

CALORIMETRIC STUDY ON INCLUSION OF SOME ALCOHOLS INTO α -CYCLODEXTRIN CAVITIES

Molecular mechanical calculation of hydration Gibbs energies

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The enthalpies of transfer 2-propanol, 1,2-butanediol (BD) and 1-hexanol from aqueous to aqueous α -cyclodextrin (CD) solutions have been determined by microcalorimetry at various mole fractions at 298.15 K. To clarify stabilities of inclusion complexes in aqueous solutions, hydration Gibbs energies calculation of inclusion complex of CD-alcohol were performed by using the molecular mechanics with the MMFF94s force field in the generalized born/surface area (GB/SA) model. The largest stabilization in Gibbs energy is obtained by the hydration ($\Delta_{\text{hyd}}H$) of α -CD-1,2-butanediol complex among α -CD- butanediol isomers complexes.

Keywords: cyclodextrins, enthalpy of inclusion, hydration Gibbs energy, molecular mechanics, molecular recognition

Introduction

In liquid phase a vast crowd of molecules gather closely, oscillating and rotating violently. Colliding with each other, they distinguish a kind of molecules from other ones. In particular, stereospecific interactions due to neighboring surfaces may play the leading role in, e.g., enzyme-substrate reactions, antigen-antibody reactions, some kinds of mechanisms of senses of smell and taste, and so on. Therefore, elucidating the role of asymmetric intermolecular interactions owing to the stereospecific structures of molecules is really important for understanding the mechanisms of chemical and biochemical reactions.

The accumulation of accurate and quantitative values of the changes in thermodynamic functions on molecular inclusion are required as basic information for understanding the mechanisms of molecular recognition and discrimination.

To clarify the mechanism of molecular recognition and discrimination in aqueous solutions, we have determined systematically thermodynamic functions for the molecular inclusion of simple alcohols into CD cavities in aqueous solutions [1–6]. CD-guest complexes were characterized using TG by other researchers [7, 8].

In this paper, the molar enthalpies, entropies and Gibbs energies of inclusion of 2-propanol, 1,2-butanediol and 1-hexanol into α -CD cavities at 298.15 K in dilute aqueous solutions were determined at 298.15 K, and the determination of the hydration Gibbs energies of inclusion compounds by using molecular mechanics

were described, in order to realize stabilities of inclusion complexes in aqueous solutions.

Experimental

Materials

1,2-BD (Tokyo Kasei Co.) was first treated by repeated fractional recrystallisation. Next 1,2-BD and 1-hexanol (Kishida Chemical Co., G.R. grade) were distilled fractionally under reduced pressure nitrogen through a spinning-band column with freshly activated molecular sieves 4Å. The water contents analyzed by Karl-Fischer titration were 0.01 for 1,2-BD, and 0.08 for 1-hexanol by mass percent. Details of careful purification used for the α -CD [1], water [9], 2-propanol [10] were described elsewhere. All solutions were prepared by mass. The aqueous 1,2-BD mixtures prepared were stirred for 10 min at room temperature on magnetic stirrer. Then, they were stirred vigorously for ca. 15 min at room temperature with a weak sonic washer (Taga Electric Co., Ltd., model baliba 7500, output frequency: 42 kHz, 70 W) before charging them into mixing vessels to make sure that the mixtures are easy to reach equilibrium in holding time for measurement. Takagi *et al.* had found that the mixtures of water and 1,4-butanediol required a lot of time (max.: ca. 15 h) to reach equilibria at room temperatures [4]. Then, they were vigorously stirred for ca. 15 min at room temperature with a supersonic washer (Taga Electric Co., Ltd., model UW-25, out-put frequency: 38 kHz, 45W).

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Apparatus and procedures

A rocking twin-microcalorimeter of a heat-conduction type, laboratory designation RMC, was used for the determination of enthalpies of dilution and mixing. All the measurements were carried out at 298.15 K under the atmospheric pressure. Enthalpy changes were measured automatically with an on-line system described elsewhere [11]. Details of the apparatus and procedures, including the mixing vessels [2], are similar to those described previously [3, 4].

