COSMO (conductor-like screening model) volume, which is the volume of the screening space in the COSMO algorithm with an effective solvent radius of $R_{\text{eff}} = 1 \text{ \AA}$ and a dielectric constant of $\varepsilon = 78.4$, respectively [40]. The calculations were first performed by using MOPAC 2002 with a PM5 Hamiltonian [41], and then the difference between the molecular volumes for each amino acid and glycine ΔV_R was employed as an index of the volume of the side chain.

$$\Delta V_R = V(\text{amino acid}) - V(\text{Gly}) \quad (7)$$

Figure 3 shows the enthalpy of micelle formation at 288.15 K as a function of ΔV_R . It is seen that the enthalpy increases with increasing ΔV_R at first, but decreases adversely above $\Delta V_R = 35 \text{ \AA}^3$, which corresponds to the middle volume between the C12Val and C12Leu systems. The increase in the enthalpy of micelle formation with enlargement of the amino acid residue of the surfactants suggests that dehydration occurs around the side chain of the amino acid, as well as around the hydrophobic acyl chain of the surfactant by micelle formation. On the contrary, it is supposed that the contribution of the interaction between the side chains in micelles is superior to that of dehydration for large amino acid systems. However, the enthalpy of micelle formation for the C12Gln and C12Thr systems deviate remarkably from the tendency of other amino acid systems. This might suggest that the chemical property of the amino acid side chains should be considered in addition to the size. Therefore, the influence of the amino acid residues of the surfactants on the enthalpy of micelle formation was examined with respect to the hydrophobicity. Engelman et al. presented the transfer free energy for amino acid residues in helices, from a water environment to one of a nonpolar nature involving the dielectric 2 (ΔG_α) as a hydrophobic index of the amino acids [42]. Then, the $\Delta_w^M h$ values were plotted against ΔG_α of the corresponding amino acid in Fig. 4. With the exception of the Phe system, a close negative correlation between the enthalpy of micelle formation and the hydrophobic index of the amino acids would be noted. In the case of aliphatic amino acids, namely Leu, Val, and Ala, the increase in hydrophobicity produces a larger collapse of hydrophobic hydration, i.e. an increase in the entropy by micellization. In the meantime, it is suggested that the micelle formation of C12Phe, which has an aromatic hydrophobic side

chain, gains less entropy by dehydration around the benzyl group, but lowers the enthalpy by the interaction between the side chains. We have reported some peculiarities of acyl phenylalanine type surfactants and the interaction between the side chains in molecular aggregates [18,19,21,43]. It is noted that the $\Delta_w^M h$ value of C12Gln is close to that of C12Gly in spite of the gap between their respective hydrophobic indices. This means that the side chain of Gln in the micelle does not face the micellar core, but faces the aqueous medium, and then the state of hydration of this side chain remains unchanged by micelle formation, because of its high hydrophilicity and flexibility. On the other hand, it is supposed that the ability of the hydration bond of the hydroxide group in Thr has a limited effect on the micellar state.

We can obtain the heat capacity change accompanied by micelle formation $\partial \Delta_w^M h / \partial T = \Delta_w^M c$ from the slope of the curve in Fig. 2. The values were also shown in Table 1 and plotted against the hydrophobic index in Fig. 5. With the exception of the Phe system, it is seen that a good correlation between the heat capacity change and the hydrophobic index of amino acid would be observed again. This correlation indicates that the increase in the hydrophobicity of the amino acid side chain brings about a large variation of hydration accompanied by micelle formation. In the case of C12Phe, it was presumed that the effect of dehydration from micellization was cancelled by the effect of orientation from the interaction between the benzyl groups. By using the heat capacity data and the CMC at certain temperature, for example at 298.15K, the CMC data at other temperatures can be calculated by the following equation [6]:

$$\Delta_w^M h = T \Delta_w^M c + \text{const} = -RT^2 (\partial \ln \text{CMC} / \partial T)_p \quad (8)$$

The constant values were also shown in Table 1. According to the definition by

Phillips [44], the point of inflection ($\partial^3 m_1^m / \partial m_1^3 = 0$) on these diagrams is regarded as the CMC. In order to estimate the CMC value, the derivatives $\partial m_1^m / \partial m_1$ have to be reproduced by a function of total molality m_1 . It was found that the following linear combination of hyperbolic tangent and polynomial is one of the best fitting functions with respect to parameters P_i for reproducing the data in Fig.1b.

$$(\partial m_1^m / \partial m_1)_{T,p} \times \Delta_w^M h = P_1 \tanh[P_2(m_1 - P_3)] + P_4 m_1^2 + P_5 m_1 + P_6 \quad (9)$$

It is seen that the experimental values represented by circles are reproduced satisfactorily by the fitted functions drawn by the solid lines in Fig.1b. The CMC corresponds to the value of P_3 approximately for this case. The value of the CMC was obtained by the fitting function for all systems and shown in Table 2 with the CMC calculated using eq. 8. The agreement is relatively good. In contrast to the enthalpy of micelle formation, the CMC value decreased monotonously with increasing hydrophobicity of the amino acid residue. It is well-known that the CMC is relevant to the standard Gibbs energy of micelle formation. Therefore the $\Delta_w^M h$ value was plotted against $\log(\text{CMC})$ in Fig. 6 at 288.15 and 308.15 K. We can confirm again that there are negative correlation between them with the exception of the Phe system. That is, an increase of entropy generally governs the process of micelle formation of C12-amino acid surfactants, while a decrease of enthalpy is essential in C12Phe system. Further it is seen that the slope of the correlation decreases with rising temperature. This suggests that a contribution of entropy for micelle formation is relatively reduced at higher temperature.

