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On The Relationship of The Enthalpies of Inclusion by Cyclodextrins And The Interaction Energies

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The enthalpies of transfer of ethanol from aqueous to aqueous α - or β -cyclodextrin (CD) solutions have been determined by microcalorimetry at various mole fraction at 298.15 K. The molar enthalpy of ethanol with α -CD was negative, whereas that with the α -CD system was positive. In order to clarify the major contribution of the interaction energy of CD's and guest molecules, the dispersion energies were determined using dispersion-corrected density functional theory calculations. In the case of α -CD, the dispersion energies increase with an increase in the number of carbon atoms of the guest molecules.

Keywords: Microcalorimetry; Molecular Recognition; cyclodextrin; DFT-d: dispersion energy

1. Introduction

Molecular recognition and discrimination may be caused by interactions involving contact among molecules through their collisions in solutions and mixtures. In particular, stereospecific interactions arising from the presence of neighboring surfaces may play an important role in, for example, enzyme-substrate reactions, antigen-antibody reactions, and certain mechanisms of the senses of smell and taste. Therefore, elucidating the role of asymmetric intermolecular interactions characteristic to the stereospecific structures of molecules is of prime importance for understanding the mechanisms of chemical and biochemical reactions.

Accurate and quantitative measurements of the changes in thermodynamic functions upon molecular inclusion form a basic requirement 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 molecules into cyclodextrin (CD) cavities in aqueous solutions¹⁻⁶.

In this study, the molar enthalpies, entropies, and Gibbs energies of inclusion of ethanol into α - and β -CD cavities at 298.15 K in dilute aqueous solutions were determined at 298.15 K. Our aim was to confirm the major contribution of the interaction energy of CD's and guest molecules. The dispersion energies were calculated using dispersion-corrected density functional theory (DFT) calculations because the second-order Møller-Plesset perturbation (MP2) calculation was а resource-intensive computation. The relationship between the enthalpy of inclusion, which was determined through microcalorimetry, and the dispersion energy were discussed.

2. Experimental

2.1 Materials

(Kishida Chemical Co., S.R. grade Ethanol for chromatography) was passed through a 1 m column packed with The water contents analyzed by a Karl-Fischer Helipac. titration were 0.01 for ethanol, in mass percent. The gas-liquid chromatography (g.l.c.) results obtained from a Hitachi Model 163 gaschromatograph by using a 3 m column (3 mm) of Thermon-1000 (10 %) and H_3PO_4 (1 %) on Chromosorb W (80 to 100 mesh) supplied by Wako Pure Chemical Ind., Ltd. with FID showed that the purity of the alcohols was 99.95 mass percent ethanol after excluding water. The water content obtained from the analyses involving Karl-Fischer titrations was the value of ethanol in mass percent. Details on the methodical purification used for α -CD¹, β -CD², and water⁷ have been described elsewhere. All the solutions were prepared by mass.

2.2 Apparatus and Procedures

A rocking twin-microcalorimeter of the heat-conduction type, with the laboratory designation RMC, was used for the determination of the enthalpies of dilution and mixing. All the measurements were carried out at 298.15 K under the ambient atmospheric pressure. Enthalpy changes were measured automatically with an online system described elsewhere⁸⁾.

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Details pertaining to the apparatus and procedures, including the mixing vessels, are similar to those described previously³⁻⁴).

3. Results and Discussion

3.1 Enthalpy of Dilution

The experimental results for the enthalpy changes on diluting the dilute aqueous ethanol solutions ranging from 2.1×10^{-3} to 1.3×10^{-2} mole fraction value to final solutions ranging from 1.0×10^{-3} to 6.4×10^{-3} mole fraction value at 298.15 K under the ambient atmospheric pressure are given in Table 1. In the table, n_3 denotes the amount of ethanol in the solutions and x_i and x_f respectively denote the mole fractions before and after the dilution. The results were fitted to eq. (1) by a least-squares calculation.

