July 1990 *Chem. Pharm. Bull.* **38**(7) 1819—1823 (1990)

Kinetic Study on the Release of Thiamine Disulfide (TDS) from TDS–Higher Fatty Acids Complexes. II.[1] Effect of Odd-Numbered Fatty Acids

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The rates of release of thiamine disulfide (TDS) from odd-numbered fatty acids–TDS complexes, $(C_{2n-1})_6$(TDS), were determined at various temperatures, and the thermodynamic quantities in the kinetics for the release of TDS from the complexes were estimated.

The rate of release of TDS from the complexes decreased with increasing carbon number in the odd-numbered fatty acid and increased at a higher temperature. The values of activation Gibbs energy ΔG^{+} and activation enthalpy ΔH^{+} for the release of TDS from the complexes were positive. The value of activation entropy ΔS^{+} was negative.

The results obtained for $(C_{2n-1})_6$(TDS) were compared with the previous results obtained for the even-numbered fatty acids–TDS complexes, $(C_{2n})_6$(TDS). The plots of the release rate constant of TDS from the complexes against the carbon numbers of the constituent fatty acids showed a zig-zag pattern which indicates a downward convex at an odd-numbered position. Furthermore, the plots of the positive values of ΔH^{+} against the carbon numbers of the constituent fatty acids showed a zig-zag line which indicates an upward convex at an odd-numbered position, while the plots of the negative values of ΔS^{+} showed a zig-zag line which indicates a downward convex at an odd-numbered position. The release of TDS from $(C_{2n-1})_6$(TDS) is more disadvantageous from the activation enthalpic viewpoint and more advantageous from the activation entropic viewpoint than $(C_{2n})_6$(TDS). It is found that the release of TDS from $(C_{2n-1})_6$(TDS) is an enthalpically controlled reaction, making the release more disadvantageous due to the enthalpic effect. The zig-zag line for the release rate of TDS from the complexes can be explained by the thermodynamic parameters of the transition intermediate.

Keywords thiamine disulfide; complex; higher fatty acid; release; release rate; activation energy; activation Gibbs energy; activation enthalpy; activation entropy; kinetics

Thiamine disulfide (TDS)–higher fatty acids (FA) complexes are expected to be useful as drug products. In previous papers[1,2] we reported the release of TDS from the complexes. In the studies, very interesting results were obtained as the length of the alkyl chain of FA was changed; nemely, the plots of T_{50} or T_{80} which are the times required for 50% or 80% of TDS to release showed a zig-zag line owing to the difference between even- and odd-carbon numbered FA.[2] In the previous paper,[1] the effect of even-numbered FA (tetradecanoic acid (C14), hexadecanoic acid (C16), and octadecanoic acid (C18)) on the release of TDS from the TDS–FA complexes was investigated in terms of thermodynamic parameters in reaction kinetics. As a result, it was found that the release of TDS from the complex is an enthalpically controlled reaction: that is, the release of TDS becomes more disadvantageous due to the enthalpic effect and the activation energy for the release of TDS becomes larger as the length of the alkyl chain of even-numbered FA is increased.

On the other hand, the plots of the melting points of FA against the carbon numbers of the constituent FA indicate a zig-zag pattern which indicates an upward convex at an even-numbered position, but those for the TDS–FA complexes do not show a zig-zag line. Furthermore, the melting points of the complexes formed from even-numbered FA are about 10 °C higher than those of the original even-numbered FA, while the melting points of the complexes formed from odd-numbered FA are about 15 °C higher than those of the original odd-numbered FA.[3] Namely, it is suggested that the complexes formed from odd-numbered FA is more thermostable than those formed from even-numbered FA. It is, therefore, expected that the effect of the difference of FA on the release rates of TDS from the complexes might be explained by the thermodynamic parameters in the release kinetics.

From these points of view, the release rates of TDS from the complexes formed with odd-numbered FA (pentadecanoic acid (C15) and heptadecanoic acid (C17)) were determined at various temperatures to investigate in detail the effect of FA. The results obtained for odd-numbered FA–TDS complexes, $(C_{2n-1})_6$(TDS), are compared with the results[1] obtained for even-numbered FA–TDS complexes, $(C_{2n})_6$(TDS), and the effects of the difference in FA will be discussed from the thermodynamic viewpoint of release kinetics.

