Molecular Recognition Study on Supramolecular System. 14.[1] Synthesis of Modified Cyclodextrins and Their Inclusion Complexation Thermodynamics with L-Tryptophan and Some Naphthalene Derivatives

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A series of β-cyclodextrin derivatives, carrying pyridinio (**4**−**6**), phosphonyl (**7**, **8**), seleno (**9**−**11**), *m*- and *p*-picolinyl (**12**, **13**), *o*-chloroanilino (**16**), 8-quinolyl (**17**), furfuryl (**18**), and 9-fluorenyl (**19**) moieties in the side chain, were newly synthesized, and their complexation behavior was assessed and discussed thermodynamically, using L-tryptophan and a few naphthalene derivatives as representative guests. Calorimetric titrations have been performed at 25.0 °C in buffered aqueous solution (pH 7.20) to give the complex stability constants and thermodynamic parameters for the 1:1 inclusion complexation of these guests with the native and modified α-, β-, and/or γ-cyclodextrins (**1**−**20**). All of the chemical modifications to the primary side of cyclodextrins examined led to significant changes in complex stability and thermodynamic parameters, which are elucidated in terms of the conformational, electrostatic, hydrogen-bonding, and hydration effects. Thermodynamically, the inclusion complexation is mainly enthalpy-driven with a negative or minor positive entropic contribution, which in some cases determines the complex stability. The induced circular dichroism spectral analyses of these cyclodextrin derivatives indicated that the aromatic moiety in modified β-cyclodextrins (**4**−**6**, **9**−**19**) only shallowly penetrates into the hydrophobic cavity of β-cyclodextrin, while the phenyl phosphate and fluorenyl moieties in **7** and **20** are embedded into the hydrophobic cavity of β-cyclodextrin because of the longer linking chain. Using all the thermodynamic data for a wide variety of cyclodextrin derivatives obtained in this and previous studies, the entropy changes ($T\Delta S$) were plotted against the enthalpy changes (ΔH) to give an excellent linear relationship. The slope (α) of 1.02 and an intercept ($T\Delta S_0$) of 4.3 of the regression line indicate substantial conformational changes and extensive desolvation caused upon complexation, respectively.

Introduction

A wide variety of modified cyclodextrins with nucleophilic or electrophilic substituents attached to the primary side of cyclodextrin have been designed and synthesized to enhance the original binding ability and selectivity of intact cyclodextrins through further ligation or stereochemical complement of the functional side arm to the anionic or molecular guests accommodated in the cyclodextrin cavity.[1−6] Indeed, some modified cyclodextrins, which feature the bifunctionalized structures capable of multipoints recognition and induced-fit interaction with the guest accommodated in the cyclodextrin cavity, have been employed successfully in several areas of separation science and technology.[7−18] Consequently, a good deal of effort has been devoted to the synthesis of various cyclodextrin derivatives in order to examine their molecular recognition behavior and has recently been focused on the studies of the models of biological substrate−receptor interactions.[19−24] Unfortunately, the

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work on the molecular recognition thermodynamics for model substances such as phenethylamine and ephedrines,[25] hydrocarbons,[26] aliphatic alcohols,[27] aliphatic diols,[28] phenols,[29] amino acids,[9,29] cyclohexane derivatives,[30] naphthalene derivatives,[31] and other aromatic compounds[29] has been concentrated mainly on natural α-, β-, and γ-cyclodextrins. So far, less attention has been paid to the inclusion complexation thermodynamics of chemically modified α-, β-, and γ-cyclodextrins.[32]

Recently, we have demonstrated that all of the derivatizations of β-cyclodextrin diminish the complex stability with 2-naphthalenesulfonate, which are mostly attributable to the highly negative entropy changes ($T\Delta S$) that exceed the increased enthalpic gains ($-\Delta H$) arising from the enhanced hydrophobic interaction with lipophilic side chain(s) in the modified cyclodextrins. Using the compiled thermodynamic parameters reported for most available host−guest combinations which interact with each other through weak forces, it was further demonstrated that the enthalpy (ΔH) and entropy (ΔS) changes of complexation are compensatory to each other, displaying good linear relationship between ΔH and $T\Delta S$. The slope and intercept of the $\Delta H - T\Delta S$ plot are used as quantitative measures of the conformational changes and the extent of desolvation caused upon complexation, respectively.[32a] These results prompted us to investigate the complexation thermodynamics of much wider variety of modified cyclodextrins with several types of guest molecules in order to obtain deeper thermodynamic insights into the factors that govern the complexation phenomena between molecular receptor (host) and model substrate (guest).