$$\Delta_{\rm dil}H = an_3(x_{\rm i} - x_{\rm f}) + bn_3(x_{\rm i}^2 - x_{\rm f}^2) + \cdots$$
(1)

The molar enthalpy of dilution of an aqueous ethanol solution having a mole fraction varying from x to 0 can be obtained by eq. (2) with the parameters a and b listed in Table 2.

$$\Delta_{\rm dil}^{\ \ \infty} H_{\rm m} = ax + bx^2 \tag{2}$$

Once an explicit expression for eq. (2) is obtained, the enthalpy of dilution per mole of alcohol from x_i to x_f may be calculated through the equation

$$\Delta_{\rm dil}H_{\rm m} = \Delta_{\rm dil}{}^{\infty}H_{\rm m}(x_{\rm i}) - \Delta_{\rm dil}{}^{\infty}H_{\rm m}(x_{\rm f}) \tag{3}$$

Table 1 Experimental enthalpies of dilution Δ dilH of dilute aqueous ethanol solutions with water at 298.15 K

10^4_{n3} mol	$10^{3}x_{i}$	$10^3 x_{\rm f}$	$-\Delta_{\rm dil}H/{ m mJ}$
7.0829	12.89	6.362	-106. ₃
4.8818 4.5844	8.780 8.154	4.423 4.029	-49. ₁ -43. ₅
4.0700	7.334	3.612	-34.9
3.3189 3.2343	6.729 5.769	3.254 2.892	-26.5 -21.4
2.2336	3.879	1.965	-9.8
1.5059 1.3484	2.584 2.381	1.311 1.178	-4. ₅ -3. ₉
1.1487	2.067	1.017	-2.8

Table 2 Parameters a and b and the calculated standard deviations of the fit $S_{\rm f}$ for least-squares representation by equation of $\Delta_{\rm dil}H_{\rm m}$ for dilute aqueous solutions of ethanol at 298.15K

Alcohol	$a / kJ mol^{-1}$	b / kJ mol ⁻¹	$S_{\rm f}/{\rm mJ}$	
ethanol	-23.0	-3.26	3.45	

3.2 Enthalpy of Transfer

The experimental enthalpies of mixing and the related quantities are summarized in Table 3. The average values of $z = (n_1' + n_1'')/n_2$ were 3071 ± 151 and 5452 ± 206 respectively, for α -CD + ethanol and for β -CD + ethanol. Here, n_1' and n_1'' represent the amounts of water in the CD solution and the alcohol solution, respectively. The experimental enthalpies of

the transfer of ethanol from dilute aqueous solutions to dilute aqueous α -CD solutions, as determined by eq. (4), are also summarized in the last column of Table 3. In the calculation with Eq. (4), the value of the enthalpy of dilution of an aqueous ethanol solution, $\Delta_{dil}H_{13}$, was determined by eqs. (2) and (3) using the parameters given in Table 2. The enthalpies of dilution of the α -CD solution and the β -CD solution, $\Delta_{dil}H_{12}$, were obtained from our earlier papers³⁻⁴⁾.

$$\Delta_{\rm trf} H = \Delta_{\rm mix} H - \Delta_{\rm dil} H_{12} - \Delta_{\rm dil} H_{13} \tag{4}$$

For the equilibrium of a 1:1 complex formation, as given in eq.

$$(CD)_{aq} + (ROH)_{aq} \stackrel{\rightarrow}{\leftarrow} (CD \cdot ROH)_{aq},$$
(5)

(5)

the molar ratio y of ethanol included in the cavities over the total ethanol in the solution is given by eq. $(6)^{3.4}$:

$$y = \frac{1}{2} + \frac{1-f}{2f} + \frac{(1-f)z}{2f(1+K)} - \sqrt{\left\{\frac{1}{2} + \frac{1-f}{2f} + \frac{(1-f)z}{2f(1+K)}\right\}^2 - \frac{(1-f)K}{f(1+K)}}$$
(6)

