

Enthalpy and entropy changes on molecular inclusion of pentane derivatives into α -cyclodextrin cavities in aqueous solutions

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Abstract In order to investigate the contribution of the hydrophilic parts of guest molecules of aliphatic compounds to the inclusion reaction, the thermodynamic properties of inclusion compounds of cyclodextrin (α -CD) with eight pentane derivatives into the cavity of α -CD in dilute aqueous solutions were measured by micro-calorimeter at 298.15 K. The thermodynamic properties of the inclusion reactions of pentane derivatives into α -CD were compared to the hydrophobicity and polarizability of guest molecules and discussed. The interaction energies of inclusion compounds of α -CD and pentane derivatives were determined by DFT calculation (B3LYP/6-31G (d,p)) in water and compared with the experimental results.

Keywords Thermodynamic properties · Molecular inclusion · Pentane derivatives · α -Cyclodextrin · Aqueous solutions · DFT calculation

Introduction

Cyclodextrin (CD) molecules include many kinds of guest molecules in their molecular cavities reflecting the differences in structure with those in aqueous solutions. In order to investigate the contribution of the size of the hydrophobic parts of a guest molecule on inclusion reactions,

thermodynamic properties of inclusion compounds of cyclodextrin (α -CD) with aliphatic alcohols have been investigated systematically [1–7]. The thermodynamic properties of aliphatic alcohols showed similar behaviors [7]. Enthalpies and entropies of inclusion were increased with increasing the size of aliphatic groups until pentanol. The Gibbs energies of inclusion pentane derivatives were larger than those in each homological system. The inclusion process may separate two kinds of opposite and/or cooperative effects from guest molecules. One is from aliphatic groups of the non-polar effect and the other is a functional group of polar groups usually. In order to elucidate the polar group effect of guest molecules on the inclusion properties of pentane derivatives of nitril, amine, nitro, thiol, fluoride, chloride, bromide, iodide and carboxylic acid, we determined the thermodynamic properties of pentane derivatives by solution calorimetry at 298.15 K. To elucidate the interaction energies of inclusion compounds of α -CD and pentane derivatives in aqueous solution, we performed DFT calculations.

Experimental

Materials

Aminopentane, nitropentane, pentanethiol, fluoropentane, chloropentane, bromopentane, iodopentane, hexanal and hexanoic acid (Tokyo Kasei Co.) were fractionally distilled over freshly activated molecular sieves 4A that had been evacuated at 453 K for 12 h under 10^{-2} to 10^{-3} Pa. Their chemical purities, obtained from gas chromatography by each using a 2 m column of 10% SE-30 on chromosorb and 20% PEG-1000 on Celite 545 with FID on a Yanagimoto G180FP, were more than 99.9%. Water contents were shown to be less

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than 0.01 mol percent by Coulometric Karl-Fischer method on a Moisturemeter (Mitsubishi Chemical Ind., CA-02).

Apparatus

A twin-microcalorimeter of the heat-conduction type, Thermal Activity Monitor (Thermometric AB, Järfälla, Sweden) with 3 cm³ volume of mixing vessels, which we previously modified [8, 9], was used for the measurements of excess enthalpies at 298.15 K. A reliability test of the microcalorimeter system and the procedures used had been performed using binary mixtures of (1 - *x*)1,4-dimethylbenzene + *x*1,3-dimethylbenzene and (1 - *x*)1,4-dimethylbenzene and *x*1,2-dimethylbenzene as reported previously [8] for exothermic and endothermic systems.

Details of the careful purification used for the α -CD [1] and water [10] have been described previously. All solutions were prepared by mass to keep five significant figures. The aqueous mixtures prepared were stirred for 30 min at room temperature with a magnetic stirrer. Then, they were stirred vigorously for ca. 15 min at room temperature with a supersonic washer (Taga Electric Co., Ltd., model UW-25, output frequency: 38 kHz, 45 W).

Results and discussion

Enthalpy of transfer

The experimental results for the enthalpy changes on diluting the dilute aqueous aminopentane, nitropentane, fluoropentane, chloropentane, bromopentane, iodopentane, hexanoate, hexanoic acid and α -CD solutions at 298.15 K were determined and listed in Table 1 in the same concentration range of mole fraction. Those of pentanethiol were negligibly small and within experimental error in the same concentration range of mole fraction and were treated as zero. Those of α -CD solution [2], $\Delta_{\text{dil}}H_{12}$, were obtained from our earlier papers. Here 1 and 2 showed water and α -CD, respectively. The experimental enthalpies of mixing and the related quantities are summarized in Table 2. The experimental enthalpies of transfer of pentane derivatives from dilute aqueous solutions to dilute aqueous α -CD solutions determined by Eq. 1 [3, 4] are also summarized in the last column of Table 2.

$$\Delta_{\text{trf}}H = \Delta_{\text{mix}}H - \Delta_{\text{dil}}H_{12} - \Delta_{\text{dil}}H_{13} \quad (1)$$

Here $\Delta_{\text{trf}}H$, $\Delta_{\text{mix}}H$, $\Delta_{\text{dil}}H_{12}$, $\Delta_{\text{dil}}H_{13}$ showed enthalpies of transfer of pentane derivatives, enthalpies of mixing of aqueous solution of α -CD and of pentane derivatives, enthalpies of dilution of aqueous solution of α -CD, enthalpies of dilution of aqueous solution of pentane derivatives, respectively. By the least-squares treatment of

Table 1 Experimental molar enthalpies of solution $\Delta_{\text{soln}}H_m$ of pentane derivatives in water at 298.15 K

