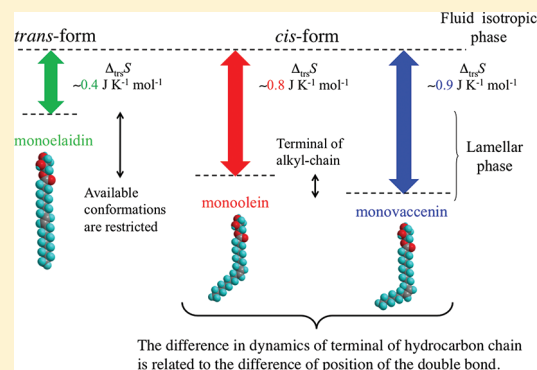


Effect of *Cis* and *Trans* Double Bonds on Conformational Disordering of the Hydrocarbon Chain of Lipid, Unsaturated Monoacylglycerols, in the Lamellar Phase of a Binary System with Water

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ABSTRACT: To clarify the influence of *cis* and *trans* double bonds on conformational disordering of unsaturated hydrocarbon-chain of lipids in bilayer formed in the binary system with water, calorimetric study was conducted for systems of unsaturated monoacylglycerols; monoolein (MO), monovaccenin (MV), and monoelaidin (ME). Heat capacities of the binary systems were measured by adiabatic calorimetry. The observed entropies of transition ($\Delta_{\text{trs}}S$) from lamellar phase (L_α) to fluid isotropic (FI) phase are very small and depend on lipids: $\Delta_{\text{trs}}S$ of MO/water, MV/water, and ME/water were ca. $0.8 \text{ J K}^{-1} (\text{mol of lipid})^{-1}$, ca. $0.9 \text{ J K}^{-1} (\text{mol of lipid})^{-1}$, and ca. $0.4 \text{ J K}^{-1} (\text{mol of lipid})^{-1}$, respectively. These show that the conformational disordering of the hydrocarbon chain over *gauche* and *trans* conformations is suppressed in L_α phase. Through the comparison of $\Delta_{\text{trs}}S$ among the binary systems, the suppressed conformational disordering of hydrocarbon chain in the bilayer is discussed.



INTRODUCTION

Amphiphilic molecules consisting of hydrophilic and hydrophobic groups, such as surfactant or lipid, form various aggregates in the binary system with water; e.g., (spherically) micellar, lamellar (L_α), hexagonal, and cubic structures.¹ Formation of the aggregates is closely related to the effective shape of the constituent molecules besides hydrophobic interaction, surface tension, and intermolecular force. Israelachvili et al.^{2–4} summarized the relation between the average shape of lipid molecules and the aggregation structure through geometric packing considerations using the dimensionless packing parameter or shape factor, which is defined as v/a_0l_c for the amphiphilic molecule with an optimal surface area a_0 , volume of hydrophobic group (hydrocarbon) v , and critical hydrocarbon chain length l_c . Although the packing parameter is, of course, not a perfect criterion,⁵ it has been very useful in understanding the aggregation mode. The value of v/a_0l_c depends on not only static (chemical) structure of amphiphilic molecule but also its dynamics associated with intramolecular degrees of freedom of the hydrocarbon chain. The intramolecular dynamics mainly involves dynamical disordering among one *trans* and two *gauche* conformations around carbon–carbon single bonds. Since the conformational disordering becomes vigorous with increasing temperature, the packing parameter varies depending on temperature. The change of the packing parameter often yields phase transitions between various aggregates in binary systems.

The intramolecular dynamics of hydrocarbon chain of amphiphilic molecules has extensively been investigated by theoretical or computational methods^{6–17} and by ^2H NMR method,^{18–26} the latter of which is the study of conformational order parameter

at each carbon atom of hydrocarbon chain(s) of selectively deuterated lipids. A deuteron quadrupolar splitting observed by ^2H NMR provides a deuteron bond order parameter, S_{CD} , which is a measure of the motional anisotropy of the C–D bond.^{18,20,21} The S_{CD} is related to the so-called molecular segmental order parameter, S_{mol} , through $S_{\text{mol}} = -2S_{\text{CD}}$ assuming axial symmetry of the segmental motion.^{18,20,21} The S_{mol} is a measure of the conformational order of an individual methylene group and ranges between 0 (complete disorder) and 1 (complete order).^{18,20,21} When the bilayer consists of the lipid with the hydrocarbon chain having about 15 carbon atoms, the S_{mol} is almost constant from the hydrophilic group end to the 8th–9th carbon atom, because the conformational disordering is strongly suppressed by surrounding molecules packed densely.^{19,20} The S_{mol} decreases on going from the 8th–9th carbon atom to the terminal methyl group, where the conformational disorder of the chain is vigorous. Such a profile of the S_{mol} has commonly been observed in various types of saturated hydrocarbon chain of lipids.^{19–25}

