CALORIMETRIC DETERMINATION OF ENTHALPIES,GIBBS ENERGIES,AND ENTROPIES OF INCLUSION OF SOME ALCOHOLS INTO α- AND β-CYCLODEXTRINS IN AQUEOUS SOLUTIONS[†]

Sadao Takagi and Mune Maeda
Department of Chemistry, Faculty of Science and
Technology, Kinki University
3-4-1 Kowakae,Higashi-osaka,Osaka 577
Japan

ABSTRACT. The enthalpies of transfer of cyclohexanol from aqueous to aqueous α- or β-cyclodextrin solutions have been measured at various mole fractions at 298.15 K on a rocking twin-microcalorimeter of heat-conduction type and the molar enthalpies,Gibbs energies, and entropies of inclusion in the aqueous solutions have been determined by the method proposed by the authors [*Netsu Sokutei* 10,103(1983)] ,to elucidate the "driving force" of the molecular inclusion. Discussions are given for all the systems obtained by the authors, concluding that the "driving force" is the enhancement of the entropy.

1. INTRODUCTION

Making clear the role of asymmetric intermolecular interactions due to the stereospecific structures of molecules is really significant for understanding the mechanisms of reactions in chemistry and biochemistry. The senior author measured the enthalpies of mixing aqueous solutions of some D- and L-optical isomers earlier with Amaya and found that measurable amounts of heats of mixing were obtained even in aqueous media.[1] For the molecular inclusion phenomena also the stereospecific structures of molecules concerned must play important roles.

The main aims of this investigation were to get quantitative answers to the following questions on the basis of reliable values of the thermodynamic functions:
(1) What is the "driving force" for the molecular inclusion of some simple alcohols into the cavities of α-cyclodextrin (α-CD) and β-CD in aqueous solutions ? (2) How do the alcohol molecules distinguish between their circumstances in the cavities of CD's and bulk water energetically and entropically ? (3) How do the CD cavities recognise the differences of molecular structures of alcohols in water ?

The present paper reports the experimental procedures and new results of the determination of the enthalpies, the Gibbs energies, and the entropies of inclusion of cyclohexanol into the cavities of α-CD and β-CD

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in aqueous solutions at 298.15 K. Discussions are also given with all the systems which have been studied by the authors.[2-5] Those include methanol,1-propanol,1-pentanol,2-propanol,and cyclohexanol.

2. MATERIALS AND METHODS

Cyclohexanol produced by Tokyo Kasei Kogyo Co.,Ltd.,guaranteed reagent, was dried with calcium oxide and fractionally distilled twice through a spinning-band column under reduced pressure. The final purity obtained by g.l.c.[6] was 99.55 mass per cent,except water, and the water content obtained by Karl Fischer titration was 0.24 mass per cent.

α- and β-CD's,guaranteed reagents with assay certificates,produced by Hayashibara Biochemical Laboratories,Inc.,were carefully purified. The purities of final products were 99.8 – 99.4 per cent (α-CD) and 100 – 99.7 per cent (β-CD),respectively.[5] Most of the impurities were thought to be moisture.

Details of the careful purification used for the α-CD,[2,5] β-CD,[3,5] distilled water,[6,7] and mercury[6] have been described elsewhere. All solutions were prepared by mass and corrected for the water content of the cyclohexanol.