$10^6 x_i$	$10^6 x_f$	$10^6 \Delta n_j$	$\Delta\Delta_{\text{soln}}H$ (kJ)	$\Delta_{\text{soln}}H_m$ (kJ mol ⁻¹)
<i>x</i> 1-C ₅ H ₁₁ CN + (1 - <i>x</i>) H ₂ O, <i>j</i> = 3				
3.2956	6.5911	16.445	-27.326	-1.6617
6.5225	9.7837	16.445	-27.828	-1.6922
6.5857	9.8785	16.445	-28.403	-1.7272
6.5911	9.8866	16.445	-26.755	-1.6269
9.7837	13.045	16.445	-26.722	-1.6249
9.8785	13.171	16.445	-27.726	-1.6860
13.045	16.306	16.445	-27.526	-1.6738
13.171	16.464	16.445	-25.889	-1.5743
16.306	19.567	16.445	-26.137	-1.5894
16.478	19.773	16.445	-26.777	-1.6283
23.050	26.342	16.445	-25.676	-1.5613
26.342	29.635	16.445	-26.197	-1.5930
29.659	32.955	16.445	-24.780	-1.5069
<i>x</i> 1-C ₅ H ₁₁ NO ₂ + (1 - <i>x</i>) H ₂ O, <i>j</i> = 3				
3.9340	5.2454	13.098	374.21	28.570
5.2454	7.8680	13.098	381.51	29.127
5.2454	6.5567	6.5490	197.59	30.170
5.2454	7.8680	6.5490	209.62	32.008
7.8680	9.1794	6.5490	218.63	33.383
9.1794	10.491	13.098	429.17	32.766
10.491	13.113	13.098	432.55	33.024
18.359	20.981	13.098	444.89	33.966
<i>x</i> 1-C ₅ H ₁₁ COOH + (1 - <i>x</i>) H ₂ O, <i>j</i> = 1				
1.905	1.883	15.156	-0.223	-1.471
1.883	1.863	15.156	0.130	0.8551
1.863	1.843	15.156	0.019	1.299
1.843	1.823	15.156	-0.033	-0.2168
1.823	1.804	15.156	0.030	-0.1950
1.804	1.785	15.156	0.026	0.1743
1.785	1.766	15.156	-0.050	-0.3296
1.766	1.748	15.156	0.018	0.1137
1.748	1.730	15.156	-0.024	-0.1534
1.730	1.713	15.156	-0.007	-0.0511
<i>x</i> 1-C ₅ H ₁₁ NH ₂ + (1 - <i>x</i>) H ₂ O, <i>j</i> = 3				
3.4344	5.1517	8.5905	-204.00	-23.747
3.4416	5.1624	8.5905	-213.27	-24.826
5.1624	6.8832	8.5905	-201.17	-23.418
6.8805	10.321	17.181	-393.98	-22.931
8.6040	10.325	8.5905	-202.80	-23.607
10.320	13.761	17.181	-372.31	-21.670
10.325	12.046	8.5905	-191.53	-22.295
13.761	17.201	17.181	-386.55	-22.499
13.766	15.487	8.5905	-203.66	-23.708
15.487	17.208	8.5905	-193.15	-22.484
17.201	20.641	17.181	-373.17	-21.720
20.641	24.081	17.181	-355.26	-20.678

Table 1 continued

$10^6 x_i$	$10^6 x_f$	$10^6 \Delta n_j$	$\Delta\Delta_{\text{soln}}H$ (kJ)	$\Delta_{\text{soln}}H_m$ (kJ mol ⁻¹)
24.081	27.521	17.181	-388.80	-22.629
27.521	30.961	17.181	-353.33	-20.565
$x1\text{-C}_5\text{H}_{11}\text{F} + (1-x)\text{H}_2\text{O}, j = 3$				
1.9567	3.9135	8.7686	188.61	21.510
3.9117	5.8675	8.7686	188.51	21.498
5.8702	7.8269	8.7686	191.99	21.896
7.7779	9.7223	8.7686	207.33	23.645
7.8233	9.7791	8.7686	189.85	21.651
9.7791	11.735	8.7686	203.11	23.164
9.7836	11.740	8.7686	197.08	22.476
11.735	13.691	8.7686	211.74	24.147
17.602	19.558	8.7686	208.01	23.722
17.610	19.567	8.7686	212.49	24.233
$x1\text{-C}_5\text{H}_{11}\text{Cl} + (1-x)\text{H}_2\text{O}, j = 1$				
1.792	1.773	15.248	-0.07175	-0.4706
1.773	1.754	15.248	-0.1499	-0.9831
1.754	1.735	15.248	-0.2434	-1.596
1.735	1.717	15.248	-0.3158	-2.071
1.717	1.699	15.248	-0.3925	-2.574
1.699	1.681	15.248	-0.4771	-3.129
1.681	1.664	15.248	-0.5641	-3.699
1.664	1.647	15.248	-0.6284	-4.122
1.647	1.630	15.248	-0.7002	-4.592
1.630	1.614	15.248	-0.7580	-4.971
$x1\text{-C}_5\text{H}_{11}\text{Br} + (1-x)\text{H}_2\text{O}, i = 1$				
1.770	1.755	15.257	-0.200	-1.313
1.755	1.740	15.257	0.024	0.1572
1.740	1.726	15.257	0.007	0.0450
1.726	1.712	15.257	-0.004	-0.0236
1.712	1.699	15.257	0.031	0.2038
1.699	1.685	15.257	0.019	0.1250
1.685	1.673	15.257	-0.019	-0.1259
1.673	1.660	15.257	0.018	0.1159
1.660	1.648	15.257	-0.015	-0.0999
1.648	1.635	15.257	0.004	0.0257
$x1\text{-C}_5\text{H}_{11}\text{I} + (1-x)\text{H}_2\text{O}, i = 1$				
1.587	1.569	15.278	-0.1747	-1.144
1.569	1.553	15.278	-0.3628	-2.374
1.553	1.536	15.278	-0.5365	-3.512
1.536	1.520	15.278	-0.6428	-4.208
1.520	1.504	15.278	-0.7132	-4.668
1.504	1.488	15.278	-0.7554	-4.944
1.488	1.473	15.278	-0.8056	-5.273
1.473	1.458	15.278	-0.8421	-5.512
1.458	1.444	15.278	-0.8776	-5.744
1.444	1.429	15.278	-0.9130	-5.976