It seems natural to imagine that the conformational disorder of unsaturated hydrocarbon is different between *cis*- and *trans*-forms. Indeed, the ^2H NMR study on bilayers of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC) and 1-palmitoyl-2-elaidoyl-*sn*-glycero-3-phosphocholine (PEPC) revealed that the unsaturated hydrocarbon chains show different profiles of the order parameter $|S_{\text{CD}}|$ between *trans*- and *cis*-forms.²⁶ That is, the $|S_{\text{CD}}|$ of the *trans*-form (elaidoyl chain in PEPC) is similar to that of the saturated

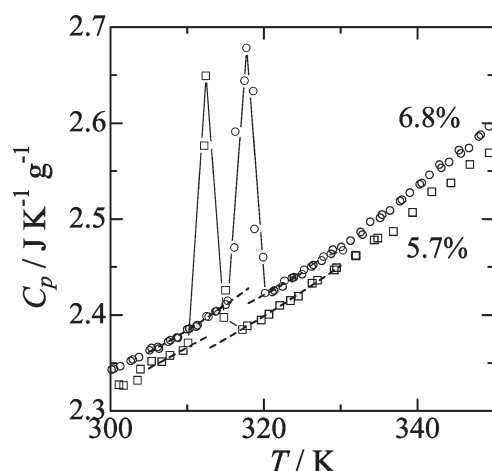
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Table 1. Thermodynamic Quantities of Associated with the L_α –FI Phase Transition of the Monoacylglycerols/Water Binary Systems

isomer	lipid	composition/% (w/w) water	$\Delta_{\text{trs}}H/\text{J g}^{-1}$	$\Delta_{\text{trs}}S/\text{mJ K}^{-1} \text{g}^{-1}$	$\Delta_{\text{trs}}S/\text{J K}^{-1} (\text{mol of lipid})^{-1}$
<i>cis</i> -form	MO	5.7	0.70 ± 0.02	2.2 ± 0.1	0.82 ± 0.03
		6.8	0.64 ± 0.01	2.0 ± 0.1	0.77 ± 0.01
	MV	6.7	0.80 ± 0.02	2.5 ± 0.1	0.95 ± 0.02
		8.5	0.75 ± 0.01	2.3 ± 0.1	0.89 ± 0.01
<i>trans</i> -form	ME	8.5	0.34 ± 0.02	1.0 ± 0.1	0.40 ± 0.03

**Figure 3.** Heat capacities of monoolein/water (MO/water) binary systems with the compositions of 5.7 and 6.8% (w/w) water. Broken curves are extrapolating curves for the L_α and FI phases.

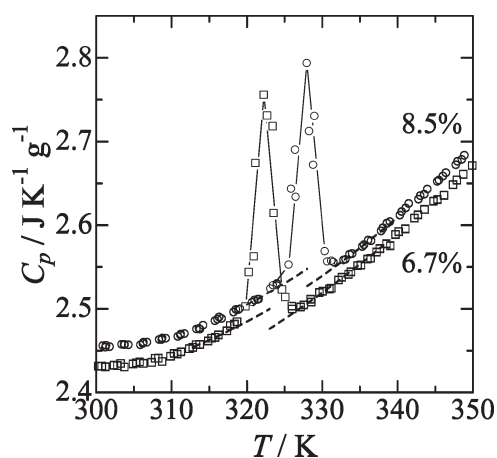
system, only one composition was used for measurement because of the narrow region of composition where the direct phase transition occurs from L_α phase to FI phase.

The samples were heated once to the FI phase to improve homogeneous mixing of the sample in the vessel. The heat capacity measurement on each sample with a different composition was carried out in the temperature range between 270 and 370 K. The sample contributed more than 25% to the total heat capacity including those of the calorimeter vessel and helium gas. While a contribution of helium gas inside the vessel was subtracted, the contribution due to the evaporation of water in the vessel was small enough to be ignored.