Experimental

Materials TDS, C15, and C17 were the same as those used for the previous studies.[2,3] Complexes composed of TDS and FA were prepared as previously described.[3] The purity of each complex was examined as described in the previous paper.[2] Crystals of complexes were passed through 48 and 60 mesh sieves, and the particles of 48—60 mesh were taken for the release test.

Measurement of Release of TDS from Complexes The release of TDS from the complexes was determined in a JP XI dissolution test apparatus (paddle method) in JP XI dissolution test medium No. 1 (pH 1.2) as described in the previous paper.[2] Experiments were carried out at 7, 17, 22, and 27 °C. All experiments were carried out in triplicate and the results were highly reproducible.

Quantitative Analysis of TDS The concentration of TDS was determined spectrophotometrically as previously described.[1,2]

Results

Release Behavior of TDS from Complexes Complex, FA, and TDS are in equilibrium in aqueous solution (pH 1.2) as follows:

$$(FA)_6(TDS) \rightleftharpoons (FA)_6 + TDS$$

where $(FA)_6$ indicates a host structure. It has not yet been made clear whether FA maintains a host structure after guest TDS is released from $(FA)_6(TDS)$. However, FA is almost insoluble in aqueous acidic solvent, and a solid residue remains after TDS is released. As a matter of convenience, representation of $(FA)_6$ is used. The release behavior of TDS from C15–TDS complex, $(C15)_6(TDS)$, and C17–TDS complex, $(C17)_6(TDS)$, at four temperatures is shown as a relationship between the percentage of released TDS and time in Figs. 1 and 2, respectively. The percentages of released TDS were calculated with respect to the theoretical total concentration of TDS which is contained in the complex whose composition is expressed stoichiometrically by the formula $(FA)_6(TDS)$. The equilibrium percent of released TDS was 92.5—99.2 under various conditions, as can be seen in Figs. 1 and 2. The release rate is faster under conditions of higher temperature and a shorter alkyl chain of FA.

The values of T_{50} and T_{80} obtained for $(C15)_6(TDS)$ and $(C17)_6(TDS)$ at 17 °C are plotted against the carbon numbers of FA in Fig. 3 together with the previous results[1] obtained for $(C14)_6(TDS)$, $(C16)_6(TDS)$, and $(C18)_6(TDS)$. The relationship between the carbon numbers of the constituent FA and (T_{50} or T_{80}) was a zig-zag one, similar to the results[2] obtained at 37 °C.

Rate Constants for Release of TDS from Complexes The rate constant for the release of TDS is defined as follows:

$$\ln(x_e - x) = \ln x_e - kt \qquad (1)$$

where k is the rate constant of release, x is the percentage of TDS released from the complxes during time t, and x_e is the equilibrium percent of released TDS. Plots of $\ln(x_e - x)$ *versus* t, calculated from the values shown in Figs. 1 and 2, are presented in Figs. 4 and 5. As can be seen in Figs. 4 and 5, good linear relationships were obtained in all cases. The values of release rate constant k were obtained from the slopes shown in Figs. 4 and 5. The values of k were found to depend on temperature T and the Arrhenius plots, $\ln k$ *versus* $1/T$, are shown in Fig. 6, as previously described.[1]

The values of $\log k$ obtained for $(C15)_6(TDS)$ and $(C17)_6(TDS)$ at 17 °C are plotted against the carbon

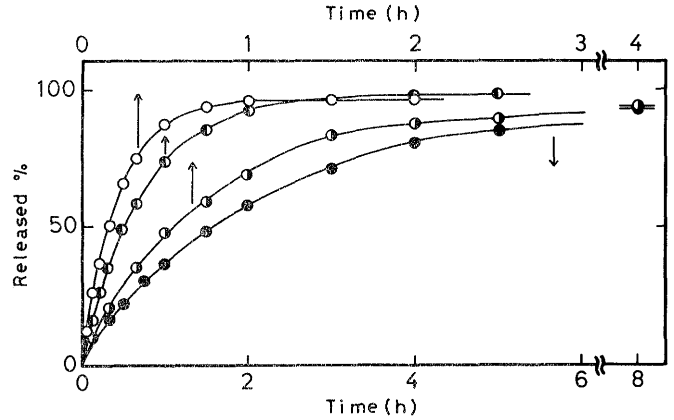

Fig. 1. Effect of Temperature on the Release Behavior of TDS from $(C15)_6(TDS)$

Temperature: ●, 7 °C; ◑, 17 °C; ◐, 22 °C; ○, 27 °C. Particle size: 48—60 mesh.