$$x_i = n_3/n_1$$

$$x_f = (n_3 + \Delta n_3)/n_1$$

the experimental values of $\Delta_{\text{trf}}H_m$ as a function of z and the mole fraction of pentane derivatives. $z = (n'_1 + n'_2/n_2)$ [3, 4]. Here and n'_1 and n'_2 showed the amounts of water before and after mixing in mole, respectively. $f = n_3/(n_2 + n_3)$, according to Eq. 9 described in an earlier paper of this series [3], limiting molar enthalpies of transfer at infinite dilution, $\Delta_{\text{trf}}H_m$, were determined as well as the equilibrium constants K of 1:1 inclusion-complex formation and limiting ratios y_{max} of pentane derivatives included over the total pentane derivatives in the systems at infinite dilution. The values of z depended on the solubility of pentane derivatives. The z of systems of pentanamine and pentanethiol by means of the solubility problem are 2.1×10^3 and 1.1×10^5 in mole fractions, respectively, but the average of others was $5.3 \pm 0.5 \times 10^3$. These quantities thus determined are summarized in Table 3. The smoothed values of $\Delta_{\text{trf}}H_m$ for mean values of z are shown in Fig. 1 against the mole fraction f . The molar enthalpies of transfer of pentane derivatives were negative values for both of the α -CD solutions as shown in Fig. 1.

Enthalpy and entropy of inclusion

From the thermodynamic functions listed in Table 3, the molar enthalpies, molar Gibbs energies and molar entropies of inclusion of pentane derivatives at infinite dilution into α -CD cavities in aqueous solutions at 298.15 K were determined and are summarized in Table 4, as well as the reported values of pentanol [1, 2] and pentanenitrile [11] for the sake of comparison. The enthalpies of inclusion of all pentane derivatives with α -CD are exothermic from -1.3 to -23 kJ mol⁻¹ and stabilized on inclusion with guest molecules. The enthalpies of inclusion of hexanoic acid and fluoropentane showed the largest and least enthalpic stabilization, respectively. Molar Gibbs energies of inclusion are also plotted in Fig. 2. All molar Gibbs energies of inclusion were negative and stabilized at more than -24 kJ mol⁻¹ on inclusion. The Gibbs energies of inclusion of iodopentane and pentanol showed the largest and least enthalpic stabilization, respectively. The sequence of Gibbs energetic stabilization in halogenated pentanes was as follows: iodide > bromide=chloride > fluoride. Iodide binds more strongly than other halide compounds because of the larger molecular size of iodide, which enhances the van der Waals interaction between the guest molecules and α -CD. The same mechanism also explains the stronger binding of bromide than fluoride and chloride compounds. Gibbs energetic stabilizations in halogenated pentanes were increased with decreasing dipole moment and the polarity of the pentane derivative. Strong interaction between water and halogenated pentane had an effect on the inclusion reaction from the viewpoint of Gibbs energy.

Table 2 Experimental enthalpies of mixing $\Delta_{\text{mix}}H$ and molar enthalpies of transfer $\Delta_{\text{trf}}H_m$ of pentane derivatives from dilute aqueous solutions to dilute aqueous α -cyclodextrin solutions at 298.15 K, where n'_1 , n''_1 , n_2 and n_3 represent, respectively, the amounts

of water in the CD solution, the amounts of water in pentane derivatives solutions, the amounts of CD in the aqueous solution and the amounts of pentane derivatives in the aqueous solutions