In the present study, we synthesized several series of α-, β-, and γ-cyclodextrin derivatives, which include novel α-, β-, and γ-cyclodextrins carrying a positively charged pyridinio group (**4**−**6**, **12**, **13**), β-cyclodextrin 6-*O*-monophosphates (**7**, **8**), mono[6-(phenylseleno)-6-deoxy]-β-cyclodextrins (**9**, **10**), mono[6-(benzylseleno)-6-deoxy]-β-cyclodextrin (**11**), β-cyclodextrin derivatives bearing an anilino moiety (**14**−**16**), mono[6-*O*-(8-quinolyl)]-β-cyclodextrin (**17**), and β-cyclodextrin derivatives bearing a (furfurylideneamino)alkylamino or (9-fluorenylamino)-alkylamino moiety (**18**−**20**), as shown in Chart 1. The inclusion complexation behavior of these novel hosts with some representative guest molecules, shown in Chart 2, was investigated by using calorimetric titration to reveal the consequences of the modifications upon complexation from the thermodynamic point of view. The induced circular dichroism (ICD) spectral study with modified β-cyclodextrins enables us to elucidate the conformation of the aromatic moiety in the hosts (**4**−**7**, **9**−**20**) and to get significant insights into conjecturing inclusion complexation mechanism.

The thermodynamic parameters for the complexation with cyclodextrin derivatives (**1**−**20**), together with those reported,[32] will serve our further understanding of this recently developing, but thermodynamically less investigated, area of chemically modified cyclodextrins. Another aspect of interest of this study is to test and discuss in further depth the general validity and the significance of the enthalpy−entropy compensation effect in the complexation of modified cyclodextrins, using a wider variety of host−guest combinations.

Experimental Section

General Procedures. Combustion analyses were performed on a Perkin-Elmer-240 instrument. ^{1}H NMR spectra were recorded at 200 or 400 MHz in [$^2H_6$]dimethyl sulfoxide (DMSO-d_6) on a Bruker AM200 or AM400 spectrometer. FT-IR and UV spectra were obtained on a Nicolet FT-IR 5DX and Shimadzu UV-2401PC spectrometer, respectively. Circular dichroism (CD) spectra were recorded on a JASCO J-720 spectropolarimeter. A TRONAC model 458 isoperibol titration calorimeter was used for all of the thermodynamic measurements.

Materials. Commercially available L-tryptophan (Tianjin Chemical Reagent Factory), sodium 3-hydroxy-2-naphthoate (Aldrich), sodium salts of 2-naphthalenesulfonate and 2,7-naphthalenedisulfonate (Nakarai) were dried in vacuo prior to use. α- and γ-cyclodextrins purchased from Nakarai were used without further purification. β-Cyclodextrin of reagent grade (Suzhou Monosodium Glutamate Works) was recrystallized twice from water and dried for 12 h in vacuo at 100 °C. *N*,*N*-Dimethylformamide (DMF) was dried over calcium hydride for 2 days and then distilled under a reduced pressure prior to use. 9-Bromofluorene and diphenyl phosphorochloridate (DojinDo) and 8-hydroxyquinoline of analytical reagent grade were used without further purification. Mono[6-(1-pyridinio)-6-deoxy]-α-, -β-, and -γ-cyclodextrins (**4**−**6**) were synthesized according to the procedures reported by Matsui et al.[33] Mono(6-*O*-diphenylphosphoro)- (**7**) and mono(6-*O*-ethoxyhydroxyphosphoro)-β-cyclodextrin (**8**) were synthesized as reported recently.[1a] Mono[6-(*m*-toluidino)-6-deoxy]-β-cyclodextrin (**15**) and mono[6-[[(9-fluorenylamino)ethyl]amino]-6-deoxy]-β-cyclodextrin (**19**) were prepared by the reported procedures.[1c] Disodium hydrogen phosphate and sodium dihydrogen phosphate were dissolved in distilled, deionized water to make a 0.10 M phosphate buffer solution of pH 7.20 for calorimetric titration.

Synthesis of Mono(6-phenylseleno-6-deoxy)-β-cyclodextrin (9). Mono[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin was prepared by a reaction of β-cyclodextrin with *p*-toluenesulfonyl chloride in dry pyridine.[33] The compound (**9**) was prepared by the following procedures. Sodium borohydride ($NaBH_4$) was added to a yellow solution of diphenyl diselenide[34a] in anhydrous ethanol with stirring under nitrogen at room tempera-