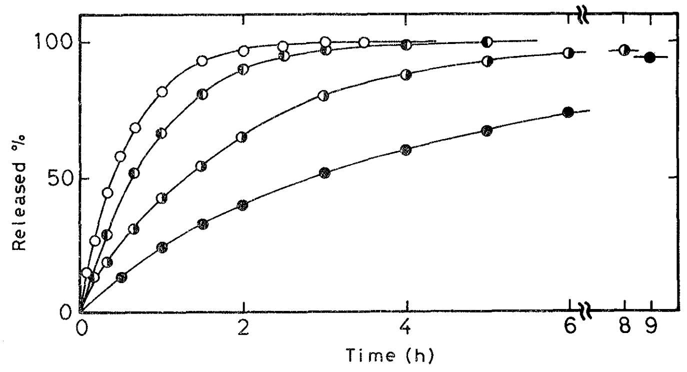

Fig. 2. Effect of Temperature on the Release Behavior of TDS from $(C17)_6(TDS)$

Symbols are the same as in Fig. 1.

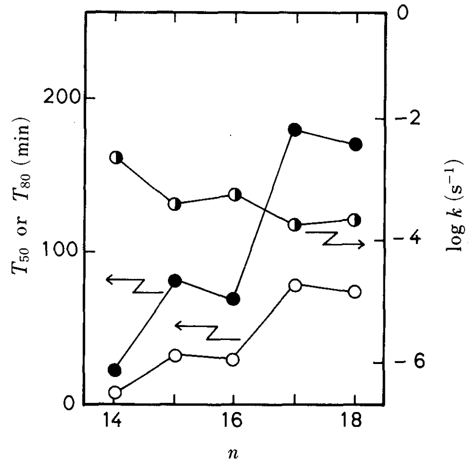

Fig. 3. Effect of FA on the Dissolution Rate of TDS from $(FA)_6(TDS)$

Dissolution rate: ○, T_{50}; ●, T_{80}; ◑, $\log k$. Temperature: 17 °C.

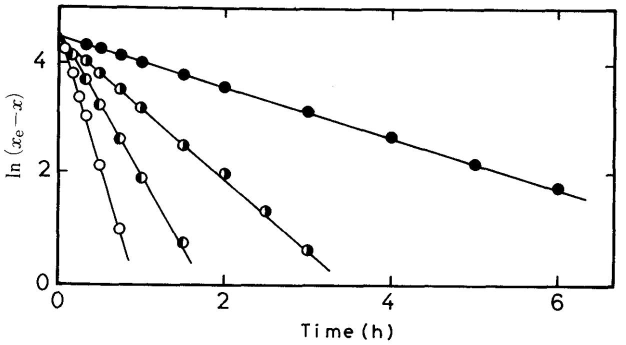

Fig. 4. Effect of Temperature on the Release of TDS from $(C15)_6(TDS)$, $\ln(x_e - x)$ *vs.* Time

Symbols are the same as in Fig. 1.

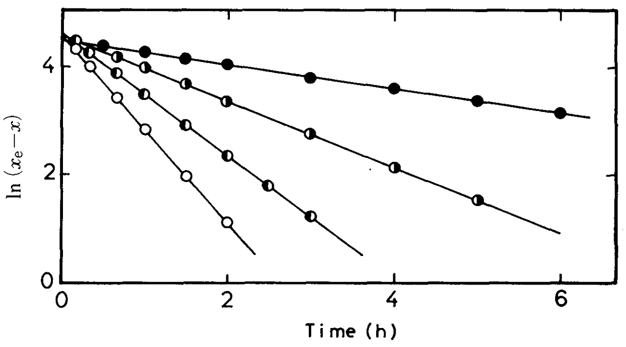

Fig. 5. Effect of Temperature on the Release of TDS from $(C17)_6(TDS)$, $\ln(x_e - x)$ *vs.* Time

Symbols are the same as in Fig. 1.

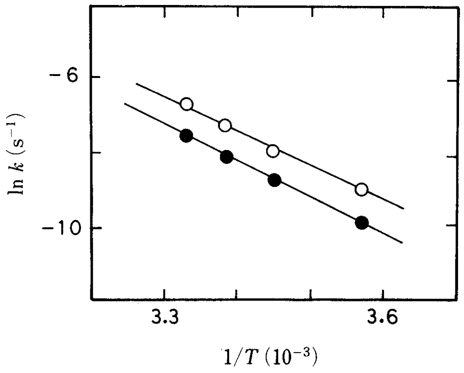

Fig. 6. Arrhenius Plots: ln*k* *vs.* 1/*T*

Complex: ○, $(C15)_6(TDS)$; ●, $(C17)_6(TDS)$.

