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Molecular Recognition Study on a Supramolecular System. Part 21. Inclusion Complexation Thermodynamics of Aliphatic Alcohols by Organoselenium Modified β-Cyclodextrins

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Abstract. The spectrophotometric titrations have been performed at 25–40 °C in aqueous solution to give the complex stability constants and the thermodynamic parameters for the stoichiometric 1 : 1 inclusion complexation of various aliphatic alcohols with mono[6-(phenylseleno)-6-deoxy]-β-cyclodextrin (**2**), mono[6-(*o*-, *m*-, *p*-tolylseleno)-6-deoxy]-β-cyclodextrin (**3–5**), mono[6-(*p*-chlorophenyl-seleno)-6-deoxy]-β-cyclodextrin (**6**), mono[6-(benzylseleno)-6-deoxy]-β-cyclodextrin (**7**) and mono[6-(naphthaleneseleno)-6-deoxy]-β-cyclodextrin (**8**). On the basis of the present and previous results, the molecular binding abilities and selectivities for guest aliphatic alcohols of the host β-cyclodextrin derivatives (**2–8**) are discussed comparatively and globally from the thermodynamic point of view. The thermodynamic parameters obtained are critical functions of the size/shape of aliphatic alcohols, and the position and type of the substituent introduced to the aromatic ring of β-cyclodextrin's sidearm, which are elucidated in terms of the conformational, electrostatic, hydrogen-bonding, and hydrophobic effects.

Key words: organoselenium cyclodextrin, aliphatic alcohols, inclusion complexation, thermodynamics.

1. Introduction

Modified cyclodextrins with nucleophilic and electrophilic substituents attached to the primary side of cyclodextrin can alter not only the original molecular binding ability but also the relative molecular selectivity significantly [1–5]. Consequently, a good deal of effort has been devoted to the synthesis of a wide variety of cyclodextrin derivatives in order to elucidate the nature of their molecular binding behavior from the several structural features and also to get insights into the factors governing the inclusion complexation phenomena of guest molecules by host cyclodextrins [6–20]. Unfortunately, the thermodynamic studies on inclusion complexation of guest molecular species have been concentrated mainly on the

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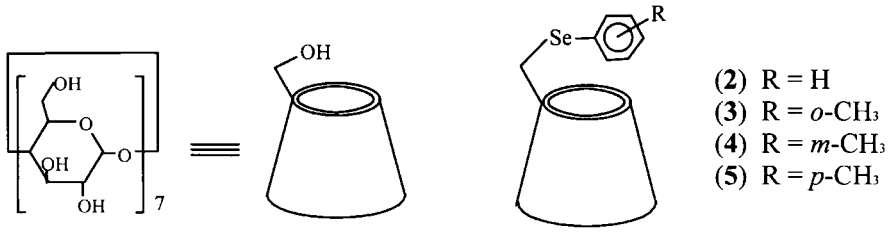
intact α-, β-, and γ-cyclodextrins [21–23], and less attention has hitherto been paid to the inclusion complexation thermodynamics of chemically modified cyclodextrins [24–26]. In particular, the influence of the substituent introduced to the aromatic sidearm attached to cyclodextrin on its molecular binding ability and selectivity has not been investigated from the thermodynamic point of view, in spite of the potential importance of such studies in discussing the relevant stereochemical complementary geometrical relationship between the biological receptor (host) and substrate (guest) interaction [1].

We have recently reported that all of the nucleophilic and electrophilic as well as hydrophobic and hydrophilic derivatizations of β-cyclodextrin diminish the complex stability with 2-naphthalenesulfonate, which is mostly attributable to the highly negative entropy changes ($T\Delta S^\circ$) that exceed even the increased enthalpic gains ($-\Delta H^\circ$) arising from the enhanced hydrophobic interaction with lipophilic side chain(s) introduced in the modified cyclodextrins [24]. More recently, we have demonstrated the modified β-cyclodextrins carrying one chromophoric anilino or pyridinio moiety as a probe for differential UV spectrometry can recognize not only the differences in the molecular size and shape of amino acids, but also the chirality of the enantiometic amino acids. The higher molecular binding ability as well as enantioselectivity for modified β-cyclodextrins are attributable to the increased enthalpic gain [1, 25]. On the other hand, Matsui *et al.* [27] reported the inclusion complexation thermodynamics of natural cyclodextrins with aliphatic alcohols, giving interesting results.

In the present study, we synthesized a series of arylseleno derivatives of β-cyclodextrin, shown in Chart 1, and investigated their inclusion complexation thermodynamics with selected aliphatic alcohols in aqueous solution at 25 °C using UV spectrometry. A series of straight-chain and cyclic alcohols are employed as guest molecules in order to examine the possible participation of several weak interactions working in the complexation with the organoselenium modified β-cyclodextrins from the thermodynamic point of view. The thermodynamic parameters for the inclusion complexation of aliphatic alcohols with organoselenium modified β-cyclodextrins, together with those for natural β-cyclodextrin (**1**) [23], will enhance our further understanding of this thermodynamically less investigated area of modified cyclodextrin chemistry [24]. It is another point of interest to examine the scope and limitations of the simple size-fit concept in the inclusion complexation of the modified β-cyclodextrins and the guests from the thermodynamic point of view.