Results and discussion

Enthalpy of dilution

The experimental results for the enthalpy changes on diluting the dilute aqueous 1,2-BD solutions ranging from 1.0×10^{-3} to 2.8×10^{-3} in mole fraction to final solutions ranging from 2.0×10^{-4} to 5.9×10^{-4} at 298.15 K under the atmospheric pressure are given in Table 1, where n_3 denotes the amount of 1,2-BD in the solutions and x_i and x_f respectively are the mole fractions before and after the dilution. The results were fitted to Eq. (1) by the least-squares calculation. The best-fit values for the parameters in Eq. (1) are listed in Table 2, as well as the calculated standard deviation of the fit s_f .

$$\Delta_{\text{dil}}H = an_3(x_i - x_f) + bn_3(x_i^2 - x_f^2) \quad (1)$$

The molar enthalpy of dilution of aqueous 1,2-BD solution having a mole fraction x to $x=0$ can be obtained by Eq. (2) with the parameters a and b listed in Table 2 along with the values of 2-propanol and 1-hexanol.

$$\Delta_{\text{dil}}^\infty H_m = ax + bx^2 \quad (2)$$

Enthalpy of transfer

The experimental enthalpies of mixing and the related quantities are summarised in Table 3. The average val-

Table 1 Experimental enthalpies of dilution $\Delta_{\text{dil}}H$ of dilute aqueous 1,2-butanediol solutions with water at 298.15 K

$10^6 n_3$ mol	$10^3 x_i$	$10^4 x_f$	$\Delta_{\text{dil}}H/\text{mJ}$
2.4732	2.825	5.918	20.8
2.4730	2.524	4.976	15.0
2.4568	2.245	4.434	15.0
2.4306	1.891	3.749	10.7
2.3686	1.603	3.175	9.0
2.0542	1.321	2.620	6.6
1.8147	1.008	2.000	5.5

Table 2 Parameters a and b and the calculated standard deviations of the fit S_f for least-squares representation by equation of $\Delta_{\text{dil}}H_m$ for dilute aqueous solutions of alcohols at 298.1 K

Alcohol	$a/\text{kJ mol}^{-1}$	$b/\text{kJ mol}^{-1}$	S_f/mJ
2-propanol	-15.24	-967.6	2.4
1,2-butanediol	-104.9	-12.8	1.8
1-hexanol	-623.7	23220	1.6

ues of $z = (n_1' + n_1'')/n_2$ were 1302 ± 93 , 4953 ± 41 and 5223 ± 162 respectively, for 2-propanol, 1,2-BD and 1-hexanol. Here n_1' and n_1'' mean the amounts of water in the CD solution and in the alcohol solution, respectively. The experimental enthalpies of transfer of 1,2-BD from dilute aqueous solutions to dilute aqueous α -CD solutions determined by Eq. (3) are also summarized in the last column of Table 3. In the calculation through Eq. (3), the enthalpy of dilution of aqueous 1,2-BD solution, $\Delta_{\text{dil}}H_{13}$, was determined by Eq. (2) with the parameters given in Table 2. Those of α -CD solution, $\Delta_{\text{dil}}H_{12}$, were obtained from our earlier papers [5].

$$\Delta_{\text{trf}}H = \Delta_{\text{mix}}H - \Delta_{\text{dil}}H_{12} - \Delta_{\text{dil}}H_{13} \quad (3)$$

For the equilibrium of a 1:1 complex formation given in Eq. (4)



the molar ratio y of 1,2-BD included in the cavities over the total 1,2-BD in the solution is given by Eq. (7):

$$\begin{aligned} y &= n_4/n_3 \\ z &= n_1/n_2 \\ f &= n_3/(n_2 + n_3) \end{aligned} \quad (5)$$

$$K = \frac{a_4}{a_2 \cdot a_3} =$$

$$\left(\frac{n_4}{n_1 + n_2 + n_3 - n_4} \right) \quad (6)$$

$$= \frac{\left\{ \left(\frac{n_2 - n_4}{n_1 + n_2 + n_3 - n_4} \right) \left(\frac{n_3 - n_4}{n_1 + n_2 + n_3 - n_4} \right) \right\}}{y = \frac{1}{2} + \frac{1-f}{2f} + \frac{(1-f)z}{2f(1+K)} - \sqrt{\left\{ \frac{1}{2} + \frac{1-f}{2f} + \frac{(1-f)z}{2f(1+K)} \right\}^2 - \frac{(1-f)K}{f(1+K)}}} \quad (7)$$

where n_1 , n_2 , n_3 , and n_4 mean, respectively, the amounts of water, CD, 1,2-BD and 1:1 complex in the aqueous solution. Since the molar enthalpy of transfer of 1,2-BD is proportional to y , an experimental function and a theoretical one are equivalent as shown in Eq. (8):