Table I. Activation Thermodynamic Quantities for the Release of TDS from $(C_{2n-1})_6(TDS)$

	$E^{\neq}$ (kJ mol^{-1})	$\Delta G^{\neq}$ (kJ mol^{-1})$^{a)}$	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ (J K^{-1} mol^{-1})
$(C15)_6(TDS)$	75.6	90.3	73.3	−56.5
$(C17)_6(TDS)$	87.3	92.1	84.6	−25.0

a) At 300 K.

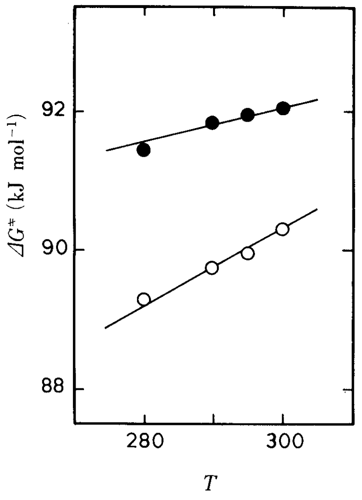

Fig. 7. Relationship between Activation Gibbs Energy and Temperature

Symbols are the same as in Fig. 6.

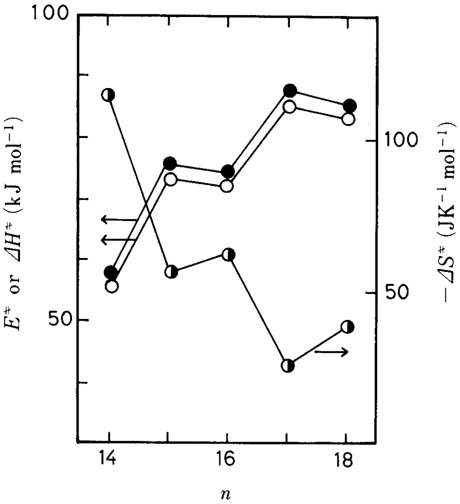

Fig. 8. Effect of FA on Activation Thermodynamic Quantities for the Release of TDS from $(FA)_6(TDS)$

Thermodynamic parameter: ○, ΔH^{+}; ●, E^{+}; ◑, ΔS^{+}.

numbers of FA in Fig. 3 together with the previous results[1)] obtained for $(C14)_6(TDS)$, $(C16)_6(TDS)$, and $(C18)_6(TDS)$. Plots of log *k* against the carbon numbers of the constituent FA which are components of the complexes showed a zig-zag line.

Discussion

Activation Energy for Release of TDS from Complexes As is clear in Fig. 6, the relationship between ln*k* and 1/*T* can be represented by a single line for each complex with a different chain length of FA. The activation energy for the release E^{+} was, therefore, obtained from the value of the slope, and the results are summarized in Table I. As can be seen in Table I, the positive value of activation energy for $(C_{2n-1})_6(TDS)$ with a longer alkyl chain of FA is larger, indicating the same tendency as reported for $(C_{2n})_6(TDS)$.[1)]

Activation Thermodynamic Quantities for Release of TDS from Complexes The activation Gibbs energy, ΔG^{+}, for the release of TDS from the complex can be represented in terms of the release rate constant, *k*, as follows:

$$\Delta G^{+} = -\boldsymbol{R}T\ln k + \boldsymbol{R}T\ln(\boldsymbol{k}_B T/\boldsymbol{h}) \qquad (2)$$

where $\boldsymbol{R}$, $\boldsymbol{k}_B$ and $\boldsymbol{h}$ are the gas constant, Boltzmann constant and Planck constant, respectively. The transmission coefficient was assumed to be unity. Furthermore, ΔG^{+} is related to activation enthalpy ΔH^{+} and activation entropy ΔS^{+} as follows:

$$\Delta G^{+} = \Delta H^{+} - T\Delta S^{+} \qquad (3)$$

The values of ΔG^{+} were estimated from the values of ln*k* shown in Fig. 6, and the values of ΔG^{+} were plotted against temperature *T* in Fig. 7. The values of ΔG^{+} are all positive as graduated at ordinate in Fig. 7, and the value is larger for the complex with a longer alkyl chain length of FA, indicating that the release of TDS is more difficult from $(C17)_6(TDS)$ than $(C15)_6(TDS)$. As can be seen in Fig. 7, the relationship between ΔG^{+} and *T* can be represented by a single line for each complex with a different chain length of FA. The activation entropy ΔS^{+} was, therefore, obtained from the values of the slope. The activation enthalpy ΔH^{+} was approximately estimated from the intercept, which agreed well with the value from the slope of $\Delta G^{+}/T$ *vs.* $1/T$ and nearly with the approximate evaluation, $E^{+} - \boldsymbol{R}T$. The results are summarized in Table I. As can be seen in Table I, the value of ΔH^{+} is positive and the value of ΔS^{+} is negative. These are the same tendencies as the results calculated from the values[1)] of *k* for $(C_{2n})_6(TDS)$ by using Eqs. 2 and 3.

Effect of FA on Activation Thermodynamic Quantities It is suggested that the zig-zag lines shown in Fig. 3 are caused by the activation thermodynamic parameters. Therefore, the values of E^{+}, ΔH^{+}, and ΔS^{+} for the release of TDS from the complexes are represented graphically against the carbon numbers of the constituent FA in Fig. 8 together with the values of E^{+} obtained in the previous study[1)] and with the values of ΔH^{+} and ΔS^{+} derived from the values[1)] of k. As can be seen in Fig. 8, the plots of $E^{\ddagger}$ *vs.* n indicate a zig-zag line which indicates an upward convex at an odd-numbered position, indicating that the value of $E^{\ddagger}$ for $(C_{2n-1})_6(TDS)$ is larger than that for $(C_{2n})_6(TDS)$ whose alkyl chain of FA is one more carbon number longer. This indicates that the release of TDS from $(C_{2n-1})_6(TDS)$ is more disadvantageous than that from $(C_{2n})_6(TDS)$ from the viewpoint of energy barrier. Furthermore, the plots of positive values of $\Delta H^{\ddagger}$ *vs.* n indicate a zig-zag line which indicates an upward convex at an odd-numbered position, while the plots of negative values of $\Delta S^{\ddagger}$ *vs.* n indicate a zig-zag line which indicates a downward convex at an odd-numbered position. This indicates that the release of TDS from $(C_{2n-1})_6(TDS)$ is more disadvantageous enthalpically but more advantageous entropically as compared with that from $(C_{2n})_6(TDS)$. Furthermore, the positive value of $\Delta H^{\ddagger}$ increases and the negative value of $\Delta S^{\ddagger}$ decreases with an increasing carbon number in only even- or odd-numbered FA. This indicates that the release of TDS from the complex with a longer alkyl chain of FA is more disadvantageous enthalpically but more advantageous entropically. The release of TDS from the complex is an enthalpically controlled reaction,[1] leading to a positive larger value of $\Delta G^{\ddagger}$ for the complex with a longer alkyl chain length of FA.

The zig-zag lines for the release rate of TDS from the complexes shown in Fig. 3 can be explained by the activation thermodynamic parameters in the release kinetics.

The crystal structure of $(FA)_6(TDS)$ has not yet been determined. However, the powder X-ray diffraction patterns[3] of the complexes suggest that the crystal structures of complexes with odd-numbered FA are a little different from those with even-numbered FA. Namely, it is suggested[2] that the interaction between odd-numbered FA and TDS might be stronger than that between even-numbered FA and TDS.

It is suggested that FA form aggregates, $(FA)_6$, in 1,2-dichloroethane before FA form complexes with TDS. The aggregation of FA in 1,2-dichloroethane is suggested in our recent study by using a fluorescent probe, and the results will be reported in a later paper.