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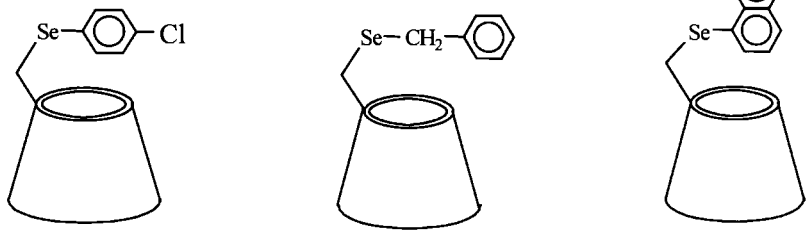

(**6**) (**7**) (**8**)

Chart 1.

2. Experimental

2.1. SPECTROSCOPY

UV spectra were obtained on a Shimadzu UV-2401PC spectrometer. Circular dichroism (CD) spectra were recorded on a JASCO J-720 spectropolarimeter.

2.2. MATERIALS

Guest aliphatic alcohols employed were commercially available (Tianjin Chemical Reagent Plant) and were used as received. A series of organoselenium modified β-cyclodextrins, bearing phenylseleno (**2**), *o*-, *m*-, and *p*-tolylseleno (**3–5**), *p*-chlorophenylseleno (**6**), benzylseleno (**7**), and 1-naphthylseleno (**8**) groups were synthesized in 40–55% yields, respectively, by the reaction of mono[6-*O*-(*p*-tolylsulfonyl)]-β-cyclodextrin with the corresponding aromatic selenide anions in DMF, according to the procedures reported recently [28]. The host compounds (**2–8**) were dissolved in distilled, deionized water to make a 2×10^{-4} mol dm^{-3} aqueous solution for the photometric titration.

2.3. SPECTRAL MEASUREMENTS

The molecular binding constants for the inclusion complexation of modified β-cyclodextrins (**2–7**) with some selected aliphatic alcohols were determined using differential UV spectrometry. The sample solution was kept at a given temperature ($\pm$ 0.1°C) by circulating thermostated water through the jacket. In order to determine thermodynamic quantities (ΔH° and ΔS°) for the complexation equilibrium, the spectral titrations of the solutions containing β-cyclodextrin derivatives (**2–7**) (2×10^{-4} mol dm^{-3}) with a series of the guest alcohols were repeatedly performed in aqueous solution at 25.0, 30.0, 35.0, and 40.0 °C.

3. Results and Discussion

3.1. CD SPECTRUM

As can be seen from Figure 1, the circular dichroism spectrum of modified β-cyclodextrin (**4**) in aqueous solution showed a strong negative Cotton effect peak, corresponding to the ^1L_a band, at 229 nm ($\Delta\epsilon = -6.75$) and a weak positive Cotton effect for the ^1L_b band at 271 nm ($\Delta\epsilon$ = 0.96). According to the sector rule proposed by Kajtar et al. [29], the Cotton effects observed for the ^1L_a and ^1L_b bands indicate that the aromatic moiety penetrates deeply into the hydrophobic cavity of cyclodextrin [28], which would favor inclusion complexation with a short chain aliphatic alcohol as a spacer. Furthermore, ICD spectra enable us to elucidate the conformation of the aromatic moiety on modified β-cyclodextrins and molecular recognition mechanism upon guest inclusion.

3.2. UV SPECTRAL TITRATIONS

As can be seen from Figure 2, in the titration experiments using UV spectrometry, the ^1L_b-band maximum of the aromatic group gradually increased upon addition of various concentrations of aliphatic alcohols (1.0–5.0 $\times$ 10^{-2} mol dm^{-3}), while the ^1L_a-band maximum decreased with an isosbestic point at 237 nm. This result indicates that modified β-cyclodextrins must suffer substantial conformational changes upon guest inclusion. This substantial conformational change is used to determine complex stability constants. Assuming the 1 : 1 stoichiometry, the inclusion complexation of aliphatic alcohols (G) with modified β-cyclodextrins (H) is expressed by Equation (1).

$$\mathrm{H} + \mathrm{G} \overset{K_s}{\rightleftharpoons} \mathrm{G} \cdot \mathrm{H}. \tag{1}$$

Under the conditions employed, the concentration of β-cyclodextrin derivatives is much smaller than that of aliphatic alcohols, i.e., $[\mathrm{H}]_0 \ll [\mathrm{G}]_0$. Hence, the sta-