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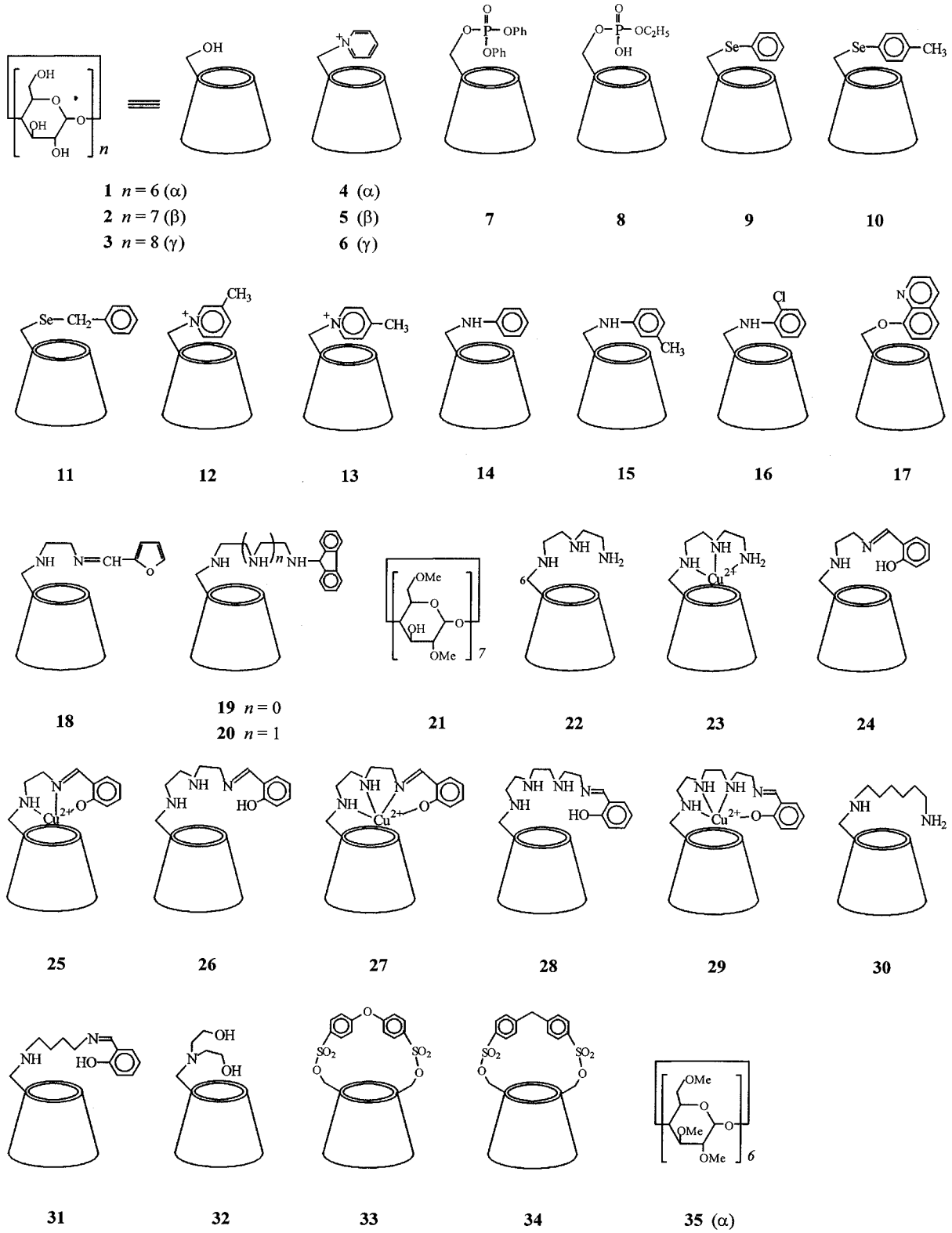
Chart 1. Cyclodextrin Derivatives (Mostly *β*-Cyclodextrin, unless Noted Otherwise)

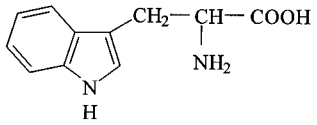


1 *n* = 6 (α)
2 *n* = 7 (β)
3 *n* = 8 (γ)
4 (α)
5 (β)
6 (γ)
7
8
9
10
11
12
13
14
15
16
17
18
19 *n* = 0
20 *n* = 1
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35 (α)

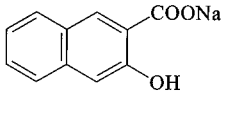
ture. After the solution turned colorless, a solution of mono[6-*O*-(*p*-toluenesulfonyl)]-*β*-cyclodextrin in DMF was added dropwise into the solution, heated to 60 °C for 2 h with stirring. The resulting solution was evaporated under a reduced pressure to give light-yellow powder, which was dissolved in a minimal amount of hot water and then poured into acetone (100 mL). The participate was collected by filtration to obtain white powder (yield 45%): ^{1}H NMR (DMSO-d_6, TMS) δ 2.8−3.9 (m, 40H), 4.0−4.6 (m, 8H), 4.8−5.2 (m, 7H), 5.3−5.8 (m, 14H), 7.1−7.9 (m, ArH); FT-IR (KBr) ν 3386.5, 2914.5, 1731.7, 1698.5, 1629.2, 1600.7, 1558.2, 1537.6, 1513.6, 1397.7, 1363.5, 1302.6, 1273.5, 1232.8, 1170.3, 1149.3, 1073.2, 1023.2, 939.7, 883.5, 830.0, 774.6, 751.5, 726.9, 699.1, 661.6 cm^{-1}. Anal. Calcd for $C_{48}H_{74}O_{34}Se\cdot 2H_2O$: C, 43.48; H, 5.93. Found: C, 43.57; H, 5.55.