Ueno *et al.* have reported the effect of alkyl chain length on the surface properties of octaethyleneglycol-*n*-alkyl ethers.[4] In their papers it was reported that the plots for the molecular area at the air–water interface show a zig-zag curve for the difference of the even-odd numbered carbon atoms and that the molecular area for the surfactants with an odd carbon number is larger than that for the surfactants with an even carbon number, indicating that the packing for the former is looser than that for the latter. On the basis of these reports[4] and our finding of aggregation of FA in 1,2-dichloroethane, it is suggested that the internal diameter for the aggregation formed from odd-numbered FA is slightly larger than that formed from even-numbered FA. Furthermore, it might be considered that the internal diameter of the cavity, which is a cylindrical structure formed from odd-numbered FA, is better fit in the conformation of TDS, leading to stronger interaction between the aggregation formed with odd-numbered FA and TDS. These estimations can explain the retardation in the release rate and the larger positive value of $E^{\ddagger}$ for the release of TDS from $(C_{2n-1})_6(TDS)$. A regular increase in the positive value of $E^{\ddagger}$ with an increase of the alkyl chain length for only even-numbered or odd-numbered FA is suggested to be caused by the length of the cylindrical host structure formed with FA in addition to the hydrophobic character of FA. This suggestion, however, is in the presumption stage.

Regarding the inclusion compounds formed with cyclodextrins (CD) and guest compounds, it has been reported[5] that the binding forces between the CD and the guest molecule are provided by hydrogen bonding, van der Waals forces, and hydrophobic interactions. The formation of inclusion compounds have been found[5d,6] to have a negative value of $\Delta H^{\ddagger}$ and a negative or slightly positive value of $\Delta S^{\ddagger}$. A combination of hydrophobic ($\Delta H^{\ddagger} \approx 0$; $\Delta S^{\ddagger}$ positive) and van der Waals ($\Delta H^{\ddagger}$ negative: $\Delta S^{\ddagger}$ negative) forces has accounted for the thermodynamic parameters guest molecule binding to CD.[6b] The more exothermic (negative) $\Delta H^{\ddagger}$ has been found[6b] for the larger guests, and this is consistent with the dominant role of van der Waals forces in the binding of guest to host. The values of positive $\Delta H^{\ddagger}$ and negative $\Delta S^{\ddagger}$ for the release of large molecule TDS from $(FA)_6(TDS)$ are, therefore, reasonable. It is suggested that the formation of $(FA)_6(TDS)$ is related to van der Waals forces and hydrophobic interactions between TDS and FA.

Furthermore, the negative larger value of $\Delta H^{\ddagger}$ has been found[5d] for a deeper penetration of the guest into the CD cavity. This fact satisfies the regular increase in positive value of $\Delta H^{\ddagger}$ for the release of TDS from $(FA)_6(TDS)$ with an increase of the alkyl chain length for only even-numbered or odd-numbered FA.

It is thought that $(FA)_6(TDS)$ at least have a property of inclusion compound. Further studies are necessary to discuss the difference between $(C_{2n-1})_6(TDS)$ and $(C_{2n})_6(TDS)$. We are now studying calorimetrically the heat of dissolution for $(C_{2n-1})_6(TDS)$ and $(C_{2n})_6(TDS)$.

Conclusion

The plots of the release rates of TDS from complexes against the carbon numbers of the constituent FA showed a zig-zag line which indicates a downward convex at an odd-numbered position. As the results of activation thermodynamic investigation, it has been found that the plots of $E^{\ddagger}$ *vs.* n indicate a zig-zag line which indicates an upward convex at an odd-numbered position. The release of TDS from $(C_{2n-1})_6(TDS)$ is more disadvantageous than that from $(C_{2n})_6(TDS)$ from the viewpoint of activation energy. The zig-zag lines for the release of TDS from complexes shown in Fig. 3 can be explained by the thermodynamic parameters in the kinetics.

The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the release of TDS from $(FA)_6(TDS)$ were positive and negative, respectively. The plots of $\Delta H^{\ddagger}$ *vs.* n showed a zig-zag line which indicates an upward convex at an odd-numbered position, while the plots of $\Delta S^{\ddagger}$ *vs.* n showed a zig-zag line which indicates a downward convex at an odd-numbered position. Therefore, it is suggested that $(FA)_6(TDS)$ is formed at least by van der Waals forces and hydrophobic interactions and that van der Waals forces are dominant for the formation of $(C_{2n-1})_6(TDS)$ and hydrophobic interactions are dominant for the formation of $(C_{2n})_6(TDS)$.

From these results, it is suggested that the crystal structure of $(C_{2n-1})_6$(TDS) is a little different from that of $(C_{2n})_6$(TDS). It might be suggested that the cylindrical cavity formed from odd-numbered FA is more suitable for the inclusion of TDS.

Acknowledgment We express our sincere thanks to Miss Yukiko Ohata for contributing to this work. Helpful comments from Prof. Hiroshi Kishimoto, Nagoya City University, on the manuscript are gratefully acknowledged.

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