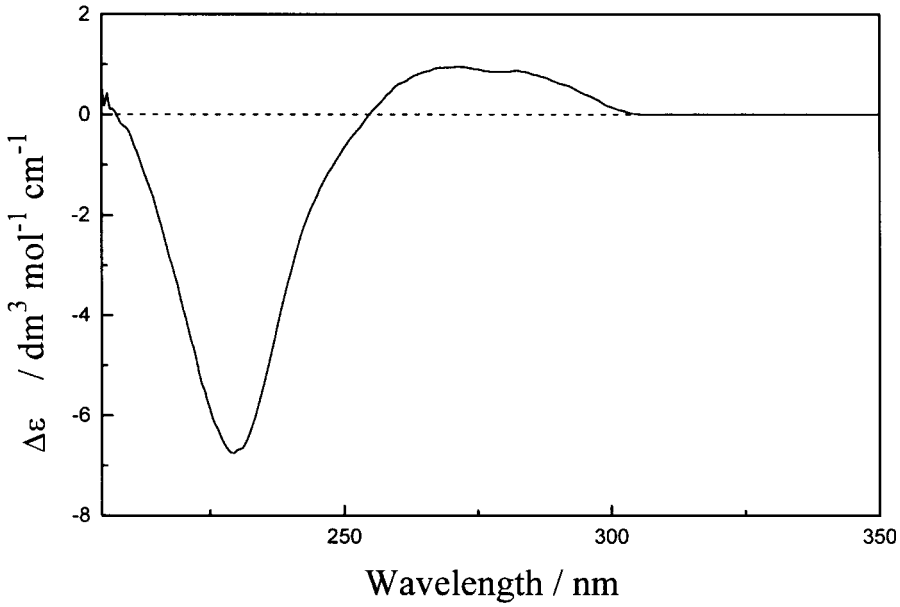

Figure 1. Circular dichroism spectrum of β-cyclodextrin derivative (**4**) (5×10^{-5} mol dm^{-3}) in aqueous solution at 25 °C.

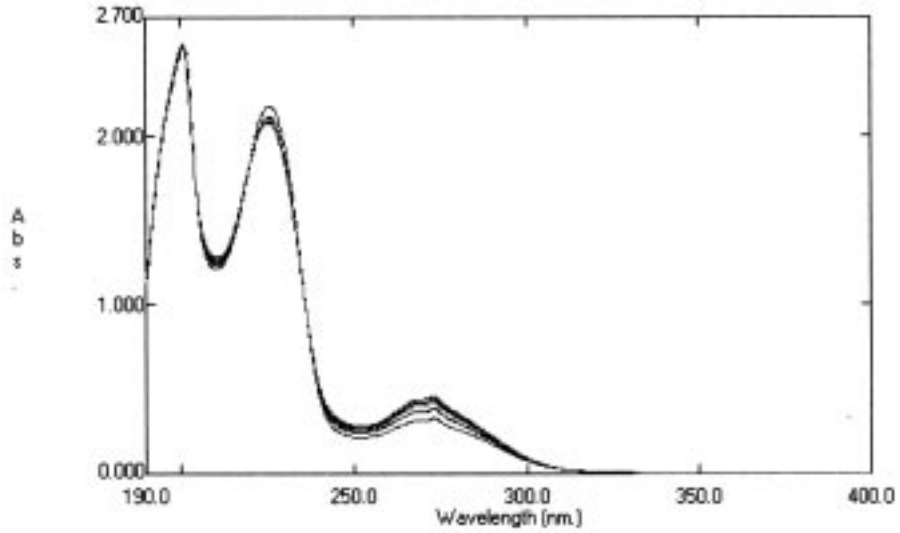

Figure 2. Spectrum of β-cyclodextrin derivative (**6**) at varying 1-hexanol concentration at 25.0 °C. The concentration of **6** is 2×10^{-4} mol dm^{-3}. The concentrations of 1-hexanol increase in the range of 0–5×10^{-2} mol dm^{-3} from bottom to top.

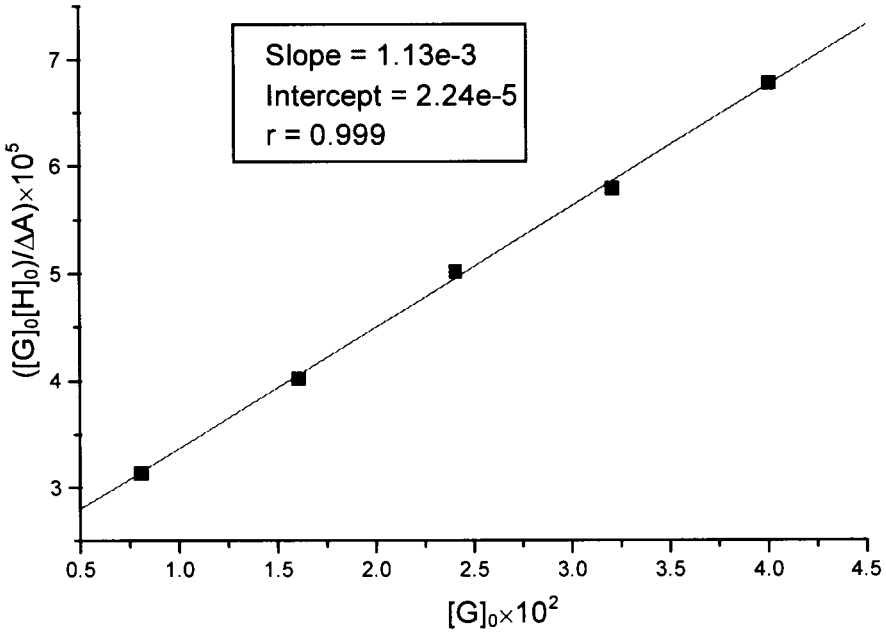

Figure 3. Typical plots of $[G]_0[H]_0/\Delta A$ versus $[G]_0$ for the host-guest complexation of 1-hexanol with **6** at 25 °C.

