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Entropy Changes in the Inclusion Complex Formation of α-Cyclodextrin with Alcohols as Studied by the Titration Calorimetry[†]

Hideaki FUJIWARA,* Haruyuki ARAKAWA, Saburo MURATA, and Yoshio SASAKI
Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-Oka, Suita, Osaka 565

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The inclusion complex formation of α-cyclodextrin(α-CD) with various alcohols has been studied by means of titration calorimetry. The titration curve was analyzed successfully by the formation of a 1:1 host-guest complex, and the thermodynamic parameters were determined. The entropies of reaction are estimated from the statistical thermodynamics of molecules. However, the estimated values are found to deviate by an order of magnitude from the experimental ones. To resolve such a discrepancy, α-CD in solution is assumed to include a definite number(n) of water molecules which are replaced by a guest molecule with the progress of reaction. The entropies thus estimated depend extensively on the value of n, and a value of n is determined for each alcohol so that it reproduces just the experimental entropy. The resulting n values are nearly constant for various alcohols studied and are within a reasonable range expected from the data reported in crystal, supporting the model of interpretation.

In a previous report of this series,[1] we have studied with especially the entropy term of reactions of dichlorodimethylstannane with pyridine measured by the titration calorimetry: A solvation model was presented to interpret discrepancy between the entropies observed and those estimated by statistical thermodynamics. To investigate further the validity of such a simple treatment of the entropy term for an elucidation of the role of solvent in reactions, the model is extended to the inclusion complex formation of α-cyclodextrin with alcohols in the present study.

Cyclodextrins are well-known in their ability to form inclusion complexes with various kinds of compounds. They are applied widely in industry,[2] such as for the pharmaceutics and food chemistry as well as for the analytical chemistry. They are also interested as an enzyme model in biochemistry.[3–5] All these applications make use of the "hydrophobic" cavity in cyclodextrin which can "include" different kinds of organic molecules, leading to the inclusion complexes. The inclusion complex formation has been studied quantitatively by not a few investigators and equilibrium constants and enthalpies and entropies have been discussed in relation to the driving forces for the inclusion phenomena.[2,3,5–9] Hitherto, hydrophobic, van der Waals, and hydrogen-bonding interactions between the host and guest molecules, conformational changes in cyclodextrin, and solvation of species in water are pointed out to be responsible to this phenomenon. Here, a release of less hydrogen-bonded water molecules in the cavity to the fully hydrogen-bonded bulk water surely contributes *enthalpically* much to the stabilization of the complex. This effect is pronounced in α-cyclodextrin (α-CD), where smaller number of water molecules are located in the cavity before inclusion occurs and hence hydrogen bonding between these water molecules is less extensive.

In the present study, the entropy changes observed in the inclusion complex formation of α-CD with several alcohols in aqueous solution are interpreted on the basis of the statistical thermodynamics, from which the number of water molecules included in a free state of α-CD *in solution* can be estimated.

Experimental

Alcohols were all distilled in a glass vessel and α-CD from Tokyo Kasei Co. was recrystallized from water. Calorimetric titration was performed on a Tronac 558 isothermal/isoperibol calorimeter equipped with a CCP930 Programmer under an isothermal mode.[10a)] α-CD was dissolved in the reaction vessel at a constant molarity, and alcohol was dissolved in the titrant solution. A total of 2 ml titrant was added in 20 steps to 50 ml solution in a stainless steel reaction vessel. Also a 20 ml titration buret was used for 1-hexanol and cyclohexanol, for which solubility in water is not so high as the other alcohols. The heat of reaction was measured within an error of ±0.04 J at 25.0 °C (±0.2 m°C).

Analysis of the titration data was made in a similar way as stated in Ref. 10.b. All these calculations and the calculation of the entropy terms discribed below were done on a NEAC ACOS-1000 computer at the Computation Center in Osaka University. Personal computers NEC PC-9800 were also used for the treatment of experimental data.