Synthesis of Mono[6-[(*p*-tolyl)seleno]-6-deoxy]-*β*-cyclodextrin (10). Compound **10** was prepared from mono[6-*O*-(*p*-toluenesulfonyl)]-*β*-cyclodextrin and di(*p*-tolyl) diselenide[34a] according to procedures similar to those employed in the synthesis of **9** (yield 47%). **10**: ^{1}H NMR (DMSO-d_6, TMS) δ

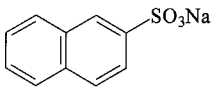
Chart 2



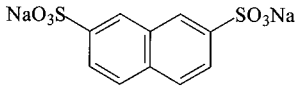
L-Tryptophan



Sodium 3-hydroxy-2-naphthoate



Sodium 2-naphthalenesulfonate



Disodium 2,7-naphthalenedisulfonate

2.1 (s, 3H), 3.1−3.8 (m, 40H), 4.0−4.6 (m, 8H), 4.8−5.2 (7H), 5.3−5.8 (m, 14H), 7.1 (t, 4H); FT-IR (KBr) ν 3383.0, 2914.0, 1731.8, 1698.0, 1632.0, 1556.3, 1512.7, 1397.8, 1364.9, 1297.3, 1267.4, 1233.8, 1149.3, 1072.9, 1023.3, 939.6, 890.2, 830.9, 799.4, 772.9, 751.5, 699.7, 660.2 cm^{-1}. Anal. Calcd for $C_{49}H_{76}O_{34}Se\cdot 2H_2O$: C, 44.40; H, 6.09. Found: C, 44.32; H, 6.01.

Synthesis of Mono(6-benzylseleno-6-deoxy)-β-cyclodextrin (11). Compound **11** was prepared from mono[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin and dibenzyl diselenide[34b] according to procedures similar to those employed in the synthesis of **9** (yield 50%). **11**: ^{1}H NMR (DMSO-d_6, TMS) δ 3.1−3.9 (m, 40H), 4.1−4.6 (m, 8H), 4.8−5.2 (9H), 5.3−5.8 (m, 14H), 7.3 (t, 5H). FT-IR (KBr) ν 3369.0, 2912.5, 1730.9, 1701.5, 1638.6, 1615.4, 1574.6, 1536.7, 1514.6, 1398.6, 1365.0, 1336.5, 1302.9, 1273.9, 1235.1, 1149.4, 1127.1, 1073.8, 1022.3, 938.4, 885.6, 789.7, 769.3, 692.7, 658.7 cm^{-1}. Anal. Calcd for $C_{49}H_{76}O_{34}Se\cdot 6H_2O$: C, 42.15; H, 6.35. Found: C, 42.12; H, 6.10.

Synthesis of Mono[6-(*m*-picolinyl)-6-deoxy]-β-cyclodextrin (12).[33] Mono[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin (2 g) was added to *m*-picoline (30 mL), and the solution was refluxed for 12 h under nitrogen atmosphere. The resulting solution was evaporated under a reduced pressure to give yellow residue, which was subjected to column chromatography on Sephadex G-25 with the elution of aqueous ammonium hydrogen carbonate solutions (yield: 91%). **12**: FAB-MS *m*/*z* 1210; ^{1}H NMR (DMSO-d_6, TMS) δ 1.07 (t, CH_3), 3.3−3.6 (m, 42H), 8.0 (t, 1H), 8.4 (d, 1H), 8.8 (d, 2H); FT-IR (KBr) ν 3372.5, 2910.0, 1629.5, 1479.2, 1403.4, 1377.9, 1328.9, 1293.4, 1147.6, 1115.9, 1073.8, 1023.0, 937.5, 832.2, 750.6, 699.4, 679.3, 601.2, 567.1 cm^{-1}. Anal. Calcd for $C_{49}H_{77}O_{37}N\cdot 3H_2O$: C, 44.38; H, 6.31; N, 1.06. Found: C, 44.30; H, 6.06; N, 1.35.