bility constant (K_s) of the inclusion complex formed can be calculated according to the modified Hildebrand–Benesi Equation (2) [30, 31].

$$\frac{[G]_0[H]_0}{\Delta A} = \frac{1}{K_s\,\Delta\epsilon} + \frac{[G]_0}{\Delta\epsilon}, \tag{2}$$

where $[G]_0$ and $[H]_0$ refer to the total concentration of aliphatic alcohols and β-cyclodextrin derivatives, respectively, $\Delta\epsilon$ is the difference between molar extinction coefficients for free and complexed β-cyclodextrin derivatives, ΔA denotes the changes in absorbance of the β-cyclodextrin derivative upon step-wise addition of the guest alcohol. For all host compounds examined, the plots of calculated $[G]_0[H]_0/\Delta A$ values as a function of $[G]_0$ give good straight lines, except for host compound (**8**), for which the spectral changes due to the inclusion complexation is too weak to be observed. A typical plot is shown in Figure 3 for the inclusion complexation of β-cyclodextrin derivative **6** with 1-hexanol, where the calculated $[G]_0[H]_0/\Delta A$ values are plotted against $[G]_0$ to give an excellent linear relationship (r = 0.999) with a slope of 1.13×10^{-3} mol dm^{-3} and an intercept of 2.24×10^{-5} mol^2 dm^{-6}. The results obtained verified the 1 : 1 stoichiometry of complexation as assumed above. The experiments were repeatedly performed at 25.0, 30.0, 35.0, and 40.0 °C and the stability constants (log K_s) from the slope and the intercept are listed in Table I.

Table I. Stability constants (log K_s) for the inclusion complexation of aliphatic alcohols with modified cyclodextrins (**2–8**) at 25–40 °C in aqueous solution*

Host	Guest	log K_s			
		25.0 °C	30.0 °C	35.0 °C	40.0 °C
2	1-pentanol	1.64	1.67	1.72	1.78
	1-hexanol	1.55	1.80	2.00	2.28
	1-heptanol	2.55	3.00	3.32	3.68
	cyclopentanol	2.04	2.09	2.10	2.14
	cyclohexanol	0.40	0.39	0.34	0.29
3	1-pentanol	1.52	1.48	1.37	1.35
	1-hexanol	1.85	1.74	1.72	1.64
	1-heptanol	2.60	2.79	3.16	3.40
	cyclopentanol	2.09	2.07	2.05	2.04
	cyclohexanol	1.15	1.11	1.02	0.96
4	cyclopentanol	2.04	1.92	1.84	1.78
	cyclohexanol	0.68	0.78	0.85	0.93
5	1-pentanol	1.05	1.56	2.00	2.44
	1-hexanol	1.68	1.59	1.43	1.31
	1-heptanol	3.50	3.25	3.03	2.84
	cyclopentanol	2.09	2.07	2.05	1.99
	cyclohexanol	1.40	1.39	1.37	1.35
6	1-pentanol	1.83	1.81	1.77	1.76
	1-hexanol	1.70	1.77	1.81	1.95
	1-heptanol	2.46	2.61	2.70	2.89
	cyclopentanol	2.26	2.25	2.17	2.10
	cyclohexanol	1.16	1.17	1.18	1.19
7	1-pentanol	0.95	1.10	1.26	1.79
	1-hexanol	1.67	1.88	1.91	2.06
	1-heptanol	3.35	3.17	3.08	2.91
	cyclopentanol	1.78	1.81	1.94	2.03
	cyclohexanol	0.96	0.94	0.87	0.74
8	All alcohols used above	No inclusion phenomena were observed			

The log K_s values are the average of two or three independent runs: error $< 5\%$ of the reported value.