The measurements of enthalpies of mixing aqueous alcoholic solutions and aqueous CD solutions at 298.15 K were carried out on a rocking twin-microcalorimeter of a heat-conduction type (laboratory designation RMC-II).[8] Circulating water was controlled at 298.15 K within ± 0.0005 K in a room thermostatted within ± 0.01 K. In each run about 3.0 g of aqueous CD solution and about 0.75 g of aqueous cyclohexanol solution were loaded. The rocking was carried out ten times in each run.
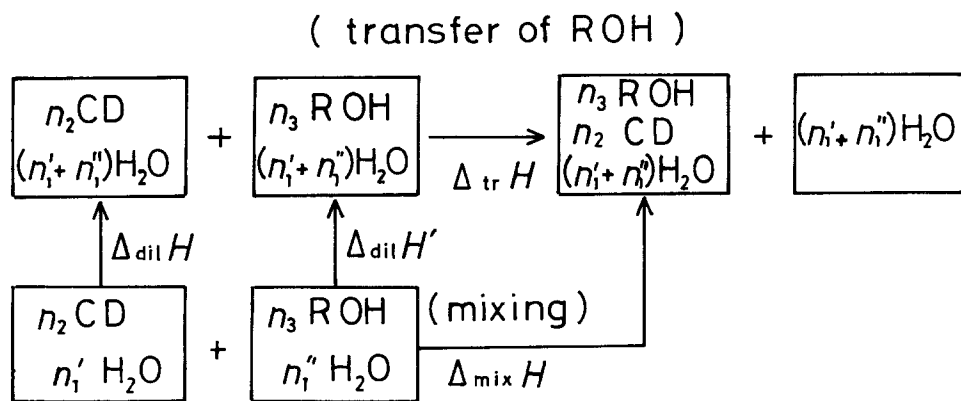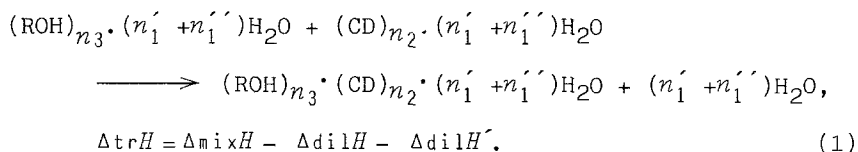
(transfer of ROH)

Figure 1.   The thermochemical cycle for the enthalpy of transfer.

The method for obtaining the enthalpy of inclusion was as follows. (1)The enthalpies of mixing $\Delta_{mix}H$ of dilute aqueous solutions were measured at various mole fractions $f=n_3/(n_2+n_3)$,by keeping $z=(n_1'+n_1'')/n_2$ constant. (2)According to the thermochemical cycle shown in Fig.1,the enthalpies of transfer $\Delta_{tr}H$ of cyclohexanol from aqueous to aqueous CD so-

lutions were determined by Eq(1), for the corresponding mole fractions f,

$$(ROH)_{n_3} \cdot (n_1' + n_1'')H_2O + (CD)_{n_2} \cdot (n_1' + n_1'')H_2O$$

$$\longrightarrow (ROH)_{n_3} \cdot (CD)_{n_2} \cdot (n_1' + n_1'')H_2O + (n_1' + n_1'')H_2O,$$

$$\Delta_{tr}H = \Delta_{mix}H - \Delta_{dil}H - \Delta_{dil}H'. \tag{1}$$

by using the enthalpies of dilution $\Delta_{dil}H$ and $\Delta_{dil}H'$ already reported.[2, 3, 6] (3)The equilibrium constant K of the formation of 1:1 inclusion compound and the limiting molar ratio of the cyclohexanol included y_{max} and the limiting molar enthalpy of transfer $\Delta_{tr}H_m^\infty$ at $f \approx 0$ were determined according to the procedures proposed earlier by the present authors.[4] The molar enthalpy of inclusion $\Delta_{inc}H_m$ of cyclohexanol into CD cavities in aqueous solution was obtained by

$$\Delta_{inc}H_m = \frac{\Delta_{tr}H_m^\infty}{y_{max}} \tag{2}$$

3. RESULTS

The experimental enthalpies of mixing and the related quantities are summarised in Table I. The values of z were 4666 and 5243 for α-CD and β-CD systems,respectively. The experimental enthalpies of transfer were determined by the method mentioned above and the molar values of them are listed in Table I. From these experimental values of $\Delta_{tr}H_m$ as a function of f, $\Delta_{tr}H_m^\infty$, y_{max},and K were determined by the successive approximation to K with least squares calculations.[4] Residuals of $\Delta_{tr}H_m$(obs) over the $\Delta_{tr}H_m$(calc) are given in the last column of Table I and the standard deviations s are given in Table II as well as K, $\Delta_{tr}H_m^\infty$,and y_{max}. The relative values of the enthalpies of transfer $\Delta_{tr}H_m / \Delta_{tr}H_m^\infty$ are plotted against f in Fig.2,where the solid lines are the smoothed values obtained. Agreements between them are good. The molar enthalpies of inclusion determined for the present systems are listed in Table III as well as those determined earlier.