Synthesis of Mono[6-(*p*-picolinyl)-6-deoxy]-β-cyclodextrin (13). Compound **13** was synthesized from mono[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin and *p*-picoline according to the procedures described above (yield: 89%). **13**: FAB-MS *m*/*z* 1210; ^{1}H NMR (DMSO-d_6, TMS) δ 1.08 (m, CH_3), 3.1−3.7 (m, 42H), 7.9 (d, 2H), 8.8 (d, 2H); FT-IR (KBr) ν 3376.0, 2908.0, 1640.0, 1580.2, 1555.8, 1513.1, 1405.8, 1380.3, 1346.8, 1295.9, 1140.1, 1116.6, 1074.2, 1024.6, 935.2, 835.4, 809.9, 748.4, 699.1, 678.3, 604.1, 566.1 cm^{-1}. Anal. Calcd for $C_{49}H_{77}O_{37}N$: C, 46.26; H, 6.10; N, 1.10. Found: C, 46.06; H, 5.88; N, 1.50.

Synthesis of Mono(6-anilino-6-deoxy)-β-cyclodextrin (14). The 6-anilino-β-cyclodextrin was prepared by the reaction of mono[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin (2 g) with aniline (10 mL) in *N*,*N*-dimethylformamide (20 mL) at 85 °C with stirring for 12 h under a nitrogen atmosphere. The reaction mixture was evaporated in vacuo at 40 °C to dryness. The residue was dissolved in water, and the resulting mixture was poured into acetone to give gray precipitate. After drying, the precipitate was purified by recrystallization from water twice; 0.85 g (yield 45%) of light yellow solid was obtained: ^{1}H NMR (DMSO-d_6, TMS) δ 0.85, 1.23 (m, 1H, N−H), 2.65 (d, 2H, CH_2), 3.2−4.4 (m, C−H, O−H), 6.7−7.5 (m, 4H, Ar−H); FT-IR (KBr) ν 3385.9, 2926.6, 1638.7, 1605.9, 1507.4, 1417.2, 1368.0, 1335.2, 1302.3, 1253.1, 1237.0, 1154.7, 1080.9, 1031.6, 941.4, 859.4, 752.7, 703.5, 572.3 cm^{-1}. Anal. Calcd for $C_{48}H_{75}O_{34}N\cdot 3H_2O$: C, 45.61; H, 6.4; N, 1.11. Found: C, 45.9; H, 6.51; N, 1.14.

Synthesis of Mono[6-(*o*-chloroanilino)-6-deoxy]-β-cyclodextrin (16). Compound **16** was prepared from mono[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin and *o*-chloroaniline as above.[1c] **16**: FAB-MS *m*/*z* 1244; ^{1}H NMR (DMSO-d_6, TMS) δ 3.2−4.3 (m, 42H), 6.7−7.5 (m, ArH); FT-IR (KBr) ν 3385.9, 2926.6, 1638.7, 1605.7, 1507.4, 1417.2, 1368, 1335.2, 1302.3, 1253.1, 1237, 1154.7, 1080.9, 1031.6, 941.4, 859.4, 752.7, 703.5, 572.3 cm^{-1}. Anal. Calcd for $C_{48}H_{74}O_{34}Cl\cdot 3H_2O$: C, 44.41; H, 6.17; N, 1.08. Found: C, 44.22; H, 6.35; N, 1.02.

Synthesis of Mono[6-*O*-(8-quinolyl)]-β-cyclodextrin (17). This compound was prepared by the reaction of mono[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin (2 g) with 8-hydroxyquinoline (1 g) in the presence of potassium carbonate (0.3 g) in *N*,*N*-dimethylformamide (30 mL) with stirring at 90 °C for 20 h under a nitrogen atmosphere. A workup procedure similar to that above gave yellow precipitate. After drying, the precipitate was purified by column chromatography using Sephadex G-25; 0.93 g (yield 41.4%) of light yellow solid was obtained: ^{1}H NMR (DMSO-d_6, TMS) δ 3.2−4.3 (m, β-cyclodextrin protons); 7.1−9.2 (m, 8-quinolyl protons); FT-IR (KBr) ν 3320, 2910, 2160, 1652, 1625, 1503, 1407, 1370, 1328, 1258, 1200, 1153, 1078, 1025, 940, 860, 820, 788, 752, 710 cm^{-1}. Anal. Calcd for $C_{51}H_{75}O_{35}N\cdot 6H_2O$: C, 44.70; H, 6.30; N, 1.02. Found: C, 44.44; H, 5.96; N, 1.17.

Synthesis of Mono[6-[[(furfurylideneamino)ethyl]amino]-6-deoxy]-β-cyclodextrin (18). To an ethanol solution (4 mL) of furfural (0.2 mL) was added an aqueous solution (10 mL) of mono[6-(ethylenediamino)-6-deoxy]-β-cyclodextrin (0.5 g)[35] with stirring at 0 °C. The mixture was stirred for additional 1 h and filtrated to give a precipitate, which was washed twice with ethanol and then subjected to column chromatography on a Sephadex G-25 to yield the product, 0.35 g (yield 66%): FAB-MS *m*/*z* 1255; ^{1}H NMR (DMSO-d_6, TMS) δ 7.1−7.4, 7.5−7.8, 8.1−8.2 (furyl); FT-IR (KBr) ν 3385.9, 2926.6, 1638.7, 1556.6, 1409.6, 1354, 1335.2, 1244.9, 1154.7, 1080.9, 1031.6, 941.41, 752.7, 703.5, 580.5 cm^{-1}. Anal. Calcd for $C_{49}H_{79}O_{35}N_2\cdot 4H_2O$: C, 44.18; H, 6.41; N, 1.97. Found: C, 44.18; H, 6.54; N, 1.97.