3.3. THERMODYNAMIC PARAMETERS

The free energy changes (ΔG°) for inclusion complexation of the modified β-cyclodextrins with aliphatic alcohols are calculated from the equilibrium constant K_s by Equation (3) and is related to the enthalpic and entropic changes (ΔH° and ΔS°) through the Gibbs–Helmholtz Equation (4).

$$\Delta G^\circ = -RT \ln K_s, \tag{3}$$

$$\Delta G^\circ = \Delta H^\circ - T\,\Delta S^\circ, \tag{4}$$

$$\ln K_s = -\Delta H^\circ/RT + \Delta S^\circ/R. \tag{5}$$

Combining Equations (3) and (4), we obtain Equation (5) which describes the temperature dependence of K_s. Thus, the $\log K_s$ values, shown in Table I, are plotted as a function of the inverse temperature to give good linear relationships. A typical Van't Hoff plot for the inclusion complexation of 1-hexanol with host **2** is shown in Figure 4. The thermodynamic parameters obtained for each modified β-cyclodextrin are listed in Table II, along with the differential free energy change ($\Delta\Delta G^\circ$) for each CH_2 increment in both acyclic and cyclic alcohols. For comparison purpose, the thermodynamic quantities reported for the inclusion complexation with parent β-cyclodextrin (**1**) in aqueous solution are also included in Table II. It is quite interesting to note that, in sharp contrast to the constant increment in ΔG° around 3 kJ mol^{-1} per CH_2 unit, the $\Delta\Delta G^\circ$ values obtained for the present arylseleno cyclodextrins exhibit apparently random changes independent of the methylene number in the guest.

3.4. MOLECULAR BINDING ABILITY

In the present study, all of the organoselenium modifications to the primary side of β-cyclodextrin led to significant changes in molecular binding ability and thermodynamic quantities. As can be seen from Tables I and II, the complex stability constants, relative molecular selectivity, and thermodynamic parameters for inclusion complexation are affected drastically by several structural factors of β-cyclodextrin derivatives (**2–8**) and guest aliphatic alcohols, which include the relative size and the stereochemical complementary relationships between the host and the guest, the induced dipole of the functional sidearm attached to the edge of the cyclodextrin cavity, the microenvironmental hydrophobicity, and so on. Typically, the spectroscopic changes for modified β-cyclodextrin (**8**) upon addition of guest aliphatic alcohols are too weak to observe the inclusion complexation phenomena. One plausible explanation from the examinations of the CD spectra is that the naphthylseleno group in host (**8**) is embedded so tightly in the cavity that the aliphatic alcohols cannot appreciably exclude the self-included naphthyl group from the cavity. In fact, we have demonstrated recently [21] that native β-cyclodextrin forms

Table II. Thermodynamic parameters (in kJ mol^{-1}) for the inclusion complexation of aliphatic alcohols with modified β-cyclodextrins **2–8** at 25 °C in aqueous solution

Host	Guest	$-\Delta G°$/ kJ mol^{-1}	$-\Delta\Delta G°$/ kJ mol^{-1}	$-\Delta H°$/ kJ mol^{-1}	$T\Delta S°$/ kJ mol^{-1}	Ref.
1	1-pentanol	10.3		−4.6	14.9	a
	1-hexanol	13.3	3.0	−0.4	13.7	a
	cyclopentanol	12.8		4.6	8.2	a
	cyclohexanol	15.3	2.5	10.0	5.1	a
2	1-pentanol	9.3		−17.1	26.4	b
	1-hexanol	8.8	−0.5	−87.0	96.0	b
	1-heptanol	14.7	5.9	−134	150	b
	cyclopentanol	11.7		−11.6	23.2	b
	cyclohexanol	2.5	−9.2	18.2	−15.7	b
3	1-pentanol	8.7		21.7	−13.0	b
	1-hexanol	10.6	1.9	22.9	−12.4	b
	1-heptanol	14.8	4.2	−97.9	113	b
	cyclopentanol	11.9		5.94	5.99	b
	cyclohexanol	6.6	−5.3	24.1	−17.5	b
4	cyclopentanol	11.6		31.4	−19.8	b
	cyclohexanol	3.9	−7.7	−30.5	34.4	b
5	1-pentanol	6.4		−110	116	b
	1-hexanol	9.6	3.2	42.3	−32.8	b
	1-heptanol	19.9	10.3	77.8	−57.8	b
	cyclopentanol	12.1		15.8	−3.67	b
	cyclohexanol	5.6	−6.5	18.6	−13.0	b
6	1-pentanol	10.5		9.11	1.4	b
	1-hexanol	9.8	−0.7	−29.2	39.1	b
	1-heptanol	14.0	4.2	−49.5	63.5	b
	cyclopentanol	12.9		18.7	−5.75	b
	cyclohexanol	6.6	−6.3	−4.16	10.8	b
7	1-pentanol	5.1		−93.7	99.0	b
	1-hexanol	9.4	4.3	−45.8	55.2	b
	1-heptanol	19.0	9.6	48.1	−29.1	b
	cyclopentanol	10.1		−30.5	40.5	b
	cyclohexanol	6.3	−3.8	42.7	−33.4	b
8	All alcohols used above	No inclusion phenomena were observed				b

[a] Ref. 27.
[b] This work.