f^a	$10^2 n'_1$ (mol)	$10^2 n''_1$ (mol)	$10^6 n_2$ (mol)	$10^6 n_3$ (mol)	$\Delta_{\text{mix}}H$ (mJ)	$\Delta_{\text{trf}}H_m$ (kJ mol ⁻¹)
H ₂ O(1) + α -CD(2) + pentanamine(3)						
0.1046 ₄	15.008	0.33309	7.0165	0.82001	-6.70	-7.01
0.1894 ₆	15.008	0.66618	7.0165	1.6400	-12.3	-6.93
0.2595 ₉	15.008	0.99927	7.0165	2.4600	-17.5	-6.62
0.3185 ₆	15.008	1.3324	7.0165	3.2801	-21.9	-6.33
0.3688 ₃	15.008	1.6655	7.0165	4.1001	-25.7	-6.04
0.4121 ₉	15.008	1.9985	7.0165	4.9201	-29.2	-5.75
0.4499 ₇	15.008	2.3316	7.0165	5.7401	-32.4	-5.49
0.4831 ₉	15.008	2.6647	7.0165	6.5601	-35.6	-5.28
0.6412 ₁	14.891	1.5000	7.0703	13.502	-51.6	-4.23
0.6650 ₇	14.891	1.6667	7.0703	15.002	-54.8	-4.04
H ₂ O(1) + α -CD(2) + pentanethiol(3)						
0.1050 ₆	95.117	0.27754	8.4576	1.0037	-3.54	-3.57
0.1901 ₅	95.117	0.55508	8.4576	2.0074	-7.02	-3.54
0.2604 ₅	95.117	0.83263	8.4576	3.0111	-10.1	-3.38
0.3195 ₃	95.117	1.1102	8.4576	4.0149	-13.0	-3.27
0.3698 ₆	95.117	1.3877	8.4576	5.0186	-15.5	-3.13
0.4132 ₆	95.117	1.6653	8.4576	6.0223	-17.9	-3.01
0.4510 ₇	95.117	1.9428	8.4576	7.0260	-20.1	-2.89
0.4843 ₀	95.117	2.2203	8.4576	8.0297	-22.1	-2.78
0.5137 ₄	95.117	2.4979	8.4576	9.0334	-24.0	-2.68
0.5399 ₉	95.117	2.7754	8.4576	10.037	-25.7	-2.59
H ₂ O(1) + α -CD(2) + nitropentane(3)						
0.1837 ₄	15.046	0.16655	2.8035	0.58291	-1.38	-2.53
0.3104 ₄	15.046	0.33310	2.8035	1.1658	-2.65	-2.35
0.4031 ₀	15.046	0.49964	2.8035	1.7487	-3.82	-2.24
0.4738 ₀	15.046	0.66619	2.8035	2.3316	-4.93	-2.16
0.5295 ₃	15.046	0.83274	2.8035	2.9145	-5.93	-2.07
0.5745 ₈	15.046	0.99929	2.8035	3.4975	-6.82	-1.98
0.6117 ₆	15.046	1.1658	2.8035	4.0804	-7.75	-1.93
0.6429 ₆	15.046	1.3324	2.8035	4.6633	-8.65	-1.88
H ₂ O(1) + α -CD(2) + hexanoic acid(3)						
0.1684 ₂	0.16648	14.980	0.57608	2.8531	-7.60	-12.8
0.2882 ₈	0.33296	14.980	1.1522	2.8531	-14.3	-12.4
0.3779 ₄	0.49944	14.980	1.7283	2.8531	-20.2	-11.7
0.4475 ₄	0.66592	14.980	2.3043	2.8531	-25.4	-11.0
0.5031 ₄	0.83240	14.980	2.8804	2.8531	-30.0	-10.4
0.5485 ₆	0.99888	14.980	3.4565	2.8531	-34.0	-9.79
0.5863 ₈	1.1654	14.980	4.0326	2.8531	-37.4	-9.21
0.6183 ₅	1.3318	14.980	4.6087	2.8531	-40.1	-8.65
0.6457 ₃	1.4983	14.980	5.1848	2.8531	-42.5	-8.12
0.6694 ₅	1.6648	14.980	5.7608	2.8531	-44.8	-7.67
H ₂ O(1) + α -CD(2) + fluoropentane(3)						
0.1454 ₀	0.16648	15.033	0.58291	2.6854	-0.653	-0.968
0.2538 ₈	0.33296	15.033	1.1658	2.6854	-1.30	-0.966
0.3379 ₂	0.49944	15.033	1.7487	2.6854	-1.81	-0.891

Table 2 continued

f^a	$10^2 n'_1$ (mol)	$10^2 n''_1$ (mol)	$10^6 n_2$ (mol)	$10^6 n_3$ (mol)	$\Delta_{\text{mix}}H$ (mJ)	$\Delta_{\text{trf}}H_m$ (kJ mol ⁻¹)
0.4049 ₅	0.66592	15.033	2.3316	2.6854	-2.23	-0.821
0.4596 ₆	0.83240	15.033	2.9145	2.6854	-2.63	-0.774
0.5051 ₅	0.99888	15.033	3.4975	2.6854	-2.99	-0.729
0.5435 ₇	1.1654	15.033	4.0804	2.6854	-3.28	-0.679
0.5764 ₆	1.3318	15.033	4.6633	2.6854	-3.56	-0.642
H ₂ O(1) + α -CD(2) + chloropentane(3)						
0.09827 ₁	0.16600	15.116	0.29936	2.8651	-1.93	-1.77
0.1789 ₆	0.33201	15.116	0.59873	2.8651	-3.82	-1.74
0.2463 ₉	0.49801	15.116	0.89809	2.8651	-5.66	-1.70
0.3035 ₉	0.66402	15.116	1.1975	2.8651	-7.37	-1.67
0.3527 ₁	0.83002	15.116	1.4968	2.8651	-9.02	-1.58
0.3953 ₆	0.99603	15.116	1.7962	2.8651	-10.6	-1.52
0.4327 ₄	1.1620	15.116	2.0955	2.8651	-12.2	-1.47
0.4657 ₇	1.3280	15.116	2.3949	2.8651	-13.6	-1.39
0.4951 ₆	1.4940	15.116	2.6943	2.8651	-15.0	-1.32
0.5214 ₉	1.6600	15.116	2.9936	2.8651	-16.3	-1.25
H ₂ O(1) + α -CD(2) + bromopentane(3)						
0.09714 ₅	0.16600	15.151	0.29200	2.7139	-2.42	-1.82
0.1770 ₉	0.33201	15.151	0.58400	2.7139	-4.53	-1.78
0.2440 ₂	0.49801	15.151	0.87600	2.7139	-6.49	-1.74
0.3008 ₉	0.66402	15.151	1.1680	2.7139	-8.29	-1.67
0.3498 ₀	0.83002	15.151	1.4600	2.7139	-10.1	-1.64
0.3923 ₁	0.99603	15.151	1.7520	2.7139	-11.7	-1.58
0.4296 ₁	1.1620	15.151	2.0440	2.7139	-13.4	-1.52
0.4625 ₉	1.3280	15.151	2.3336	2.7139	-14.9	-1.47
0.4919 ₇	1.4940	15.151	2.6280	2.7139	-16.4	-1.42
0.5183 ₀	1.6600	15.151	2.9200	2.7139	-17.8	-1.36
H ₂ O(1) + α -CD(2) + iodopentane(3)						
0.1112 ₉	0.16600	15.142	0.30090	2.5281	-2.30	-1.80
0.2003 ₀	0.33201	15.142	0.60180	2.5281	-4.40	-1.76
0.2731 ₀	0.49801	15.142	0.90270	2.5281	-6.35	-1.73
0.3337 ₅	0.66402	15.142	1.2036	2.5281	-8.12	-1.70
0.3850 ₅	0.83002	15.142	1.5045	2.5281	-9.80	-1.61
0.4290 ₃	0.99603	15.142	1.8054	2.5281	-11.4	-1.56
0.4671 ₃	1.1620	15.142	2.1063	2.5281	-13.0	-1.50
0.5004 ₆	1.3280	15.142	2.4072	2.5281	-14.4	-1.40
0.5298 ₇	1.4940	15.142	2.7081	2.5281	-15.7	-1.29
0.5560 ₁	1.6600	15.142	3.0090	2.5281	-17.0	-1.20