Results

The titration experiments were done several times for each alcohol. A typical run is shown in Fig. 1. The titration data were analyzed by the program CONDEP modified to the calorimetric experiments[10b)] on the basis of a 1:1 complex formation. Standard deviation σ between the observed and the recalculated heats was smaller than 0.04 J, and systematic deviations were not observed between them. In the program CONDEP, integrated heat Q_i was dealt with originally under the incremental addition of titrant. In the present study, data were also processed with the differential heat q_i. These two calculations were confirmed to afford consistent results.[11)]

[†] Solvation Effect on the Reactions in Solution. II. See Ref. 1 for I.

The equilibrium constants determined are 9.7, 29.1, 81.4, 326, 801, and 56.4 $dm^3 mol^{-1}$ for ethanol, 1-propanol, 1-butanol, 1-pentanol, 1-hexanol, and cyclohexanol, respectively, at 25 °C. The enthalpies and entropies are summarized in Table 1 together with those hitherto published by other investigators. Reproducibility of these parameters was better than 95, 90, and 90% for K, ΔH^0, and ΔS^0, respectively, in the repeated experiments in the present study. The unit of concentration adopted is mol dm^{-3} (M) in the present study, and thermodynamic parameters also correspond to this unit. In Table 1, values cited from other sources are converted to correspond to the same unit when necessary.[14] In the Table, ΔH^0's for the same alcohol are rather in good agreement although method and experimental conditions differ among different investigators. As this contrast, ΔS^0 changes more or less depending on the sources of data. This would be inevitable because of the small contribution of ΔS^0 as judged by comparing $T\Delta S^0$ with ΔH^0.

Table 1. Enthalpies and Entopies for the Inclusion Complex Formation of α-Cyclodextrin with Several Alcohols[a)]

Alcohol	ΔH^0			ΔS^0		
	This work	Ref. 12	Ref. 13	This work	Ref. 12	Ref. 13
Ethanol	−2.4			11.2		
1-Propanol	−6.1	−6.8		7.7	4.6	
2-Propanol		−0.55			30.1	
1-Butanol	−10.2		−12	2.2	2.0	−2
1-Pentanol	−14.8	−14.1	−16	−1.4		−5
1-Hexanol	−17.2		−19	−2.1		−8
Neopentyl alcohol			−12			−12
Cyclohexanol	−12.2	−8.1	−14	−7.3	2.0	−14

a) ΔH^0 and ΔS^0 are given in units of kJ mol^{-1} and J $K^{-1} mol^{-1}$, respectively, the unit of concentration corresponding to mol dm^{-3}.

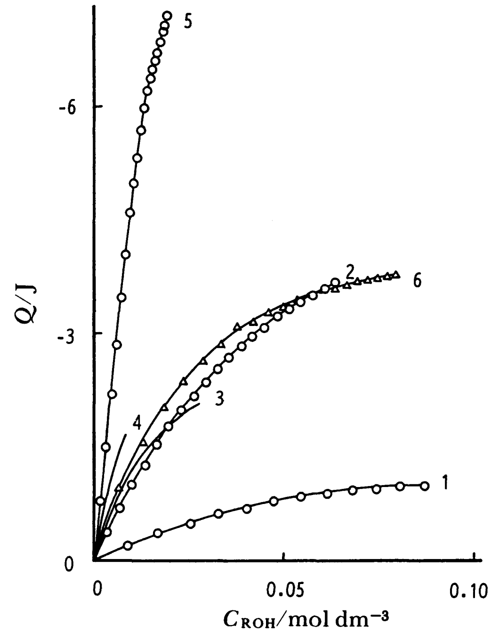

Fig. 1. The calorimetric titration curves for the α-CD plus alcohol systems.
The molarity of alcohol is plotted in abscissa and in ordinate plotted is the integrated heat of reaction.
1; Ethanol, 2; 1-propanol, 3; 1-butanol, 4; 1-pentanol, 5; 1-hexanol, 6; cyclohexanol.
The molarity of α-CD changes:
1; 0.014—0.012 M, 2; 0.0194—0.0187 M, 3; 0.0067—0.0064 M, 4; 0.0042—.0.0040 M, 5; 0.015—0.009 M, 6; 0.012—0.007 M. A half of C_{ROH} is plotted in curve 1 to save a space in the Figure.