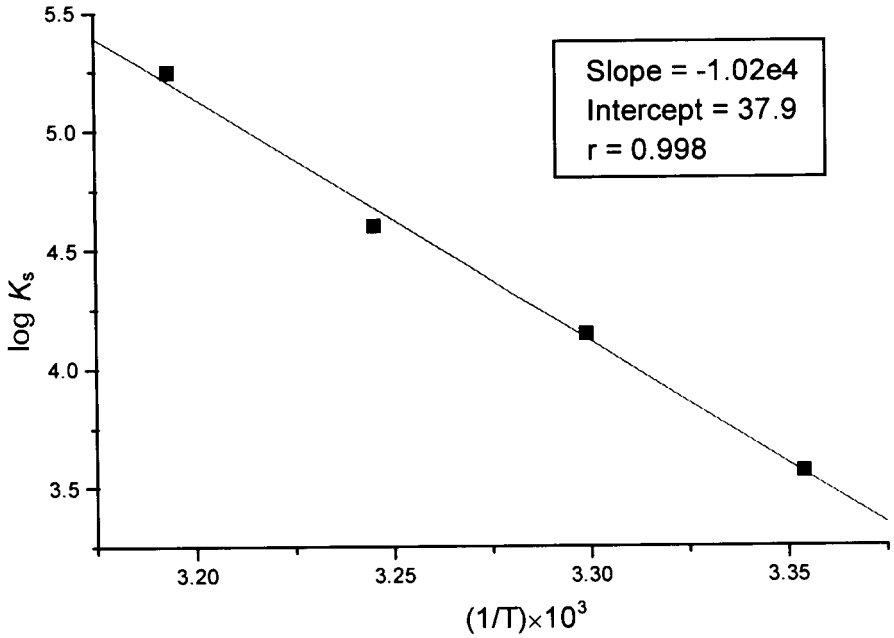

Figure 4. Typical plots of log K_s versus $1/T$ in spectrophotometric titrations of 1-hexanol with host compound (**2**) at 25 °C (■), 30 °C (●), 35 °C (▽) and 40 °C (▲).

tight inclusion complexes with several naphthalene derivatives with very high K_s in the order of 10^5 mol^{-1} dm^3. Hence, it seems reasonable that the aliphatic alcohols, which show much lower K_s mostly less than 10^3 mol^{-1} dm^3 for the other hosts (**2–7**), cannot compete with the originally self-included naphthyl sidearm of host (**8**). These results obtained indicate that the self-inclusion of the β-cyclodextrin's sidearm plays an important role in determining how the guest molecule fits into the host cavity, according to the sidearm's size, shape, dipole, charge, and functional group. In order to visualize the inclusion complexation behavior of modified β-cyclodextrins (**2–7**) with aliphatic alcohols from the thermodynamic point of view, the free energy ($-\Delta G°$), enthalpy ($-\Delta H°$), and entropy changes ($T\Delta S°$) on inclusion complexation of β-cyclodextrin (**1**) and its derivatives (**2–7**) are plotted as a function of chain length or size of aliphatic alcohols in Figure 5.

3.5. EFFECTS OF INTRODUCTION OF AROMATIC SIDEARMS

It is readily recognized from Figure 5 and Table II that the introduction of the aromatic sidearms to β-cyclodextrin leads to larger, more dynamic variations in both $\Delta H°$ and $\Delta S°$ for most guest molecules, while the $\Delta G°$ value is reduced more or less in all cases examined as a consequence of the overcancelling of the gain in $\Delta H°$ or $\Delta S°$ by the accompanying loss in $\Delta S°$ or $\Delta H°$.