However, the enthalpies and entropies of inclusion had a more complicated correlation as shown in Fig. 2. This might be an effect on not only the polarity of halogen for interaction with water but also a result for the molecular fitting on the wall of α -CD cavities.

From a thermodynamic point of view, there are two kinds of inclusion mechanism as shown in Fig. 2. One is entropy driven inclusion such as pentanenitrile, aminopentane, nitropentane, pentanethiol, fluoropentane, and chloropentane as previously reported [3]. However, the

inclusion processes of pentanol and hexanoic acid were different from each other. Their mechanism of enthalpy driven inclusion is shown in Fig. 2. The inclusion mechanism of the system α -CD + pentanol + H₂O has already been reported by conformation change of pentanol in the cavity of α -CD. However, the system α -CD + hexanoic acid + H₂O might have not only the conformational change of the aliphatic group but also another effect such as strong hydrogen-bonding with water or deionization of the carboxyl group in water.

Table 3 Equilibrium constants for the formation of 1:1 inclusion complexes, ratios of water molecules over the cyclodextrin molecules, limiting molar enthalpies of transfer of pentane derivatives, and the limiting molar ratios y_{\max} of pentane derivatives at 298.15 K

Guest	$\log_{10}K$	z	$\Delta_{\text{trf}}H_m$ (kJ mol ⁻¹)	y_{\max}
Pentanamine	4.73 ± 4.86	21390	-7.09 ± 0.19	0.715 ± 0.14
Pentanethiol	5.41 ± 4.95	112466	-3.66 ± 0.02	0.694 ± 0.06
Nitropentane	4.42 ± 3.45	53668	-2.60 ± 0.02	0.331 ± 0.02
Hexanoic acid	4.66 ± 3.71	52518	-13.7 ± 0.05	0.579 ± 0.02
Fluoropentane	5.18 ± 5.09	43888	-0.968 ± 0.02	0.776 ± 0.04
Chloropentane	5.24 ± 5.09	52758	-1.79 ± 0.04	0.768 ± 0.08
Bromopentane	5.23 ± 4.22	55846	-1.86 ± 0.01	0.753 ± 0.02
Iodopentane	5.57 ± 5.21	60178	-1.82 ± 0.04	0.861 ± 0.04

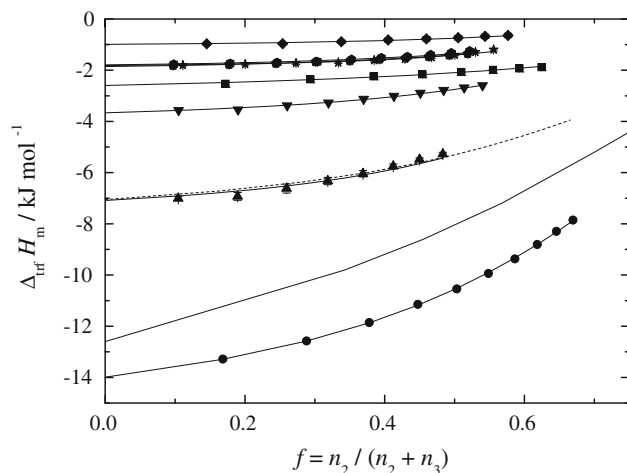


Fig. 1 Molar enthalpies of transfer of pentane derivatives from aqueous to aqueous α -CD solutions at 298.15 K as a function of $f = n_2 / (n_2 + n_3)$: filled circle COOH, filled triangle NH₂, filled inverted triangle SH, filled square NO₂, filled hexagon F, filled diamond Cl, filled pentagon Br, filled star I, solid line OH, broken line CN

Stability of guest molecules in the α -CD cavity by means of Gaussian calculation

There are two kinds of mechanism of the inclusion process even in the case where the α -CD cavity is hydrophobic. The dispositions of the guest molecule in the α -CD cavity can have two states. One is where the guest molecule is