Synthesis of Mono[6-[[[[(9-fluorenylamino)ethyl]amino]ethyl]amino]-6-deoxy]-β-cyclodextrin (20). A solution of mono(6-alkylamino-6-deoxy)-β-cyclodextrin[35] and 9-bromofluorene in dry DMF (30 mL) was stirred for 10 min under nitrogen at 0 °C. A solution of triethylamine (10 mL) was added dropwise into the clear solution in 1 h with stirring under nitrogen. The solution was allowed to warm and stirred for additional 6 h at room temperature, and then the resultant mixture was evaporated under reduced pressure. The residue was dissolved in water and then poured into acetone to give a yellow precipitate, which was washed with acetone. The crude product was purified by the column chromatography on Sephadex G-25 with the elution of distilled, deionized water: FAB-MS *m*/*z* 1384; ^{1}H NMR (DMSO-d_6, TMS) δ 3.58−4.7 (m, 42H), 7.30−7.80 (m, ArH); FT-IR (KBr) ν 3377.7, 2926.6, 1704.3, 1638.7, 1425.4, 1368, 1302.3, 1296.7, 1154.7, 1080.9, 1031.6, 941.4, 851.1, 752.7, 703.5, 580.6, 539.4 cm^{-1}. Anal. Calcd for $C_{59}H_{90}O_{34}N_4\cdot 3H_2O$: C, 48.76; H, 6.60; N, 3.86. Found: C, 48.52; H, 6.88; N, 3.51.

Spectral Measurements. Circular dichroism spectra were measured in a buffer solution (pH 7.20) at room temperature in order to elucidate the inclusion of the host's aromatic moiety into the cyclodextrin cavity.

Calorimetric Measurements. Calorimetric titrations in an aqueous buffer solution were performed at pH 7.20 in a temperature-controlled water bath maintained at 25 °C, by using a TRONAC model 458 isoperibol titration calorimeter connected to a personal computer for automated titration and data processing.[36] Typically, a solution of 2-naphthalene-

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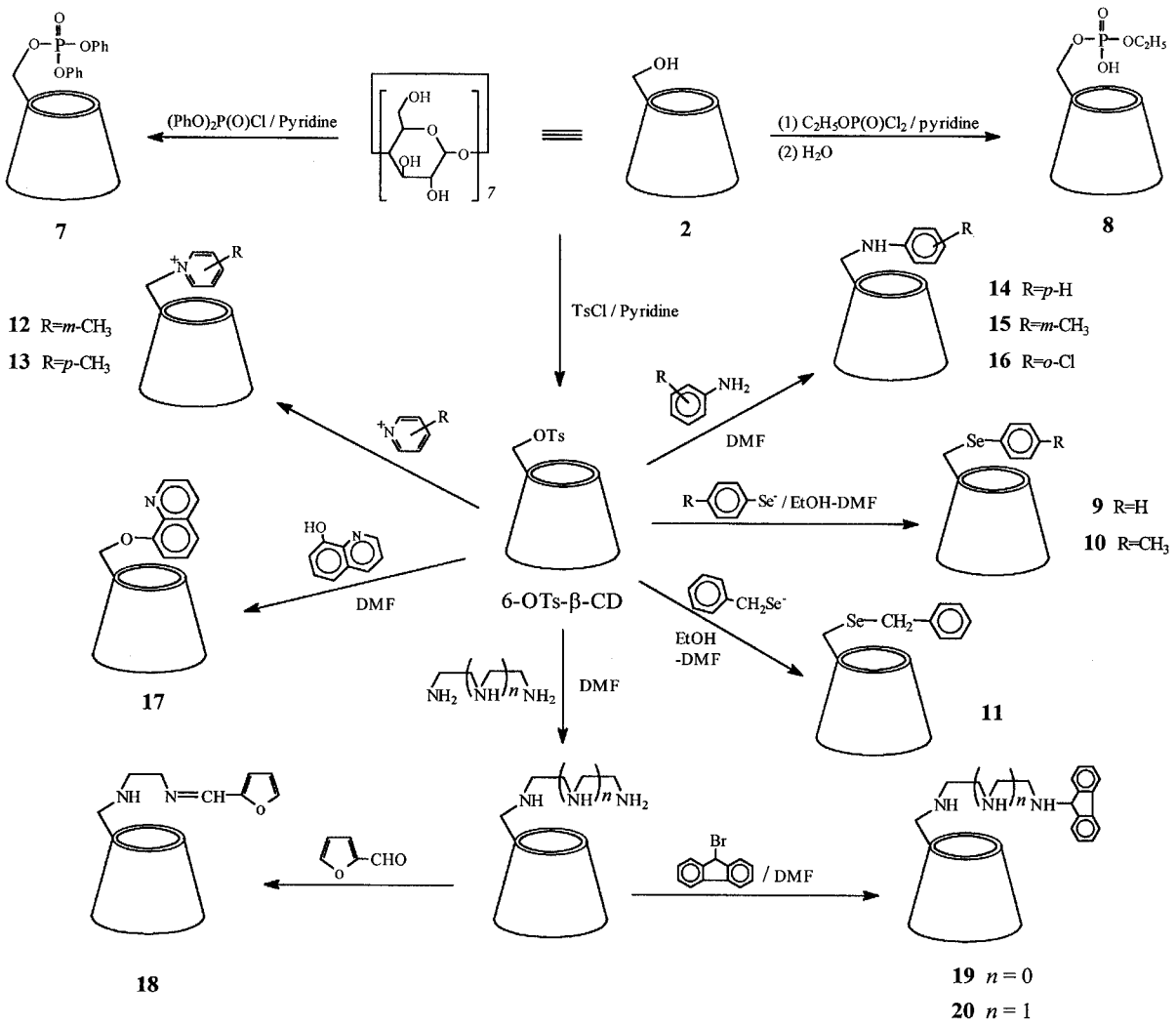
(36) Liu, Y.; Han, B.-H.; Li, Y.-M.; Chen, Y.-T.; Ouchi, M.; Inoue, Y. *J. Phys. Chem.* **1996**, *100*, 17361.