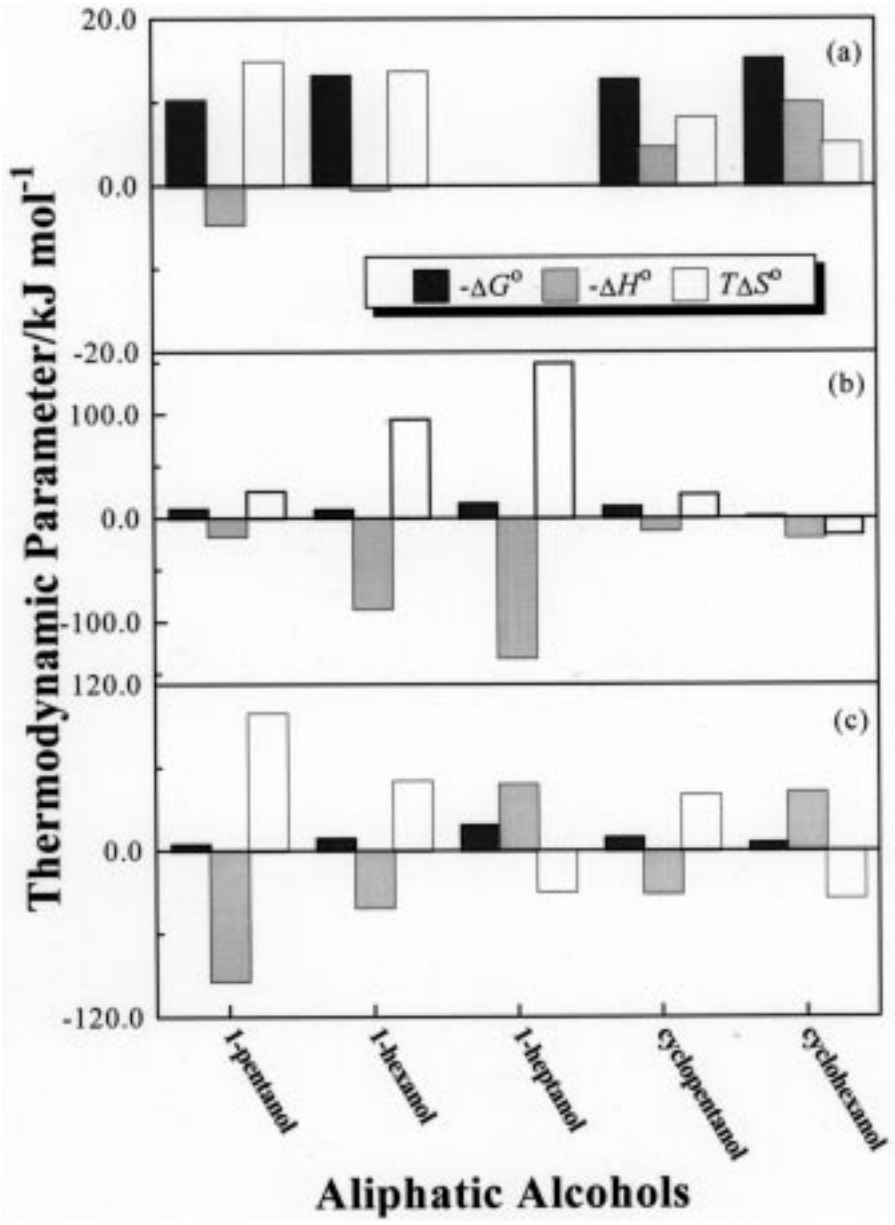

Figure 5. Free energy ($-\Delta G°$), enthalpy ($-\Delta H°$), and entropy changes ($T\Delta S°$) for the inclusion complexation of aliphatic alcohols with β-cyclodextrin (**1**) (a), **2** (b), and **7** (c) at 25 °C.

A more intriguing feature of the complexation thermodynamics of modified cyclodextrins **2–7** is the quite irregular changing profiles of the K_s value as well as other thermodynamic quantities for the series of acyclic and cyclic alcohols employed as guests. It is well-known that the log K_s value for α- and β-cyclodextrin is proportional to the number of methylene groups incorporated in the guest molecule. For the complexation of *n*-alkanols with β-cyclodextrin **1**, this unit increment per CH_2 group can be calculated as 3.0 kJ mol^{-1} from the data cited in Table II. Similar tendencies have been reported for the complexation of various categories of guest molecules with α- and β-cyclodextrins. Therefore, it is expected that each modified cyclodextrin **2–7** gives the highest K_s value for 1-heptanol, the longest acyclic alcohol. In sharp contrast to the original selectivity of **1**, all of the modified cyclodextrins examined **2–7** bind cyclopentanol 4–36 times stronger than the apparently size-matched cyclohexanol. One possible rationalization for these unusually critical guest discriminations and nonserial changing profiles is that the arylic sidearms are kept embedded in the cavity or capping the cavity opening even after the guest inclusion, working as spacers that render the cavity size in width and/or depth.

From the thermodynamic point of view, the relatively high selectivity for 1-heptanol displayed by **2**, **3** and **6** are evidently entropy-driven ($T\Delta S^\circ$ = 150, 113, and 63.5 kJ mol^{-1}, respectively). It is deduced therefore that the 1-heptanol with a flexibility skeleton can greatly change the original conformation to suit the cavity of modified β-cyclodextrin **2**, **3** and **6**, and undergo extensive desolvation of both host and guest for inclusion complexation, leading to the higher entropy change. Somewhat unexpectedly, the modified β-cyclodextrin **5** and **7** show the strongest inclusion complexation (log K_s = 3.50 and 3.35, respectively) for 1-heptanol among the aliphatic alcohols used, and form typical enthalpy-driven complexes ($-\Delta H^\circ$ = 77.8 and 48.1, respectively). This result may indicate that the inclusion of the guest's alkyl chain into the narrower cavity of modified hosts much enhance the van der Waals interaction and simultaneously reduces the guest's freedom, resulting in the large negative ΔH° and ΔS° values.