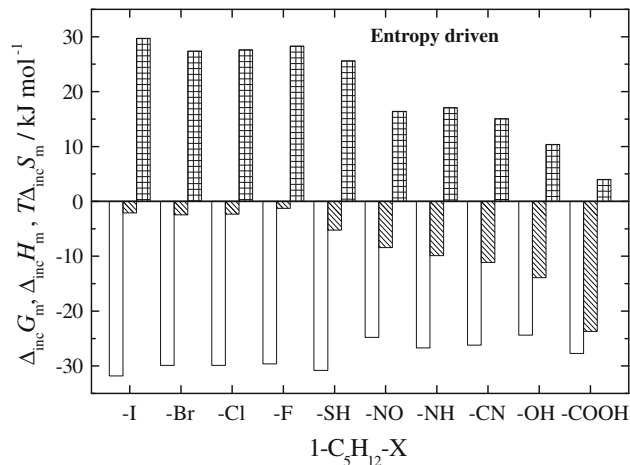


Fig. 2 Gibbs energies, enthalpies and entropies of inclusion of α -CD + C₅H₁₁-X. □ ΔG ; ▨ ΔH ; ▩ $T\Delta S$

included from the aliphatic group of pentane derivatives, the other is from polar functional groups of pentane derivatives. In order to know the irregularity of thermodynamic properties as shown in Fig. 2, stabilities of configuration of pentane derivatives around α -CD cavity were calculated. Initial geometries of conformers were estimated by means of CONFLEX BARISTA ver. 6.7 software [12] which performed semi-empirical calculation by MMFF94s [13]. Then all the calculations were performed with

Table 4 The changes of thermodynamics properties on 1:1 inclusion of pentane derivatives into α -cyclodextrin cavities in dilute aqueous solutions at 298.15 K

Guest molecules	$\Delta_{\text{inc}}H$ (kJ mol ⁻¹)	$\Delta_{\text{inc}}G$ (kJ mol ⁻¹)	$-T\Delta_{\text{inc}}S$ (kJ mol ⁻¹)	$\Delta_{\text{inc}}S$ (J K ⁻¹ mol ⁻¹)
Hexanenitrile ^a	-7.33	-24.6	-17.2	57.8
Pentanol ^b	-13.9	-24.4	-10.4	34.9
Pentanamine	-9.91	-27.0	-17.1	57.3
Pentanethiol	-5.28	-30.9	-25.6	85.8
Nitropentane	-7.85	-25.3	-17.4	58.4
Hexanoic acid	-23.7	-27.7	-4.05	13.6
Fluoropentane	-1.28	-29.6	-28.3	95.0
Chloropentane	-2.33	-29.9	-27.6	92.6
Bromopentane	-2.49	-29.9	-27.4	91.9
Iodopentane	-2.11	-31.8	-29.7	99.6

^a Cited from Ref. [11]

^b Cited from Ref. [3]

Table 5 Energy difference of configuration of guest molecules in inclusion compounds between the including side of the aliphatic and polar group by DFT B3LYP/6-31G(d,p) interaction energies ($E/kJ mol^{-1}$) of the minimum energy forms of various 1:1 α -cyclodextrin compounds calculated by PM3 in SCRF

Guest	$\Delta E1$ ($kJ mol^{-1}$)	$\Delta E2$ ($kJ mol^{-1}$)	$\Delta E3$ ($kJ mol^{-1}$)
Hexanoic acid	-66.4	7.5	-3.3
Pentanol	-4.4	-36.3	-1.5
Aminopentane	-5.6	5.9	-0.4
Hexanenitrile	-9.5	-22.6	2.2
Nitropentane	-9.0	7.1	2.3
Pentanethiol	14.4	-2.7	0.3
Fluoropentane	31.5	-31.5	1.6
Chloropentane	11.6	-20.5	-0.9
Bromopentane	31.5	-31.5	-0.7
Iodopentane	31.5	-31.5	-0.5

$\Delta E1$, $\Delta E2$ and $\Delta E3$ were the for α -cyclodextrin compounds, α -cyclodextrin and pentane derivatives, respectively. Δ shows the compounds including side of pentyl groups minus those of polar groups

GAUSSIAN 09 [14]. α -CD from the crystal structure [15] and pentane derivatives were optimized with B3LYP/6-31G(d,p) in solvent of water by self-consistent reaction field (SCRF) calculation [16]. The inclusion complex was constructed from the B3LYP/6-31G(d,p)-optimized CD and the pentane derivatives. The position of the substrate was defined by its Z -coordinate. The inclusion compounds were emulated by entering the guest molecules from the secondary hydroxyl side of the CD with both sides of guest molecules. The geometry of the complex was completely optimized with PM3 without any restriction. DFT single point calculation at the level of B3LYP/6-31G(d,p) was then performed on all the PM3-optimized species to obtain more accurate total energies in water solution by using the Onsager continuum solvation model based on SCRF calculation. This is a simpler model of solution than the continuous solvation model and only considers the solvent as a continuous dielectric with a cavity accurately modeled for the solute. The DFT single point calculation for the systems including iodopentane was calculated at the level of B3LYP/CEP-4g. The molecular interaction energies of compounds in water $\Delta E(AB)$ are calculated by the supermolecular-method [17] as follows:

$$\Delta E(AB) = E(AB) - E(A) - E(B) \quad (2)$$

Here AB, A and B is the inclusion compound of α -CD + pentane derivatives, α -CD and pentane derivatives in water, respectively. The calculated results are listed in Table 5. As shown in Table 5, the insert direction of guest molecules was not the same for pentane derivatives. It was more stable to include the guest molecules of pentanol, aminopentane and chloropentane from the aliphatic

group side. However, pentanenitrile and nitropentane were opposite and others were not different in the error. This may be due to the effect of polar interactions between the cyclodextrin cavity and the polar groups in the pentane derivatives. As the surface of the cyclodextrin cavity has many polar points of ether oxygens, the total property of the cavity was a hydrophobic environment. Also, the stabilities of guest molecules for the type of aliphatic groups were decreasing with increasing polarizabilities of pentane derivatives.