Heat capacity of the samples was measured using a laboratory-made adiabatic calorimeter, the details of which can be found elsewhere.³² Measurement was carried out by the so-called intermittent-heating adiabatic method in the heating direction. The working thermometer was a platinum resistance thermometer (MINCO, S1059), the temperature scale of which is based upon the ITS-90.

RESULTS AND DISCUSSION

1. Heat Capacities of Monoacylglycerole/Water Systems: MO/Water, MV/Water, and ME/Water Systems. The heat capacity measurements of MO/water (5.7 and 6.8% (w/w) water) and MV/water (6.7 and 8.5% (w/w) water) samples were carried out from 290 to 360 K. The measured heat capacities (C_p) of MO/water systems are shown in Figure 3. There is a sharp anomaly of C_p around 315 K in each C_p curve. Taking the phase diagram shown in Figure 2 based on the literature^{43,44} into account, the anomaly is

**Figure 4.** Heat capacities of monovaccenin/water (MV/water) binary systems with the compositions of 6.7 and 8.5% (w/w) water. Broken curves are extrapolating curves for L_α and FI phases.

reasonably assigned to the phase transition from L_α phase to FI phase. The anomalies show the temperature width of ca. 5 K, where the L_α and FI phases coexist. The temperature width is also consistent with the phase diagram.^{43,44}

To determine the thermodynamic quantities associated with the phase transition, it is necessary to draw a baseline for separating excess heat capacities. In the two-phase coexisting region, the baselines c_{base} as the function of temperature T were estimated by the following equations

$$c_{\text{base}}(T) = xc_{\text{low}}(T) + (1-x)c_{\text{high}}(T)$$

$$x = (T_{\text{high}} - T)/(T_{\text{high}} - T_{\text{low}})$$

where $c_{\text{low}}(T)$ and $c_{\text{high}}(T)$ are the extrapolations of heat capacities for L_α and FI phases, respectively, and T_{low} and T_{high} are the ends of the temperature region of the anomaly. The assumed c_{low} and c_{high} are drawn by broken curves in Figure 3. The anomalous heat capacities were separated and integrated with respect to T and $\ln T$, yielding the enthalpy ($\Delta_{\text{trs}}H$) and entropy ($\Delta_{\text{trs}}S$) of transition, respectively. The obtained thermodynamic quantities associated with the phase transition are listed in Table 1, where the errors were estimated on the basis of repeated measurements.

The measured C_p of MV/water systems for two compositions (6.7 and 8.5% (w/w) water) are shown in Figure 4. A sharp anomaly is seen around 320 K in each C_p curve. On the basis of the reported phase diagram,⁴⁴ the anomaly can be assigned to the phase transition from L_α phase to FI phase accompanying the two-phase coexisting region. The widths of the anomalies are

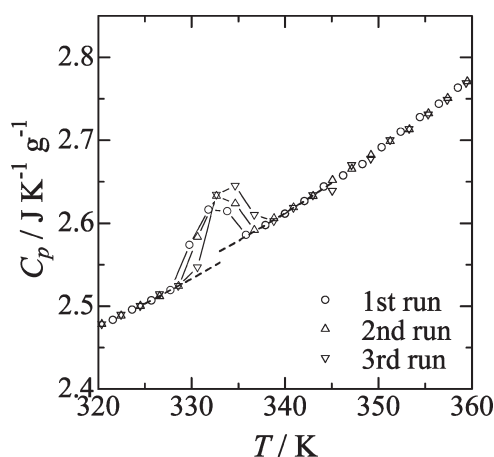


Figure 5. Heat capacity of the monoelaidin/water (ME/water) binary system with the composition of 8.5% (w/w) water. Broken curves are extrapolating curves for L_α and FI phases.

about 8 K, slightly wider than those of the MO/water system. The wider temperature widths of the anomalies are consistent with the reported phase diagram.⁴⁴ To separate excess heat capacities for the estimation of the thermodynamic quantities associated with the phase transition, the baselines (c_{base}) were determined in the same way as for the MO/water system. The determined c_{low} and c_{high} are shown in Figure 4. The resultant $\Delta_{\text{trs}}H$ and $\Delta_{\text{trs}}S$ are listed in Table 1.