Where

$$y = n_4 / n_3, \ z = n_1 / n_2, \ f = n_3 / (n_2 + n_3),$$
 (7)

And

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

$$= \frac{\left(\frac{n_4}{n_1 + n_2 + n_3 - n_4}\right)}{\left\{\left(\frac{n_2 - n_4}{n_1 + n_2 + n_3 - n_4}\right)\left(\frac{n_3 - n_4}{n_1 + n_2 + n_3 - n_4}\right)\right\}}$$
(8)

Here n_1 , n_2 , n_3 , and n_4 represent the amounts of water, CD, ethanol, and the 1:1 complex in the aqueous solution, respectively. Since the molar enthalpy of the transfer of ethanol is proportional to *y*, the experimental and theoretical functions become equivalent, as given by eq. (9):

$$100\Delta_{\rm trf} H_m(z,f) / \Delta_{\rm trf} H_m^{\infty} = 100y / y_{\rm max} \stackrel{\rm def}{=} Y(K,z,f), \tag{9}$$

Where

$$y_{\max} \stackrel{\text{def}}{=} \lim_{f \to 0} y = K / (1 + z + K)$$
 (10)

Thus, the best-fit values of *K* and $\Delta_{\text{trf}} H_m^{\infty}$ can be obtained by the least-squares calculation given by eq. (11)³⁻⁴):

$$r = \sum_{i} \left[\left(100 / \Delta_{trf} H_m^{\infty} \right) \Delta_{trf} H_m(z_i, f_i) - Y(K, z_i, f_i) \right]^2$$
(11)

The quantities determined through these calculations are summarized in Table 4. The smoothed values of $\Delta_{trf}H_m$ for the mean values of *z* are plotted in Fig. 1 against the mole fraction *f*. The molar enthalpies of the transfer of ethanol were small, and they were negative for both α - and β -CD solutions.



Fig. 1 Molar enthalpies of transfer of ethanol from aqueous to aqueous α (\bullet)- and β (\bigcirc)-CD solutions at 298.15 K as a function of $f = n_3/(n_2 + n_3)$. The solid curve represents α -CD solutions. The dotted curve represents β -CD solutions.

3.3 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 ethanol at infinite dilution into α - and β -CD cavities in aqueous solutions at 298.15 K under the ambient atmospheric pressure were determined; they are summarized in Table 5 along with the reported values of the system of other normal alkane-1-ols. The molar enthalpy of ethanol with α -CD was negative, whereas that with the α -CD system was positive. The molar enthalpy of hexanol with α -CD was negative. The entropy changes that occur upon the 1:1 inclusion for the system of ethanol are positive and large. The changes in the enthalpy and entropy promote inclusion. The increase in entropy is an important factor for promoting inclusion in aqueous solutions. The large increase in entropy might be mainly because of the excessive motion of ethanol molecules in the cavities, in particular, the molecular rotation in the CD cavities and the breaking of the hydrophobic hydration structure of the alcohol molecules in bulk water.

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

Alcohol	$\Delta_{\rm inc} H$	$\Delta_{\rm inc}G$	$-T\Delta_{inc}S$	$\Delta_{inc}S$			
	$kJ \cdot mol^{-1}$	$kJ \cdot mol^{-1}$	$kJ \cdot mol^{-1}$	$J \cdot (K \cdot mol)^{\text{-1}}$			
	α	-cyclodextri	n				
Ethanol	-0.9	-21.5	-20.6	69.0			
1-Propanol ⁴	-6.6	-17.8	-11.2	37.5			
1-Butanol ⁴	-7.9	-22.6	-14.7	49.5			
1-Pentanol ⁴	-13.9	-24.4	-10.4	34.9			
1-Hexanol ⁵	-29.1	-22.2	6.9	-23.1			
β-cyclodextrin							
Ethanol	0.4	-24.1	-24.5	82.3			