3.6. EFFECTS OF SUBSTITUTIONS ON AROMATIC SIDEARM

It should be noted from Figure 6a–d, that the free energy changes ($-\Delta G^\circ$) as well as enthalpy and entropy changes ($-\Delta H^\circ$, $T\Delta S^\circ$) are slightly sensitive to the position and the type of the substituent introduced to the aromatic ring of the β-cyclodextrin sidearm for inclusion complexation with aliphatic alcohols. All of the substituents introduced to the aromatic ring of the β-cyclodextrin sidearm led to increased inclusion complex stabilities for bulk cyclopentanol and cyclohexanol. As compared with mono[6-(*o*-tolyl)seleno-6-deoxy]-β-cyclodextrin (**3**), the *p*-isomer (**5**) forms the most stable complex with 1-heptanol (log K_s 3.50), which is mainly attributable to the increased negative enthalpy changes ($-\Delta H^\circ$). Therefore, the size or shape-fit combination between the host and guest gives the stronger van

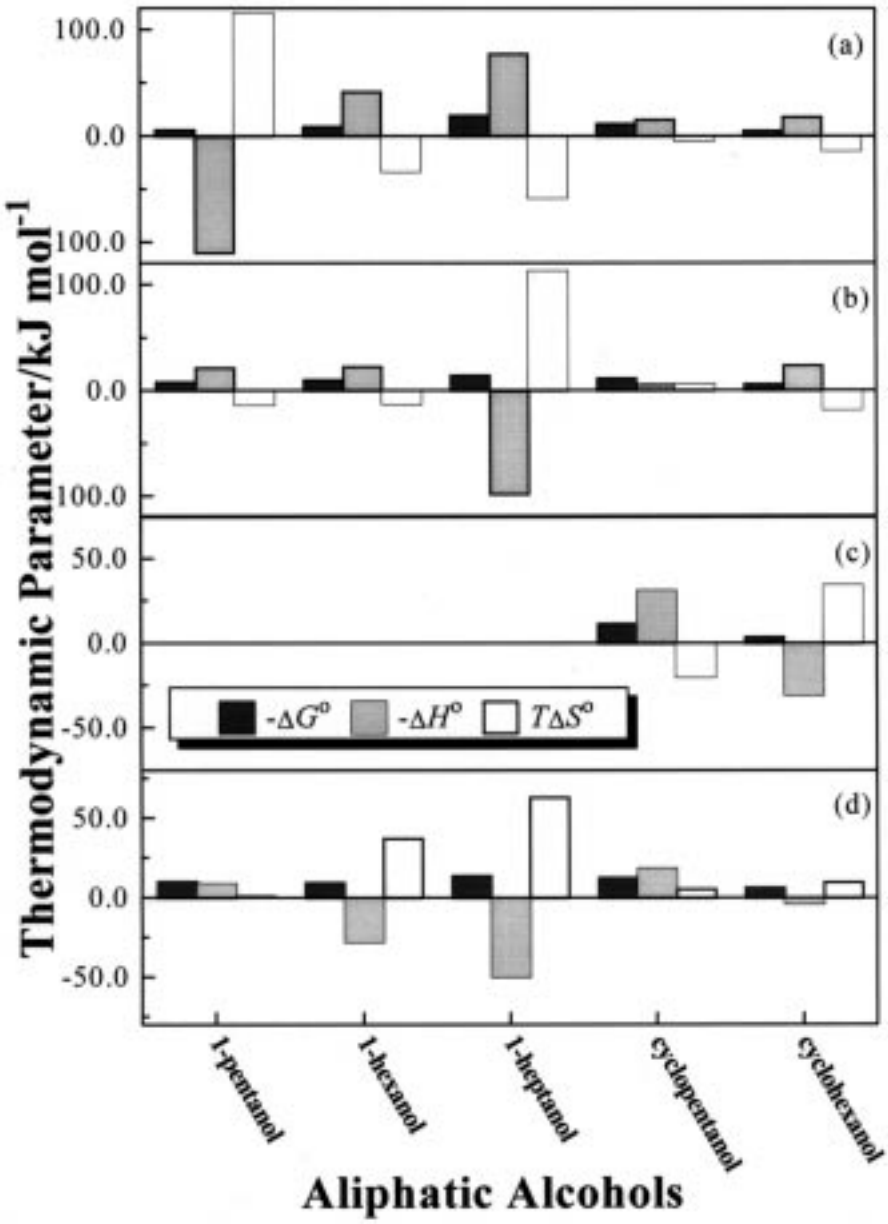

Figure 6. Free energy ($-\Delta G^\circ$), enthalpy ($-\Delta H^\circ$), and entropy changes ($T\Delta S^\circ$) for the inclusion complexation of aliphatic alcohols with **3** (a), **4** (b), **5** (c) and **6** (d) at 25 °C.

der Waals interaction to lead to the higher negative enthalpy changes and determined the complex stability to some extent. As compared with parent β-cyclodextrin and mono[6-(*o*- *m*-, and *p*-tolyl)seleno-6-deoxy]-β-cyclodextrins (**3–5**), mono[6-(*p*-chlorophenyl)seleno-6-deoxy]-β-cyclodextrin (**6**) shows poor binding abilities for 1-heptanol, giving the smallest stability constant. As one possible explanation, the chlorine atom in host compound (**6**) increased the side chain hydration in the host when compared with a methyl substituent, which is evidently assisted by the diminished enthalpic gain. These results indicate that the substitution on aromatic sidearm can affect not only the binding ability of the modified cyclodextrins with guest molecules but also the relative molecular selectivity.

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