The C_p of the ME/water (8.5% (w/w) water) sample was measured from 310 to 360 K. The C_p of the ME/water system measured in three runs are plotted in Figure 5. There is a broad anomaly around 330 K in each run, in contrast to the sharp ones of the *cis*-form systems (MO/water and MV/water) shown in Figures 3 and 4. The reported phase diagram²⁷ suggests that the anomaly is to be assigned to the phase transition from L_α phase to FI phase, though the observed temperature range of the two-phase coexistence is slightly lower than that of the reported phase diagram. To separate excess heat capacities for estimation of the thermodynamic quantities associated with the phase transition, the baselines (c_{base}) were determined in the same way as for the other systems. The assumed c_{low} and c_{high} are shown in Figure 5. The resultant $\Delta_{\text{trs}}H$ and $\Delta_{\text{trs}}S$ are listed in Table 1. It is noteworthy that the c_{low} is smaller than c_{high} around the coexisting region in the ME/water system, in contrast to the *cis*-form MO/water and MV/water systems, where c_{low} is larger than c_{high} .

2. Entropy of Transition from L_α Phase to FI Phase. The L_α phase of lipid/water binary systems has one-dimensional periodicity in space, formed by bilayers of lipids and interlayer water. The periodicity is lost at the phase transition from L_α phase to FI phase. The FI phase consists of large domains with “lamellar” structure. Although the bilayer of lipids is deformed and partially interconnected through the water layer,^{1,29} the surface structure between water and hydrophilic group of lipid is kept near the phase transition temperature: the hydrophilic groups closely adjoin each other through their hydrogen bonds in the surface, similarly to the L_α phase. The preservation of the surface structure suggests that the interfacial and the water region scarcely differ in the L_α and FI phases. Besides, the established profile of conformational order parameter along the chain^{14–16,26} implies that the interaction and resulting aggregation structure of head groups are similar among the present monoacylglycerols. On the other hand, the conformation of hydrocarbon chain is more disordered than in the L_α phase because

of the loss of flatness of the bilayer. Thus, the entropy change associated with the phase transition is attributed to the conformational change of the lipid molecules. On the basis of this consideration, we attempt to analyze the entropy of transition. The unit of the entropy of transition from $\text{J K}^{-1} \text{g}^{-1}$ is thus converted to $\text{J K}^{-1} (\text{mol of lipid})^{-1}$, which means “per 1 mol of lipid”. The similar unit conversion has been adopted in this type of study.^{34,35} The converted entropies of transition of MO/water, MV/water, and ME/water are given in Table 1. Both the $\Delta_{\text{trs}}S$ of MO/water and MV/water systems slightly and only negligibly decrease with the increase in composition of water. That is, $\Delta_{\text{trs}}S$ is regarded as nearly constant: the $\Delta_{\text{trs}}S$ of MO/water, MV/water, and ME/water systems associated with the L_α -to-FI phase transition are ca. $0.8 \text{ J K}^{-1} (\text{mol of lipid})^{-1}$, ca. $0.9 \text{ J K}^{-1} (\text{mol of lipid})^{-1}$, and ca. $0.4 \text{ J K}^{-1} (\text{mol of lipid})^{-1}$, respectively. These values are much smaller than the entropy change associated with the conformational disordering of even a single methylene group ($\sim R \ln 3 \approx 9.1 \text{ J K}^{-1} (\text{mol of } -\text{CH}_2-)^{-1}$; R , gas constant).^{30,37–42} This means that the conformation of the hydrocarbon chain is highly disordered even in the L_α phase. It is emphasized here that the $\Delta_{\text{trs}}S$ of *cis*-form lipids are twice as large as that of the *trans*-form lipid.

On the basis of Boltzmann’s principle, the entropy of transition is expressed as $\Delta S = R \ln (W_{\text{H}}/W_{\text{L}})$, where W_{H} and W_{L} are the number of available conformations of a lipid molecule in the FI and L_α phases, respectively. We can thus estimate the ratio ($W_{\text{H}}/W_{\text{L}}$) of the numbers of available conformations of a lipid molecule between FI and L_α phases. As the conformational disorder in FI phase can be considered to be equivalent among the three lipids as discussed above, W_{H} is the same among the three lipids. We are, therefore, able to compare the degrees of conformational disorder in L_α phase through $\Delta_{\text{trs}}S$ among the lipids. The ratios ($W_{\text{H}}/W_{\text{L}}$) for MO/water, MV/water, and ME/water systems are calculated to be 1.10, 1.11, and 1.05, respectively. Since the ratio ($W_{\text{H}}/W_{\text{L}}$) becomes unity in the case of $W_{\text{H}} = W_{\text{L}}$, the relation ($W_{\text{H}}/W_{\text{L}} > 1$) means that the number of available conformations of lipid molecules in L_α phase is smaller than that in the FI phase. That is, the available conformations are restricted in L_α phase. Here, we introduce a quantity f_{r} , defined by $f_{\text{r}} = (W_{\text{H}}/W_{\text{L}} - 1) \times 100$ in order to count forbidden conformations. The f_{r} are 10% (MO), 11% (MV), and 5% (ME) of the available conformations of each lipid molecule in the FI phase, as shown in Figure 6. Although the small f_{r} shows that the conformation of hydrocarbon chain is highly disordered in the L_α phase, the difference in f_{r} reflect the degree of conformational disorder in L_α among the three systems.