Table 3 Experimental enthalpies of mixing $\Delta_{\text{mix}}H$ and molar enthalpies of transfer $\Delta_{\text{trf}}H_m$ of 2-propanol and 1,2-butanediol from dilute aqueous solutions to dilute aqueous α -cyclodextrin(CD) solutions at 298.15 K, where n_1' , n_1'' , n_2 and n_3 represent respectively amounts of water in the CD solution, amounts of water in the 2-propanol and 1,2-butanediol solutions, amounts of CD in the aqueous solution and amounts of 2-propanol and 1,2-butanediol in the aqueous solutions

f^a	$10^2 n_1'/\text{mol}$	$10^2 n_1''/\text{mol}$	$10^5 n_2/\text{mol}$	$10^6 n_3/\text{mol}$	$\Delta_{\text{mix}}H/\text{mJ}$	$\Delta_{\text{trf}}H_m/\text{kJ mol}^{-1}$
H ₂ O(1)+ α -CD(2)+2-propanol(3)						
0.0845 ₆	16.001	4.210	15.947	14.730	3.60	-0.35
0.1763 ₂	16.523	4.519	16.467	35.250	-1.70	-0.31
0.2639 ₈	15.946	4.141	14.251	51.113	-1.21	-0.14
0.2731 ₆	16.668	4.106	16.612	62.430	-9.31	-0.27
0.3001 ₈	16.377	3.962	16.322	70.010	-9.39	-0.23
0.3643 ₃	16.605	4.387	16.549	94.850	-21.4	-0.29
0.3919 ₈	16.482	4.010	16.427	105.90	-18.0	-0.21
0.4045 ₃	16.631	4.264	16.575	112.60	-13.1	-0.16
0.4978 ₈	16.403	4.248	16.348	162.10	-31.8	-0.19
0.7803 ₃	14.182	4.681	12.333	438.10	-116	-0.09
H ₂ O(1)+ α -CD(2)+1,2-butanediol(3)						
0.1740 ₉	13.124	3.307	3.327	0.7013	-6.95	-1.03
0.2033 ₅	13.135	3.377	3.330	0.8509	-7.95	-0.96
0.2411 ₄	13.233	3.537	3.354	1.066	-10.2	-0.97
0.3110 ₃	13.209	3.595	3.348	1.512	-13.8	-0.90
0.4047 ₁	13.130	3.335	3.328	2.263	-19.3	-0.81
0.5286 ₂	13.379	3.276	3.391	3.803	-29.5	-0.69
0.6053 ₇	13.257	3.233	3.361	5.155	-29.8	-0.45
0.6969 ₆	13.222	3.259	3.352	7.709	-47.6	-0.43
H ₂ O(1)+ α -CD(2)+1-hexanol(3)						
0.0941 ₆	15.836	4.322	3.849	0.4001	-69.52	-17.44
0.1452 ₅	16.133	4.199	3.971	0.6748	-116.8	-17.30
0.1857 ₆	16.026	4.152	3.560	0.8122	-130.9	-16.06
0.2007 ₈	16.371	4.361	4.005	1.006	-162.8	-16.12
0.2427 ₀	16.205	4.269	3.932	1.260	-203.5	-16.04
0.2682 ₀	15.893	4.276	4.019	1.473	-234.6	-15.80
0.2998 ₁	16.079	4.296	3.902	1.671	-258.2	-15.29
0.3025 ₉	15.862	4.129	3.836	1.664	-261.4	-15.53
0.3395 ₂	16.131	4.191	3.913	2.012	-306.6	-15.02
0.3621 ₂	16.291	4.203	3.894	2.211	-330.0	-14.68
0.3659 ₁	16.041	4.183	3.934	2.270	-336.5	-14.57

$$^a f = n_3 / (n_2 + n_3)$$

$$100 \Delta_{\text{trf}} H_m(z, f) / \Delta_{\text{trf}} H_m^\infty = \quad (8) \quad r = \sum_i [(100 / \Delta_{\text{trf}} H_m^\infty) \Delta_{\text{trf}} H_m(z_i, f_i) - Y(K, z_i, f_i)]^2 (10)$$

$$\stackrel{\text{def}}{=} 100 y / y_{\text{max}} = Y(K, z, f)$$

where

$$y_{\text{max}} \stackrel{\text{def}}{=} \lim_{f \rightarrow 0} y = K / (1 + z + K) \quad (9)$$