4. DISCUSSIONS

The molar Gibbs energies and the molar entropies of inclusion of the alcohol at 298.15 K were evaluated through Eqs.(3) and (4).

$$\Delta_{inc}G_m = -RT\ln K \tag{3}$$

$$\Delta_{inc}S_m = \frac{\Delta_{inc}H_m - \Delta_{inc}G_m}{T} \tag{4}$$

They are listed in Table III as well as all of those obtained already.
    From Table III we can conclude that for all the systems studied,the "driving force" of the formation of the 1:1 inclusion complex in aqueous

Table I Experimental enthalpies of mixing $\Delta_{mix}H$, enthalpies of transfer $\Delta_{tr}Hm$, and deviation of $\Delta_{tr}Hm$'s at 298.15 K: f, $n_3/(n_2+n_3)$; n'_1, the amount of water in aqueous CD solution; n''_1, the amount of water in aqueous alcoholic solution; n_2, the amount of CD in solution; n_3, the amount of alcohol in solution

f	n'_1	$10^2 n''_1$	$10^4 n_2$	$10^4 n_3$	$10^{-1}\Delta_{mix}H^a$	$\Delta_{tr}Hm$	$\delta(\Delta_{tr}Hm)$
	mol	mol	mol	mol	mJ	kJ·mol^{-1}	kJ·mol^{-1}
			Cyclohexanol(3) + α-CD(2) + H$_2$O(1)				
0.04011	0.16805	4.361	0.4630	0.01935	-1.17	-6.4_0	-0.4_7
0.07559	0.16907	4.597	0.4658	0.03809	-1.98	-5.3_8	0.4_9
0.1289	0.16560	4.398	0.4563	0.06755	-4.0_2	-6.0_4	-0.2_4
0.1646	0.16755	4.480	0.4616	0.09097	-5.1_0	-5.6_6	0.0_7
0.2656	0.16379	4.476	0.4513	0.1632	-8.1_9	-5.0_2	0.4_8
0.3668	0.17081	4.162	0.4032	0.2336	-12.9	-5.4_9	-0.5_0
0.3693	0.16425	4.719	0.4525	0.2649	-13.5	-5.0_7	0.0_9
0.5059	0.16533	4.278	0.4555	0.4664	-19.5	-4.0_9	0.3_8
0.6281	0.16501	3.876	0.4546	0.7677	-28.3	-3.5_3	-0.0_3
			Cyclohexanol(3) + β-CD(2) + H$_2$O(1)				
0.08327	0.16598	4.368	0.3984	0.03619	-2.06	-5.6_8	-0.0_9
0.1425	0.16678	4.332	0.4003	0.06654	-3.68	-5.5_1	0.0_0
0.1816	0.16533	4.336	0.3968	0.08804	-4.9_3	-5.5_8	-0.1_2
0.2901	0.16375	4.406	0.3930	0.1606	-8.5_9	-5.3_1	-0.0_8
0.3672	0.16884	4.189	0.4052	0.2351	-11.6	-4.8_7	0.1_5
0.5305	0.16225	4.036	0.3894	0.4400	-18.1	-4.0_1	0.1_2
0.6798	0.16325	4.200	0.3918	0.8318	-23.3	-2.64	0.1_4

^{a} Corrected for the enthalpies of wetting.

Table II Equilibrium constants for the formation of 1:1 inclusion compounds, the limiting molar enthalpies of transfer of cyclohexanol, and the limiting molar ratios y_{max} of cyclohexanol included at 298.15 K

system	$\log_{10}K$	$\dfrac{\Delta_{tr}Hm^{\infty}}{kJ\cdot mol^{-1}}$	s^a	y_{max}
cyclohexanol + α-CD	4.16	-5.9_4	0.3_6	0.756
cyclohexanol + β-CD	4.36	-5.6_8	0.11	0.814