3. Conformational Disorder of Hydrocarbon Chain in the L_α Phase. Before discussing the geometrical effect of the $\text{C}=\text{C}$ double bond on the conformational disordering, we remember the available conformation of hydrocarbon chain. It is well-known that each carbon of a saturated hydrocarbon has three stable conformations around $\text{C}-\text{C}$ single bond: one *trans* (t ; $\pm 180^\circ$ around $\text{C}-\text{C}$ single bond) and two *gauche* (g^+ , g^- ; $\pm 60^\circ$) conformations. The all-*trans* form is the most stable conformation for the saturated hydrocarbon chain. Since the conformation easily fluctuates even around room temperature, the conformation changes among the *trans* and *gauche* ones, reversibly and frequently. This is the conformational disordering associated with intramolecular degrees of freedom of the hydrocarbon chain. While the hydrocarbon chain is sufficiently disordered in the FI phase, it should have the cylindrical form in the L_α phase ($v/a_0l_{\text{c}} \approx 1$) on average. To have the cylindrical form, the

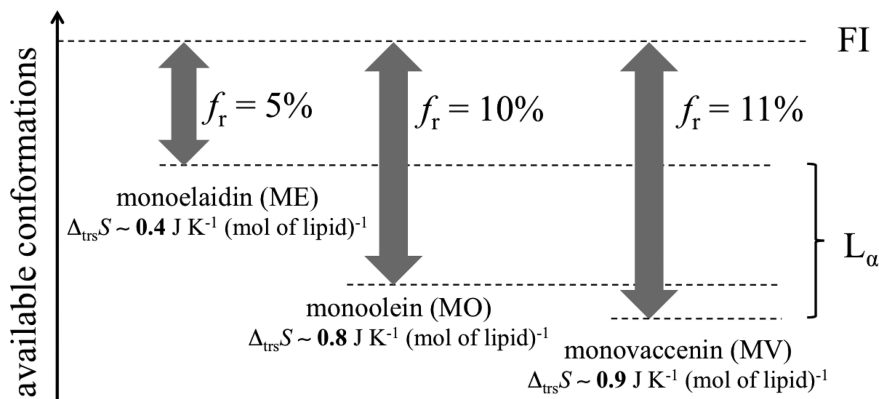


Figure 6. Schematic diagram of f_r , which is a measure of suppression of conformational disorder of lipid (see text) in monoolein (MO), monovaccenin (MV), and monoelaidin (ME) /water binary systems.

configuration of the hydrocarbon is restricted to all-*trans* or the combination including even numbers of *gauche* conformations with g^+ and g^- , such as g^+tg^- , g^-tg^+ , and g^+ttg^- .^{46–49} From such a restriction in the L_α phase, the entropy gain upon the phase transition from L_α phase to FI phase is brought about in the cases of compounds with saturated acyl chain(s).

For lipids with an unsaturated hydrocarbon chain with a C=C double bond, the restriction on the conformation of chain is more complicated. In general, the hydrocarbon with a C=C double bond takes so-called skew conformations (s^+ , s^- ; $\pm 120^\circ$) at the nearest carbon atoms to the C=C bond as the most stable conformation.^{50,51} The conformation gives a cylindrical and bent form to *trans*- and *cis*-unsaturated hydrocarbon chains, respectively. Since the ME molecule has the *trans*-unsaturated hydrocarbon chain, the cylindrical form is intrinsically the most stable. Therefore, the ME molecule easily fulfills $v/a_{olc} \approx 1$ in L_α phase while suffering only a little conformational restriction. On the other hand, MO and MV with *cis*-unsaturated hydrocarbon-chain have a bent form as the most stable conformation. Even such bent lipids must take a cylindrical form in L_α phase on average. This condition restricts the combination of conformations of the hydrocarbon chain in contrast to the *trans*-unsaturated lipids. To have the cylindrical form, for example, the *cis*-unsaturated hydrocarbon chain needs an additional *gauche* site (g^+ , g^-), at least. That is, the odd numbers of *gauche* conformations are allowed. Such a restriction reduces the available conformations of the hydrocarbon chain in the L_α phase, leading to the difference in f_r between *cis*- and *trans*-forms. Therefore, $\Delta_{trs}S$ of MO/water and MV/water systems from L_α phase to FI phase should inevitably be larger than that of the ME/water system. The present result indicates that this reduction is ca. 5% in f_r .