Thus, the best-fit values of K and $\Delta_{\text{trf}} H_m^\infty$ can be obtained by the least-squares calculation of Eq. (10):

These quantities thus determined are summarised in Table 4. The smoothed values of $\Delta_{\text{trf}} H_m$ for the mean values of z are drawn in Fig. 1 vs. the mole fraction f . The molar enthalpies of transfer of 1,2-BD, 2-propanol and 1-hexanol were all negative. Enthalpic stabilization accompanied by the transfers of 2-propanol is smaller than that of 1-propanol.

Table 4 Equilibrium constants for the formation of 1:1 inclusion complexes, ratios of water molecules over the cyclodextrin molecules, limiting molar enthalpies of transfer of alcohol, and the limiting molar ratios y_{max} of 1-heptanol included to the whole at 298.15 K

System	$\log_{10} K$	z	$\Delta_{\text{trf}} H_m^\infty / \text{kJ mol}^{-1}$	y_{max}
α -CD+2-propanol	3.37 \pm 0.66	1302 \pm 93	-0.29 \pm 0.06	0.640 \pm 0.06
α -CD+1,2-butanediol	4.41 \pm 0.29	4953 \pm 41	-0.98 \pm 0.07	0.838 \pm 0.00 ₁
α -CD+1-hexanol	3.89 \pm 0.07	5223 \pm 162	-17.38 \pm 0.30	0.587 \pm 0.01

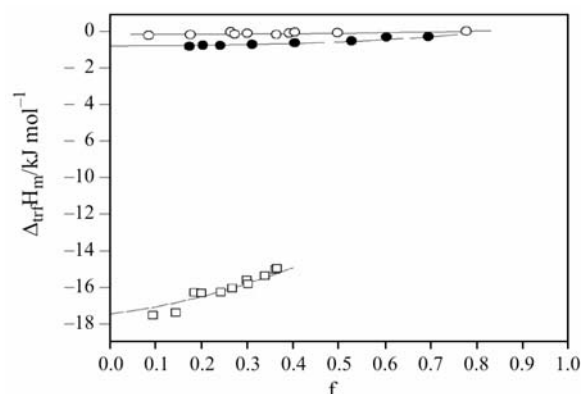


Fig. 1 Molar enthalpies of transfer of ○ – 2-propanol, ● – 1,2-butanediol and □ – 1-hexanol from aqueous to aqueous α -CD solutions at 298.15 K as a function of $f=n_3/n_2+n_3$

Enthalpy and entropy of inclusion

From the thermodynamic functions listed in Table 4, the molar enthalpies, molar Gibbs energies and molar entropies of inclusion of 1,2-BD, 2-propanol and 1-hexanol at infinite dilution into α -CD cavities in aqueous solutions at 298.15 K under the atmospheric pressure were determined and are summarised in Table 5, as well as the reported values [5, 6] for the sake of comparison. The enthalpy changes on inclusion of butanediol isomers in aqueous solutions determined for α -CD are exothermic and small. The molar entropy of inclusion of 1,2-butanediol to α -CD is largest among butanediol isomers. Due to intramolecular hydrogen bonds of 1,2-butanediol are weak, hydroxyl groups of 1,2-butanediol form intermolecular hydrogen bonds with water molecules easily, and molecular motion of 1,2-butanediol in aqueous solutions may be restricted. As a result, the molar entropies of inclusion

of 1,2-butanediol from aqueous solution to aqueous α -CD solutions are increased largely. Molecules of 1-hexanol are stabilized largely on inclusion into α -CD cavities in aqueous solution, accompanying a large entropy decrease.