Discussion

A thermochemical cycle is given in Fig. 2 for the entropies, where α-CD is assumed to include n molecules of water in solution that will be released with the progress of reaction. Following equations hold for this cycle:

$$\Delta S^0_{gas} = S^0_{CD\cdot B} + nS^0_{H_2O} - S^0_{CD\cdot nH_2O} - S^0_B \tag{1}$$

$$\Delta S^0_{soln} = \Delta S^0_{gas} + (\Delta S^s_{CD\cdot B} + n\Delta S^s_{H_2O} - \Delta S^s_{CD\cdot nH_2O} - \Delta S^s_B) \tag{2}$$

Note that nH_2O is attached to α-CD in the left-hand side of the formula in Fig. 2 to allow for the inclusion of water molecules in the cavity. These water molecules are considered to "solvate" strongly (or bind) to α-CD. That is to say, n molecules of water in the cavity are assumed to behave as if they constitute a rigid part of a whole molecule.[15] As this contrast, normal and weak "solvation" of each species is considered to be compensated for by the entropy of solution.

Estimation of ΔS^0_{gas} in Eq. 1 is not straightforward since calculation of $S^0_{CD,B}$ and S^0_{CD,nH_2O} needs detailed data on the vibrations in CD·B and CD·nH_2O which are lacking. However, most of the vibrational parts

$$\begin{tikzcd}
\text{Gas phase} & \mathrm{CD}\cdot n\mathrm{H_2O} + {} \arrow[d, "\Delta S^s_{CD\cdot nH_2O}"'] & \mathrm{B} \arrow[r, "\Delta S^0_{gas}"'] \arrow[d, "\Delta S^s_B"'] & \mathrm{CD}\cdot\mathrm{B} + {} \arrow[d, "\Delta S^s_{CD\cdot B}"'] & n\mathrm{H_2O} \arrow[d, "n\Delta S^s_{H_2O}"'] \\
\text{Liquid phase} & \mathrm{CD}\cdot n\mathrm{H_2O} + {} & \mathrm{B} \arrow[r, "\Delta S^0_{soln}"'] & \mathrm{CD}\cdot\mathrm{B} + {} & n\mathrm{H_2O}
\end{tikzcd}$$

Fig. 2. A reaction scheme for the entropy changes in the inclusion complex formation of cyclodextrin(CD) with alcohols(B).
ΔS^s's are the entropies of solution of the components. In a free state, CD is assumed to include n molecules of water, which are released with the progress of reaction.

are expected to be cancelled out between those for the reactants and those for the products. The translational and the rotational parts of entropy can be estimated according to following Eqs.:[16]

$$S_{\mathrm{tr}} = R(1.5\ln M + 2.5\ln T - \ln P - 1.1650) \qquad (3)$$

$$S_{\mathrm{rot}} = R(0.5\ln I_A I_B I_C + 1.5\ln T - \ln\sigma - 2.7106) \qquad (4)$$

where the symbols have usual meanings. Such calculations afforded $\Delta S^0_{\mathrm{gas,calcd}}$ as listed in Table 2, when n was set equal to two, a typical value reported first for a single crystal of α-CD hexahydrate.[17]

The value of $\Delta S^0_{\mathrm{gas,calcd}}$ can be converted to that of $\Delta S^0_{\mathrm{soln,calcd}}$ by means of Eq. 2 if the entropy of solution is predictable for each component. The experimental values are available for different compounds including water and alcohols, and the value is known to be linearly correlated with the thermodynamic third-law entropy of solute x in gas phase, $S^0_{298,\mathrm{x}}(\mathrm{g})$. For example, Eq. 5 is reached in aqueous solution.[18] It is later reported that the coefficients in Eq. 5 may change depending on the types of compounds treated.[19]

$$\Delta S^{\mathrm{s}}_{\mathrm{x}} = -0.46\, S^0_{298,\mathrm{x}}(\mathrm{g}) + 27.5 \qquad (5)$$