There is also a little difference in f_r between MO/water and MV/water. The difference implies that the conformational disorder of the chain in L_α phase depends on the position of the *cis*-double bond. MO has seven methylene groups in the chain on both sides of the C=C bond to the hydrophilic and terminal-methyl ends, while MV has nine and five methylenes, respectively. In general, the motion of methylene groups near the hydrophilic end is suppressed by the surrounding lipids because of the aggregation of hydrophilic groups at the interface and van der Waals forces among the hydrocarbons while the methylene groups near the terminal-methyl end are easy to change their conformations. Indeed, the conformational order parameter S_{mol} obtained by 2H NMR is almost constant in the hydrophilic side of

the chain and declines on approaching the terminal-methyl end in the case of L_α phase of monostealin,²⁵ which is a saturated monoacylglycerol with the same number of carbon atoms as monoacylglycerols in this study. In the *cis*-unsaturated hydrocarbon, the C=C bond is strongly affected by the surrounding hydrocarbon of lipids because of its bent form. This suppresses the *gauche*–*trans* conformational change and will make the order parameter almost constant at the methylene groups of the hydrophilic side up to the C=C bond. With increasing the number of the suppressed methylene groups, $\Delta_{trs}S$ and f_r increase because the suppression is released at the phase transition to FI phase. As a result, f_r of the MV/water system is slightly larger than that of MO/water one.

The discussion above is based on the assumption that the entropy of transition is wholly attributable to the conformational change of lipid molecules. The assumption is plausible because it gives a consistent explanation for the relative magnitude of the entropy of transition among three systems. However, we cannot rule out the possibility that the head groups and water molecules also contribute to the entropies of transition. This issue needs a further consideration.

4. Difference in Heat Capacity between *Cis*- and *Trans*-Chain Lipid in the L_α Phase. Adiabatic calorimetry yields the absolute magnitude of C_p with high accuracy. Its comparison is valuable for getting information concerning the energy and fluctuation of the system. While the comparison among different compositions is rather difficult in the present systems because they are a binary system including water, a comparison of C_p between L_α and FI phases in a single sample makes sense. An interesting difference in the temperature dependence of C_p is observed in this study. In the ME/water system, the C_p of FI phase is larger than that of L_α phase as seen in Figure 5. The increase is usually and widely observed on going from low-temperature ordered phase to high-temperature disordered phase. On the other hand, the MO/water and MV/water systems show the reverse trend: C_p of FI phase is smaller than that of L_α phase in the temperature region of the phase transition, as in Figures 3 and 4. Since the state and property of the water in the binary systems hardly change in such a temperature region, the difference is to be attributed to the bilayer of lipid. The decrease in C_p in the MO/water and MV/water systems, which have *cis*-type hydrocarbon chain in lipid molecules, indicates that the fluctuation of L_α phase is larger than that of the FI phase, because heat capacity is proportional to the fluctuation of enthalpy.⁵² It is

emphasized that the different shift in C_p is observed between *cis*-type and *trans*-type monoacylglycerol/water binary systems. We suggest the conformational fluctuation of the *cis*-form hydrocarbon chain and the softness of the bilayer as possible causes of the large fluctuation of L_α phase.

CONCLUSION

A comparison of entropies of transition from L_α phase to FI phase among three unsaturated monoacylglycerols/water binary systems revealed the suppressed conformational disorder of the hydrocarbon chain of lipid molecules in the L_α phase. The suppression systematically depends on the shape of the chain; *cis*- and *trans*-forms and the position of C=C bond. The present results imply that the chemical modification of hydrocarbon affects the dynamics of chain of lipid molecule in the L_α phase. A comparison of the absolute values of heat capacity revealed the enthalpic fluctuation of the systems of *cis*-form is larger than that of the *trans*-form in the L_α phase, though the microscopic origin is not clarified.

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