3.4 Dispersion energy

In order to clarify the major contribution of the interaction energy of CD's and guest molecules, the dispersion energies were determined using dispersion-corrected density functional theory (DFT-d)⁹⁾ calculations. DFT calculations were performed using the Gaussian 09 program¹⁰⁾. The initial geometries of the complexes of CDs with ethanol, 1-propanol, 1-butanol, and 1-pentanol were obtained from the crystal structure reported in the literature¹¹⁾. We set a molecule of CD that included a hexanol molecule in the center of the cavity. The hexanol molecules had trans-trans (TT) and gauche-gauche (GG) conformations. Geometry optimization by DFT calculations was carried out at the B97D/6-31G* level in a gas phase. The gas phase geometries were optimized at the B97D/6-31G* level in water. Single point calculations were carried out at the B97D/cc-pvtz level in gas, and at B971/cc-pvtz level in water. The molecular interaction energies of compounds in water $\Delta E(AB)$ are calculated by the supermolecular method¹² as follows:

$$\Delta E(AB) = E(AB) - E(A) - E(B)$$
(12)

Here AB, A, and B are the inclusion compounds of CD + alcohol, CD, and alcohol in water, respectively. The dispersion forces⁹⁾ were calculated using eq. (13) and are listed in Table 6.

$$\Delta_{\text{dispersion}} E = \Delta_{B97D} E(AB) - \Delta_{B971} E(AB)$$
(13)

The interaction energy of α -CD with ethanol is larger than that of β -CD with ethanol. Similarly, the dispersion energy of α -CD with ethanol is larger than that of β -CD with ethanol. The ethanol molecules must deform their conformations to make the nearest contacts with the atoms on the wall of α -CD cavities, with those on the walls of β -CD cavities, and with the remaining water molecules in β -CD cavities. In the case of α -CD, the dispersion energies increase with an increase in the number of carbon atoms of the guest molecules. When the molecular length of pentanol is exactly suitable for the height of α -CD cavities, the pentanol makes the closest contacts with the atoms on the wall of α -CD cavities.

The dispersion energy of α -CD with a GG-conformer of hexanol is greater than that of α -CD with a TT-conformer of hexanol. The hexanol molecules are chiefly stabilized upon inclusion into α -CD cavities in an aqueous solution and accompanied with a large entropy reduction. To explain this phenomenon, we proposed that hexanol molecules accepted GG-conformations in the cavities instead of the general TT-conformations. Moreover, when 1-hexanol molecules accept a gauche-gauche conformation, OH groups are dispersed in the water. Such conformations may result in some tight inclusion complexes in which the hexanol molecules cannot rotate around the molecular axis.

References

- 1) M. Maeda and S. Takagi, *Nippon Kagaku Kaishi*, 188 (1983)
- 2) M. Maeda and S. Takagi, Netsu Sokutei, 10, 43 (1983)
- 3) S. Takagi, M. Fujisawa, and T. Kimura, *Thermochim. Acta*, **183**, 289 (1991)
- 4) M. Fujisawa, T. Kimura, and S. Takagi, *Nestu Sokutei*, **18**, 71 (1991)
- 5) S. Takagi, T. Kimura, and M. Fujisawa, *Chem. Express*, 6, 93 (1991)
- T. Kimura, S. Fujie, T. Yukiyama, M. Fujisawa, T. Kamiyama, H. Aki, J. Incl. Phenom. Macrocycl. Chem., 70, 269 (2011)
- 7) T. Kimura and S. Takagi, *J. Chem. Thermodyn.*, **11**, 119 (1979)
- 8) T. Kimura and S. Takagi, *Thermochim. Acta*, **123**, 293 (1988)
- S. Grimme, J. Antony, S. Ehrlich, and H Krieg, J. Chem. Phys. 132, 154104 (2010)
- Gaussian 09, Revision A.1, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman,

G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, (2009)