Effect of hydrophobicity of guest molecules

The guest molecules might be stabilized in the α -CD cavity by means of hydrophobic interaction between hydrophobic parts of guest molecules and the hydrophobic cavity of the α -CD. In order to discuss the hydrophobicity of molecules in water, the partition coefficients between water and octanol have come to be used as a measure of the hydrophobicity in biochemistry. So the hydrophobicity $\log(P)$ of the guest was determined by the partition coefficient method, which was applicable at any pH. Here P is the partition coefficient. The estimated values of $\log P$ at pH = 7.0 by software of ACD/LogD [19] (Ver. 8.14) are shown in the second column of Table 6. To clarify the correlation between the hydrophobicities of pentane derivatives and the thermodynamic properties of inclusion, thermodynamic properties of inclusion and $\log P$ were examined. There was a good correlation except for the two compounds of amino and carboxylic pentane as follows:

$$\Delta_{inc}H = -20.60 + 5.59 \log P, \quad r^2 = 0.960$$

$$T\Delta_{inc}S = -1.138 + 9.074 \log P, \quad r^2 = 0.98$$

Table 6 Physicochemical properties of pentane derivatives

	$\log(P)$	α (nm^3)
Hexanoic acid	-0.37	12.51
Pentanol	1.41	10.59
Chloropentane	2.56	11.88
Iodopentane	3.44	14.98
Aminopentane	-1.54	11.30
Hexanenitril	1.68	11.80
Nitropentane	1.92	11.79
Pentanethiol	2.31	12.95
Fluoropentane	2.64	9.86
Bromopentane	2.74	12.58

$\log(P)$, Partition coefficient ($\log P$, octanol/water) of guest molecules at pH 7 calculated by Lombardo method [18] with software of ACD/LogD (Ver. 8.14, Advanced Chemistry Development Co. Ltd)

α , polarizability

$$\Delta_{\text{inc}}G = -19.52 - 3.47 \log P, \quad r^2 = 0.89$$

The hydrophobicity of guest molecules exerted an effect in two opposite directions: one direction was stabilization in the cavity of the α -CD, the other direction was hydrophobic hydration in aqueous solution. Two opposite effects on the stabilities of inclusion might be compensated together. So the correlation was not simple as shown in Fig. 3. However, Gibbs energies and entropies of inclusions were increased with increasing hydrophobicity. And enthalpies of inclusion were decreased with increasing hydrophobicity. The results showed preferential location of guest molecules in aqueous solution of α -CD. As the release of hydrophobic hydration and the degree of freedom in the cavity of α -CD of guest molecules lead to increased entropy of inclusion [3], the result was consistent with the entropy driven inclusion shown above except the system of aminopentane + α -CD + water.

Polarizabilities of guest molecules

Polarizabilities of guest molecules were also calculated by Gaussian 09 with Mp2/6-311G(d,p) basic set shown in the second column of Table 6. And the correlation between the polarizabilities of guest molecules and thermodynamic properties are shown in Fig. 4. There are two correlations

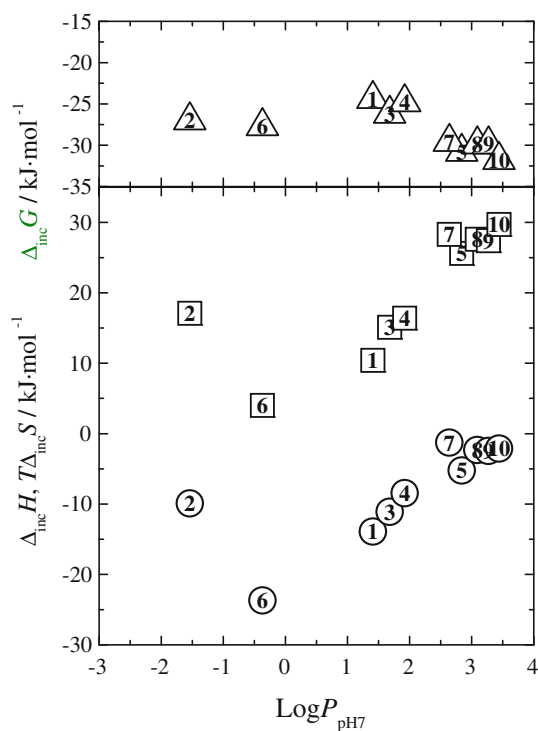


Fig. 3 Correlation between $\log P$ of guest molecules at pH 7 calculated by $\log D$ and thermodynamic properties of inclusion: *circle* $\Delta_{\text{inc}}H$, *square* $T\Delta_{\text{inc}}S$, *triangle* $\Delta_{\text{inc}}G$; 1, OH; 2, NH_2 ; 3, CN; 4, NO_2 ; 5, SH; 6, COOH; 7, F; 8, Cl; 9, Br; 10, I

shown in Fig. 4 except the system of hexanoic acid. The enthalpy and entropy of inclusion of hexanoic acid have different behaviors of dependence on polarizabilities to those of other pentane derivatives. This may be due to the ionization of carboxylic acid. The thermodynamic properties of inclusion of halogenated pentane showed small dependence on polarizabilities. And the dependences of enthalpies of inclusion of halogenated pentane on polarizabilities were very small. The dependences of entropies of inclusion of halogenated pentane on polarizabilities were slightly larger than those of the enthalpies of inclusion.