Hydration Gibbs energies of inclusion compounds of cyclodextrin

The thermodynamic functions of inclusion indicate the difference in enthalpy, etc., between the guest molecules in aqueous solutions and the guest molecules in aqueous CD solutions. To clarify stabilities of inclusion complexes in aqueous solutions, hydration Gibbs energies calculation of inclusion complex of CD-alcohol were performed by using CONLEX 5.2 [12] program with the MMFF94s force field in the generalized born/surface area (GB/SA) model [13]. This program has the following feature; the lowest energy conformer does not depend on the initial structure that user input [14]. The hydration Gibbs energy in the GB/SA model can be expressed by using the following Eq. (11),

$$\Delta_{\text{hyd}}G = \Delta_{\text{non-pol}}G + \Delta_{\text{pol}}G \quad (11)$$

where $\Delta_{\text{non-pol}}G$ is GB/SA non-polarization energy, and $\Delta_{\text{pol}}G$ is GB/SA polarization energy. The hydration Gibbs energies of inclusion compounds were decided, by calculating the mean value of all conformations with existence probability of 1% or more. These quantities thus determined are summarized in Table 6. The largest stabilization in Gibbs energy is obtained by the hydration of α -CD-1,2-butanediol complex among α -CD-butanediol isomers complexes. For the case of 1,2-butanediol, hydroxyl groups of 1- and 2-positions may expose to water molecules. The

Table 5 The changes of thermodynamic functions on 1:1 inclusion of simple alcohols into α -cyclodextrin cavities in dilute aqueous solutions at 298.15 K

Alcohol	$\Delta_{\text{inc}}H/\text{kJ mol}^{-1}$	$\Delta_{\text{inc}}G/\text{kJ mol}^{-1}$	$-T\Delta_{\text{inc}}S/\text{kJ mol}^{-1}$	$\Delta_{\text{inc}}S/\text{J K}^{-1} \text{mol}^{-1}$
Methanol[6]	0	–	–	–
Ethanol[6]	– 0.9	–22.0	–21.0	70.5
1-Propanol[6]	– 6.6	–17.8	–11.2	37.5
1-Butanol[6]	– 7.9	–22.6	–14.7	49.5
1-Pentanol[6]	–13.9	–24.4	–10.4	34.9
1-Hexanol	–29.1	–22.2	6.9	–23.2
1-Heptanol[6]	–34.6	–25.0	9.6	–32.2
2-Propanol	– 0.5	–19.2	–18.8	62.9
1,2-Butanediol	– 1.1	–25.2	–24.0	84.4
1,3-Butanediol[5]	– 1.3	–24.0	–22.7	76.1
1,4-Butanediol[5]	– 2.1	–23.0	–21.0	70.3
2,3-Butanediol[5]	– 1.1	–21.6	–20.5	68.8

Table 6 Hydration Gibbs energies of inclusion complexes

Compounds	$\Delta_{\text{pol}}G/$ kJ mol ⁻¹	$\Delta_{\text{no-pol}}G/$ kJ mol ⁻¹	$\Delta_{\text{hyd}}G/$ kJ mol ⁻¹
α -CD+methanol	-209.3	11.7	-197.6
α -CD+ethanol	-201.3	10.8	-190.5
α -CD+1-propanol	-199.1	10.5	-188.6
α -CD+1-butanol	-194.3	10.9	-183.4
α -CD+1-pentanol	-186.8	10.3	-176.5
α -CD+1-hexanol	-192.5	11.1	-181.4
α -CD+1-heptanol	-199.6	11.8	-187.8
α -CD+2-propanol	-193.7	10.9	-182.8
α -CD+1,2-butanediol	-213.4	10.8	-202.6
α -CD+1,3-butanediol	-208.3	12.3	-196.0
α -CD+1,4-butanediol	-204.8	9.7	-195.1
α -CD+2,3-butanediol	-204.1	13.2	-190.9

stabilization in Gibbs energy is obtained by the hydration of α -CD-2-propanol complex is smaller than that of α -CD-1-propanol complex. The stabilization in enthalpy is obtained by the inclusion of 2-propanol into α -CD is smaller than that of 1-propanol into α -CD. It is thought that there is a difference in these thermodynamic function values because of the following two phenomena: 1) When hydroxyl group of 2-propanol is out of the wider rim of the CD cavity, one of the methyl group of 2-propanol also will be exposed to water molecules. 2) The hydrophobic group of 1-propanol remains in the α -CD cavity though the hydroxyl group of 1-propanol is out of the wider rim of the CD cavity.

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