Scheme 1



sulfonate was continuously introduced at a rate of 0.3321 mL/min into a solution of cyclodextrin derivatives (**4**−**20**) (2−5 mM) placed in the calorimeter. To obtain the net heat of complexation (Q_{net}), the total apparent heat observed (Q_{obs}) was corrected for the dilution of titrant (Q_D), the nonchemical contributions (Q_{HL}), including agitation, heat flow between the vessel and its surrounding, and resistance heating by the thermistor used, and the temperature difference between titrant and titrate (Q_{TC}) in each run: $Q_{net} = Q_{obs} - Q_D - Q_{HL} - Q_{TC}$. A titration curve was obtained by plotting the temperature change (measured by voltage) against the amount of the aromatic guest solution added, from which the complex stability constant (K) and the enthalpy change (ΔH) were calculated. Reliability of the whole system and the calculation procedures were doubly checked as previous[37] by comparison of the obtained thermodynamic data with the reported values,[38,39] and satisfactory results were obtained.

Results and Discussion

Synthesis. As shown in Scheme 1, the modified cyclodextrins (**4**−**6**, **9**−**20**) were synthesized in satisfactory yields starting from 6-*O*-monotosylcyclodextrin, while the modified β-cyclodextrins (**7**, **8**) were synthesized by the esterification of the 6-hydroxyl group of cyclodextrin.

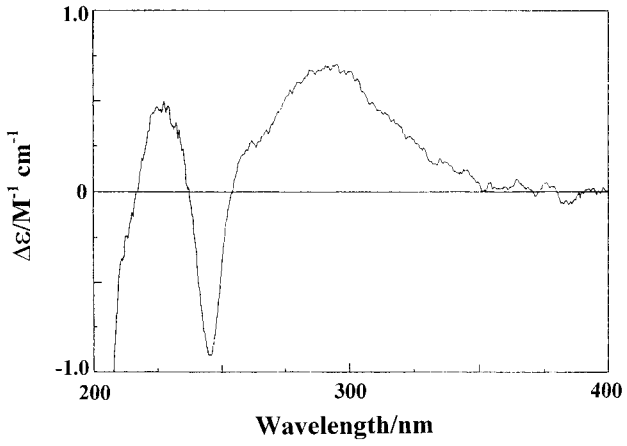


Figure 1. Circular dichroism spectrum of β-cyclodextrin derivative (**17**) (0.094 mM) in aqueous buffer solution (pH 7.20) at room temperature.

CD Spectra. Possessing a chiral cavity, cyclodextrins can accommodate the chromophoric substituent group attached to its primary side, which leads to the induced circular dichroism. As can be judged from the relatively weak induced circular dichroism (ICD) spectra exemplified in Figures 1 and 2, the aromatic moieties of most β-cyclodextrin derivatives (**5**, **9**−**19**) with lipophilic substituents are deduced to penetrate only shallowly into

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(38) Hansen, L. D.; Lewis, E. R. *J. Chem. Thermodyn.* **1971**, *3*, 35.
(39) Inoue, Y.; Hakushi, T.; Liu, Y.; Tong, L.-H.; Hu, J.; Zhao, G.-D.; Huang, S.; Tian, B.-Z. *J. Phys. Chem.* **1988**, *92*, 2371.