Gibbs energies and enthalpies of inclusion were decreased with increasing the polarizabilities of pentane derivatives, but entropies of inclusion were increased with increasing the polarizabilities of pentane derivatives. Gibbs energetic and entropic stabilization of inclusion increased with increasing the polarizabilities of pentane derivatives. However, the dependences of enthalpies of inclusion were opposite. This means that entropic stabilizations and enthalpic stabilizations of inclusion were compensated together as shown in Fig. 4. Inspection of the molecular fit by the use of a molecular modeling tool showed that the best fitting was obtained for pentanol with the cavity of α -CD [3]. The molecules of pentane derivatives might change their conformations to make the closest contacts with the inner wall of α -CD cavities and increase entropies of

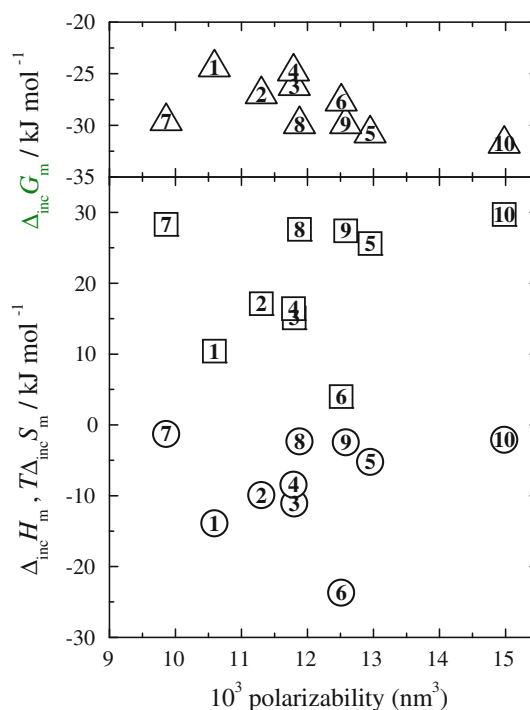


Fig. 4 Correlation between polarizabilities and thermodynamic properties of inclusion: *circle* $\Delta_{\text{inc}}H$, *square* $T\Delta_{\text{inc}}S$, *triangle* $\Delta_{\text{inc}}G$; 1, OH; 2, NH_2 ; 3, CN; 4, NO_2 ; 5, SH; 6, COOH; 7, F; 8, Cl; 9, Br; 10, I

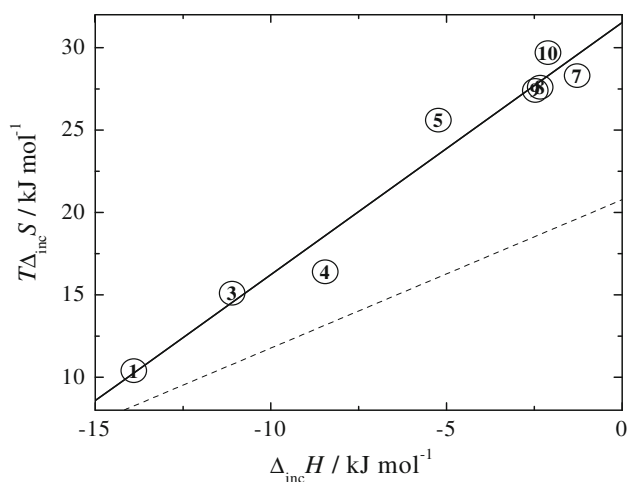


Fig. 5 Correlation between entropies and enthalpies of inclusion for α -CD + pentane derivative: 1 OH, 2 NH₂, 3 CN, 4 NO₂, 5 SH, 6 COOH, 7 F, 8 Cl, 9 Br, 10 I. $T\Delta S$ (kJ mol⁻¹) = 31.52 + 1.53 × ΔH , s_f = 1.37 kJ mol⁻¹

inclusion by releasing hydrophobic hydration of pentane derivatives in water. These inclusion processes are advantageous energetically.

Entropy and enthalpy compensation

The entropy and enthalpy of inclusion of pentane derivatives are shown in Fig. 5. There is a linear relation as shown in Fig. 5. Also a correlation between entropy and enthalpy of inclusion for aliphatic alcohols from methanol to hexanol, which have been reported [3] previously, is shown as a broken line.

$$T\Delta S \text{ (kJ mol}^{-1}\text{)} = 31.52 + 1.530 \times \Delta H, \quad (3)$$

$$s_f = 1.37 \text{ (kJ mol}^{-1}\text{)}$$

The slopes and intercepts were similar but there were small differences. The slope of the system of aliphatic alcohols was smaller than those of pentane derivatives. Also the intercept of the system of aliphatic alcohols was smaller than those of pentane derivatives. The results suggest that the size effect of aliphatic groups on inclusion stability, that is the hydrophobic interaction between the CD cavity and guest molecules, was less effective than the polar group in guest molecules.

Conclusion

The Gibbs energies of inclusion of α -cyclodextrin with ten pentane derivatives were larger than -23 kJ mol⁻¹. The forces of inclusion for α -cyclodextrin with ten pentane derivatives were driven by two factors, entropy and enthalpy. The effect of the hydrophobicities and

polarizabilities of guest molecules on inclusion showed similar behaviors. Entropy-enthalpy compensation for inclusion was shown for the inclusion compounds of α -cyclodextrin + pentane derivatives.

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