However, Eq. 5 is considered to be valid for the present case, since in Eq. 2 ΔS^{s} appears as the difference between that of water and that of alcohol and also as the difference between that of the cyclodextrin hydrate and that of its inclusion complex. Then Eq. 6 is reached from Eqs. 1, 2, and 5.

$$\Delta S^0_{\mathrm{soln}} = 0.54\, \Delta S^0_{\mathrm{gas}} + (n-1)\cdot 27.5 \qquad (6)$$

Next, a correction is necessary for the difference in standard states. The thermodynamic third-law entropy $S^0_{298}(\mathrm{g})$ corresponds to a standard state of 1 atm, whereas the entropy of reaction is given against a standard state of 1 mol dm^{-3} in the present study. Therefore, following relation holds:

$$S^0_{298,\mathrm{x}}(\mathrm{g}) = S^0_{\mathrm{x}} + R\cdot\ln 24.5 \qquad (7)$$

where S^0_{x} is the standard entropy of x in gas phase corresponding to 1 mol dm^{-3} (1/24.5 atm) at 25 °C and an ideal gas behavior is assumed. The values of $\Delta S^0_{\mathrm{soln}}$ thus estimated are also listed in Table 2.

Table 2. $\Delta S^0_{\mathrm{gas}}$ Estimated from the Translational and the Rotational Entropies for the Reaction of $\alpha\text{-CD}\cdot 2H_2O + B \rightarrow \alpha\text{-CD}\cdot B + 2H_2O$[a]

B(alcohol)	$\Delta S^0_{\mathrm{gas,calcd}}$	$\Delta S^0_{\mathrm{soln,calcd}}$
Ethanol	115.1	89.7
1-Propanol	103.2	83.2
2-Propanol	103.6	83.4
1-Butanol	100.1	81.6
1-Pentanol	92.6	77.5
1-Hexanol	86.2	74.0
Neopentyl alcohol	94.1	78.3
Cyclohexanol	88.9	75.5

a) In unit of J K^{-1} mol^{-1}

The entropies calculated are all positive and very large compared to the experimental ones. If the vibrational and internal-rotational entropies are included into the calculation, the resulting $\Delta S^0_{\mathrm{gas,calcd}}$ will be increased more or less. In fact, $\Delta S^0_{\mathrm{gas,calcd}}$ was increased by 16% in the previous case of Me_2SnCl_2 plus pyridine.[1] Therefore, it is quite clear that above calculation fails to explain the experimental values of $\Delta S^0_{\mathrm{soln}}$. As a cause of this discrepancy, an error in n can be pointed out. Hitherto, two different values have been reported other than two stated above for the number of water molecules included in the α-CD cavity in crystal, i.e., $n=1$[20] and $n=2.57$[21] for different crystal modifications. In fact, the values of $\Delta S^0_{\mathrm{gas}}$ and $\Delta S^0_{\mathrm{soln}}$ calculated were found to depend highly on the value of n. Therefore, n was determined according to Eq. 8 so as to reproduce just the experimental value of $\Delta S^0_{\mathrm{soln}}$. Equation 8 was derived from Eqs. 1, 2, 5, and 7.

$$n = \frac{\Delta S^0_{\mathrm{soln}} - 0.54(S^0_{\mathrm{CD\cdot B}} - S^0_{\mathrm{CD}\cdot n\mathrm{H_2O}} - S^0_{\mathrm{B}}) + 27.5 - 0.46R\cdot\ln 24.5}{0.54\, S^0_{\mathrm{H_2O}} + 27.5 - 0.46R\cdot\ln 24.5} \qquad (8)$$

The results are summarized in Table 3.[22] It is seen that n is nearly constant throughout the alcohols studied, although the experimental entropies do change depending on the alcohol. Such a constancy in n indicates that a same number of water molecules are released from the cavity when alcohols with a small size (ethanol) to a relatively large size (1-hexanol) are included, and supports that all of the water included in the cavity are expelled from the cavity on forming the complexes with these alcohols. This trend in solution is consistent with the results in crystal.[23] Also, the constancy in n means that $\Delta S^0_{\mathrm{soln}}$ depends only on $\Delta S^0_{\mathrm{gas}}$ (Eq. 6). This, in turn, means that $\Delta S^0_{\mathrm{soln}}$ changes linearly with S^0_{B} on changing the alcohol studied, since in Eq. 1 $S^0_{\mathrm{H_2O}}$ and $S^0_{\mathrm{CD},n\mathrm{H_2O}}$ are