- 11) Cambridge Structural Data Base System, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road Cambridge CB 2 IEW, U.K. (2011)
- 12) G. Chalasinski, and , M.M. Szczeniak, Mol. Phys., 63, 205 (1988)

fa	$10^2 n_1'$	$10^2 n_1''$	$10^{5}n_{2}$	$10^5 n_3$	$\Delta_{ m mix} H$	$\Delta_{ m trf} H_m$
J	mol	mol	mol	mol	mJ	kJ mol ⁻¹
		$H_2O(1) + \alpha$	CD(2) + Eth	anol (3)		
$.1847_{4}$	16.204	4.240	6.839	1.550	-8.35	-0.62_{1}
.22372	16.455	4.189	6.038	1.740	-7.24	-0.467
.3417 ₈	16.158	4.286	7.207	3.742	-19.16	-0.53 ₈
.38870	16.556	4.344	6.782	4.313	-20.79	-0.495
.46214	15.939	4.314	6.687	5.745	-25.57	-0.445
0.5139_0	16.124	4.348	6.673	7.054	-32.49	-0.45_0
.55086	16.810	4.097	6.810	8.352	-31.36	-0.354
.59460	16.427	3.910	6.890	10.105	-36.21	-0.30_{2}
.5954 ₅	16.427	4.376	6.316	9.296	-30.59	-0.32_{2}
0.6771_0	16.421	4.201	6.582	13.801	-62.80	-0.40_{6}
.67377	16.509	4.259	6.678	20.444	-74.56	-0.28_4
.7817 ₆	16.471	4.180	6.875	24.626	-68.46	-0.17 ₆
.8323 ₆	16.373	4.189	6.774	33.632	-96.87	-0.14 ₆
		$H_2O(1) + \beta$	-CD(2) + Et	hanol (3)		
.1653 ₈	16.021	3.856	4.471	0.886	3.01	0.344
.18469	16.266	3.723	4.890	1.029	3.20	0.316
.2124 ₄	16.467	4.004	4.459	1.203	3.65	0.309
.2176 ₆	16.816	3.868	4.475	1.245	3.75	0.307
.30454	16.355	4.694	4.397	1.926	4.31	0.231
.38067	16.427	3.907	4.362	2.681	6.45	0.253
.4417 ₅	16.362	4.070	4.539	3.592	8.43	0.25_{1}
0.5340_0	16.277	3.995	4.287	4.913	8.75	0.20_{1}
.5863 ₆	16.421	3.852	4.606	6.529	8.14	0.15 ₆
.61007	16.128	4.006	4.192	6.559	8.17	0.155

Table 3 Experimental enthalpies of mixing Δ_{mix} \underline{H} and molar enthalpies of transfer Δ_{trt} \underline{H}_m of ethanol from dilute aqueous solutions to dilute aqueous α or β - cyclodextin (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 ethanol solutions,

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

16.266

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 ethanol, and the limiting molar ratios \underline{y}_{max} of ethanol included to the whole at 298.15 K

4.890

8.307

8.89

0.149

3.723

0.62945

system	$\log_{10}K$	Z	$\Delta_{ m trf} H^{\infty}{}_{ m m}$	<i>y</i> _{max}	
α -CD + ethanol	3.76	3071	-0.58_8	0.654	
β -CD + ethanol	4.23	4551	0.30_{7}	0.789	

Table 6 Dispersion energies of inclusion complexes

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system	$\frac{\Delta_{b97D}E}{k \mathrm{L} \cdot \mathrm{mol}^{-1}}$	$\frac{\Delta_{b971}E}{k \mathrm{I} \cdot \mathrm{mol}^{-1}}$	$\frac{\Delta_{dispersion}E}{\text{kI}\cdot\text{mol}^{-1}}$
	5 11	15 0	25.2
α -CD + ethanol	-51.1	-15.8	-35.5
β -CD + ethanol	-37.6	-15.0	-22.6
α -CD + 1-propanol	-46.8	6.3	-53.1
α -CD + 1-butanol	-72.0	-11.4	-60.6
α -CD + 1-pentanol	-112.6	-46.0	-66.6
α -CD + TT hexanol	-65.5	-23.3	-42.2
α -CD + GG hexanol	-70.2	-0.6	-69.6