$^a s = \{(\Sigma\delta^2)/N\}^{1/2}$

solution is the enhancement of entropy. When fitting of the hydrophobic part of an alcohol molecule with a cavity is favourable, energetical sta-
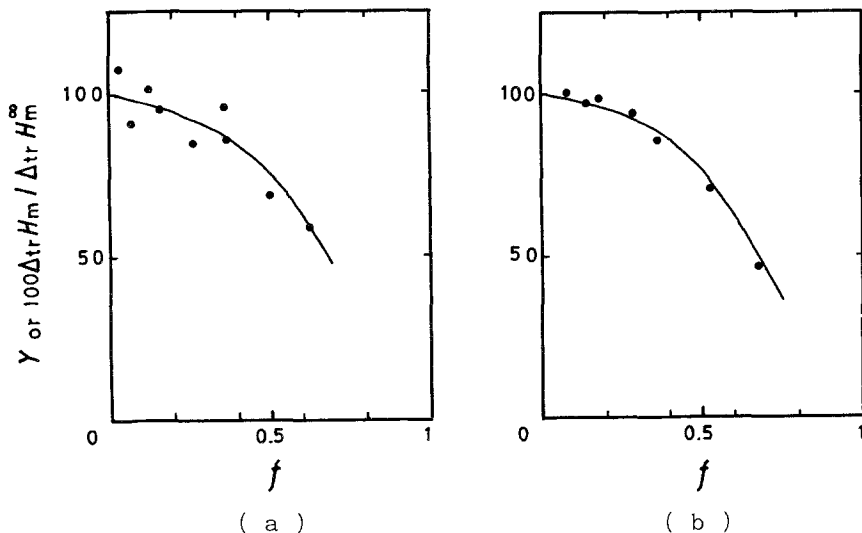
(a)   (b)

Figure 2. Comparison of the smoothed values(——) with the experimental values($\cdot$) for (a)cyclohexanol + α-CD and (b)cyclohexanol + β-CD at 298.15 K: Y means the theoretical function evaluated by the least aquares calculation.[4]

bilisation also promotes the formation of the complex. When fitting is loose,however,enthalpy change is endothermic. The molecular inclusion of 1-propanol,2-propanol,and 1-pentanol with β-CD and probably those of methanol with α-CD and β-CD are caused by merely the increase of entropy in aqueous solution. (The crystal structures of 1:1 inclusion complexes

Table III The molar values of the thermodynamic functions of inclusion in aqueous solutions at 298.15 K

guest	$\dfrac{\Delta_{inc}H_m}{kJ \cdot mol^{-1}}$	$\dfrac{\Delta_{inc}G_m}{kJ \cdot mol^{-1}}$	$\dfrac{-T\Delta_{inc}S_m}{kJ \cdot mol^{-1}}$	$\dfrac{\Delta_{inc}S_m}{J \cdot (K \cdot mol)^{-1}}$
(α-CD)				
methanol	0	——	——	——
1-propanol	−6.6	−17.8	−11.2	37.5
1-pentanol	−13.9	−24.4	−10.4	34.9
2-propanol	−0.4	−19.2	−18.8	63.0
cyclohexanol	−7.9	−23.8	−15.9	53.3
(β-CD)				
methanol	0	——	——	——
1-propanol	1.9	−17.5	−19.4	65.0
1-pentanol	2.2	−22.6	−24.8	83.2
2-propanol	1.2	−19.7	−20.9	70.1
cyclohexanol	−7.0	−24.9	−17.9	60.1

of methanol with α–CD[9] and β–CD[10] have been reported and their crystals
are obtained from corresponding aqueous solutions.) These arise from the
ordered nature of liquid water, especially the destruction of hydrophobic
hydration.

Inspection of the molecular fit   by the use of CPK precision
molecular models (Ealing Scientific) showed that the best fitting was
obtained for 1-pentanol with the cavity of α–CD and there were complete
parallelism between the fit   and the decrease in enthalpy on inclusion.
For the cases of larger cavities than the hydrophobic parts of alcohols,
energetical stabilisation due to van der Waals' forces between the alco-
hol molecules and the inner walls of the cavities may not cancel the en-
thalpy increase required for the destruction of hydrophobic hydration
around the alcohol molecules in aqueous solutions.[4] Other contributions
due to the liberation of high enthalpy-water molecules from the cavity (
exothermic contribution) and disappearance of the distorted molecular
structure of CD (endothermic)[11] will be discussed subsequently. Methanol
molecules seem not to distinguish energetically between their circum-
stances in the cavities of CD's and bulk water, presumably because they
have the "structure-making" CH_3– groups only as hydrophobic radicals.[2]

Main sources of the increase in entropy may be also the destruction
of the hydrophobic hydration and an increase in the freedom of molecular
motion, rotational and so-called configurational, of alcohols in the cavi-
ties. The large increments of entropy with β–CD suggest the enhanced con-
tribution of the latter and the additional increments in so-called commu-
nal entropy accompanied by the exchange of included water molecules for
an alcohol molecule.

Characteristics of a series of these works are: (1) the thermodynamic
functions were determined by direct microcalorimetric measurements at (2)
merely one fixed temperature, (3) on the systems $CD + ROH + H_2O$ which con-
tained no other substance except the surface of purified metallic mercury,
and (4) the systems were selected systematically.

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