Moreover, the value of the monomer concentration m_1^m can be obtained by solving the differential equation (eq. 9) as a function of total molality m_1 . Here,

the integral constants were determined by use of the condition that the monomer concentration is equal to the total concentration at infinite dilution. It is worthwhile applying the mass-action model to these experimental data to estimate an N value. The strategy to obtain N values is as follows. First, the equilibrium constant between monomers and micelles is given by:

$$K = m_{\text{mic}} / m_1^{\text{m}^N}. \quad (10)$$

Substitution of the mass balance relation of eq. 2 into eq. 10 yields the expression:

$$\ln(m_1 - m_1^{\text{m}}) = N \ln m_1^{\text{m}} + \ln NK. \quad (11)$$

Now, we can obtain the value of the monomer concentration by solving eq.9, thus the left-handed side of eq. 11 is plotted against the logarithm of the monomer molality. For example, the results for the C12Ala system at 288.15 K are shown in Fig. 7. Only the data around the CMC were fitted with the linear function, and then, the N value was obtained from the slope of the line. The values of the aggregation number for whole systems were summarized in Table 3. These values resemble the previous results which were obtained by a steady-state luminescence method using pyrene and cecylpyridinium chloride [16]. However, for some systems, where the $\Delta_{\text{w}}^{\text{M}}h$ value was less than ca. 1 kJ mol⁻¹, a reliable value for N was not obtained owing to the narrowness of the fitting range. It is seen that both C12Gly and C12Ala micelles have high aggregation number, while the N values of C12Val and C12Leu are relatively small at lower temperature. This suggests that the small head group of the surfactant is advantageous to filling to the micelle. Furthermore, the N values of these systems decrease with rising temperature, because of the activation of the thermal motion. On the other hand, the observed decrease in the N values

for the C12Thr and C12Gln systems is less remarkable compared with that of the aliphatic amino acid surfactant systems. Taking into account the fact that the side chains of these surfactant head groups were hydrated even in the micellar state, it might be considered that a closer packing accompanied by dehydration was counterbalanced by an increase in the thermal motion with rising temperature. It is reasonable that the C12Phe micelle has a large N value, because of the interaction between the residues of C12Phe, as mentioned above.

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References and Notes

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Figure Captions

Fig. 1 Experimental results by ITC for the C12Ala system. (a) Enthalpy of mixing of aqueous solution of C12Ala vs molality curves, (b) Partial molar enthalpy change of C12Ala vs molality curves. The values at $m_1 = 0$, indicated by the arrow, correspond to the enthalpy of micelle formation, respectively; (1) $T = 288.15$ K, (2) 298.15 K, (3) 308.15 K.

Fig. 2 Enthalpy of micelle formation vs temperature curves for several surfactants.

Fig. 3 Plots of the enthalpy of micelle formation as a function of the volume of the amino acid side chain ΔV_R at 288.15 K.

Fig. 4 Plots of the enthalpy of micelle formation as a function of the hydrophobic index amino acid residue ΔG_α at 288.15 K. The line is a visual guide.

Fig. 5 Plots of the heat capacity change accompanied by micelle formation as a function of the hydrophobic index of the amino acid residue ΔG_{α} . The line is a visual guide.

Fig. 6 Plots of the enthalpy of micelle formation as a function of the logarithm of the CMC. The line is a visual guide; (open circle) $T= 288.15$ K, (full circle) 308.15 K.

Fig. 7 Logarithm of the concentration of micelle vs logarithm of the concentration of monomer curves for C12Ala at 288.15 K. Full circles indicate the data used for fitting.

Table 1. Enthalpy and heat capacity changes of micelle formation of several surfactants

	$\Delta_{\text{w}}^{\text{M}}h / \text{kJ mol}^{-1}$			$\Delta_{\text{w}}^{\text{M}}c /$	$\text{const}^a /$
	288.15 K	298.15 K	308.15 K	$\text{J K}^{-1} \text{mol}^{-1}$	kJ mol^{-1}
C12Gly	5.73	1.14	-4.10	-492	147.5
C12Ala	8.83	1.32	-0.71	-477	146.4
C12Val	11.73	6.33	0.52	-561	173.3
C12Leu	11.53	5.12	-0.91	-622	190.7
C12Phe	0.92	-3.73	-8.63	-478	138.6
C12Thr	8.55	3.07	-1.96	-526	159.9
C12Gln	4.71	0.60	-3.89	-430	128.7

^a The constant values are defined in eq. 8.

Table 2. Critical micelle concentration of several surfactants

T [K]	CMC / mmol kg ⁻¹		
	288.15 K	298.15 K	308.15 K
C12Gly	3.0 (2.9)	2.8	2.9 (2.8)
C12Ala	3.2 (3.1)	2.8	3.0 (2.7)
C12Val	1.2 (1.3)	1.1	0.98 (1.0)
C12Leu	0.62 (0.61)	0.54	0.56 (0.52)
C12Phe	0.25 (0.26)	0.27	0.32 (0.30)
C12Thr	3.1 (3.0)	2.8	2.9 (2.9)
C12Gln	3.9 (3.6)	3.5	3.9 (3.6)

The values in parentheses are estimated from eq. 8 and the CMC data at 298.15 K.

Table 3. Aggregation number of several surfactants

T [K]	N		
	288.15 K	298.15 K	308.15 K
C12Gly	99	56	45
C12Ala	96	55	-
C12Val	65	47	40
C12Leu	54	37	38
C12Phe	-	77	60
C12Thr	64	76	53
C12Gln	67	-	56

Fig.1 Ohta et. al.

Fig.2 Ohta et al.

Fig.3 Ohta et al.

Fig.4 Ohta et al.

Fig.5 Ohta et al.

Fig.6 Ohta et al.

Fig.7 Ohta et al