Table 3. The Number of Water Molecules (n) Released on the Complex Formation Reactions of $\alpha\text{-CD}\cdot nH_2O + B \rightarrow \alpha\text{-CD}\cdot B + nH_2O$ Determined from the Entropy of Reaction

B(alcohol)	n[a]		
	a	*b*	*c*
Ethanol	1.37		
1-Propanol	1.40	1.38	
2-Propanol		1.58	
1-Butanol	1.37		1.34
1-Pentanol	1.38	1.40	1.35
1-Hexanol	1.43		1.35
Neopentyl alcohol			1.29
Cyclohexanol	1.37	1.56	1.30

a) Calculated from data in this work(*a*), in Ref. 12(*b*), and in Ref. 13(*c*).

constant and $S^0_{CD\cdot B}$ is almost constant for different alcohols because of an overwhelming size of cyclodextrin. In fact, ΔS^0_{soln} was observed to change linearly with the thermodynamic third-law entropy of alcohol in the present study. These correlations are under further study including various kinds of guest molecules. In this way n is said to be 1.4 on average for the alcohols studied here. Such a non-round number may result from a dynamic equilibrium of water in between the cavity and the bulk water. That is, the non-round number reflects only a statistical average of the number of water molecules included in the cavity in solution.

In conclusion, calculation of the entropy of reactions is expected to be valuable for the elucidation of the state and the role of water in the host-guest molecular interactions in solution.

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11) If an unexpectedly large error occurs in an incremental step of k in titration, the error will be included to all the integrated heat Q_i later than $i=k$, although it is included to only q_k when differential heat is treated. On this contrary, random errors which occur in every step of titration will be reduced for the integrated heat Q_k by a partial cancellation in the summation of the differential heats q_i between $i=1$ to k. The consistent results reached from the analysis of Q_i and from than of q_i may be interpreted to indicate sufficiently small errors in the present experiment.

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14) Following equations were utillized for the conversion from mole fraction to mol dm^{-3}, the primed symbols corresponding to the unit of mole fraction.

$$\ln K = \ln K' - \ln(1000/MV)$$
$$\Delta H = \Delta H' + \alpha R\cdot T^2$$
$$\Delta S = \Delta S' + R\{\ln(1000/MV) - \alpha T\}$$

Here, MV is the molar volume of solute and α is the thermal expansion coefficient of solution.

15) A fraction of the water molecules may still be included in the cavity of α-CD in CD·B. However, this is not assumed in Fig. 2 for simplicity. When this is the case, say m molecules of water "bind" strongly to CD·B, the value of n discussed below needs be replaced by that of $n-m$ which is equal to a number of water molecules released in the reaction. However, as stated in the Discussion section, all of the water molecules included within the cavity are considered to be expelled from the cavity after the reaction.

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22) The vibrational part of entropy is not included in the calculation of $S^0_{CD\cdot B} - S^0_{CD\cdot nH_2O} - S^0_B$ because of the lack of full vibrational data. This part is actually equal to that of the reaction of $CD\cdot nH_2O + B \rightarrow CD\cdot B + nH_2O$ because of a negligible amount of the vibrational part in H_2O. Accordingly, this part is expected to be small since the vibrational entropies for the latter reaction will be cancelled out between those for the reactants and those for the products. If the vibrational entropy of this kind is assumed to amount to 16% of $\Delta S^0_{gas,calcd}$ likely to the previous case,[1] $\Delta S^0_{CD\cdot B} - \Delta S^0_{CD\cdot nH_2O} - S^0_B$ in Eq. 8 is increased by 16 J K^{-1} mol^{-1} and the resulting n will be decreased by about 16%.

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