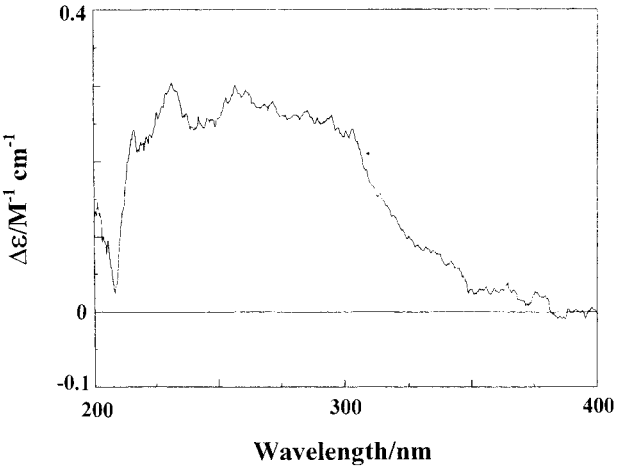

Figure 2. Circular dichroism spectrum of β-cyclodextrin derivative (**20**) (0.110 mM) in aqueous buffer solution (pH 7.20) at room temperature.

the hydrophobic cavity. In contrast, more hydrophilic and/or bulky substituents such as phosphate or 9-fluorenyl in **7** or **20** do not appear to be accommodated in the cavity. Typically, the circular dichroism spectra of mono[6-*O*-(8-quinolyl)]-β-cyclodextrin (**17**) (0.094 mM) in aqueous solution (Figure 1) shows a negative Cotton effect peak at a wavelength corresponding to the ^1L_a band (λ_{ext} 245.8 nm, $\Delta\epsilon = -0.909$) and a positive Cotton effect peak for the ^1L_b band (λ_{ext} 295 nm, $\Delta\epsilon = 0.708$). The modified β-cyclodextrin (**20**) with a fluorenyl group shows two weaker positive Cotton effect peaks for the ^1L_a band at 305 nm ($\Delta\epsilon = 0.301$) and for the ^1L_b band at 216.6 nm ($\Delta\epsilon = 0.242$) (Figure 2). According to the sector rule proposed by Kajtar et al.,[40] the Cotton effects observed for the ^1L_a and ^1L_b bands indicate that the 8-quinolyl moiety of **17** penetrates only shallowly into the hydrophobic cavity of cyclodextrin. Similarly the very weak ICD peaks observed for **20** indicates that the (9-fluorenyl)alkylamino group is perching on the edge of cyclodextrin cavity.

Calorimetry. The treatment of the calorimetric data obtained has been described previously.[41,42] Assuming a 1:1 stoichiometry for the inclusion complexation of some selected guest molecules (**G**) with native and modified cyclodextrins (**1**−**20**) (**CD**), the complex stability constant (K) and the enthalpy change ($\Delta H°$) were determined simultaneously by using the least-squares method to minimize the error square sum (U):[43,44]

$$\mathbf{G} + \mathbf{CD} \overset{K}{\rightleftharpoons} \mathbf{G{\cdot}CD} \qquad (1)$$

$$U(K,\Delta H°) = \sum_{t=1}^{m} (Q_t - \Delta H° \times N_t)^2 \qquad (2)$$

where Q_t refers to the net heat of complexation measured at time t in minutes and N_t denotes the amount in moles of the complex formed at time t and is directly related to the complex stability constant K.

The stability constant K and the enthalpy change $\Delta H°$ for the complexation of model substances with molecular receptors (**1**−**20**) were calculated by computer simulation by continuously changing K, i.e., N_t, to minimize the U value. For each host−guest combination, the measurement was repeated more than three times and the U value obtained was minimized satisfactorily to give the optimized set of K and $\Delta H°$ with standard deviations. No serious deviation was found in the fitting process, verifying the 1:1 stoichiometry of complexation as assumed above. The complex stability constants and thermodynamic parameters obtained are listed in Table 1. For comparison purpose, the thermodynamic quantities reported for the complexation with β-cyclodextrin derivatives (**21**−**35**) are also included in Table 1.

Binding Constants and Thermodynamic Parameters. Thermodynamic studies of molecular recognition by modified cyclodextrins have shown that an important feature of the inclusion complexation is simultaneous operation of several weak forces working between guest molecule and host cyclodextrin, which play important roles in determining how the guest molecule fits into the host cavity, according to its size, shape, dipole, charge, and functional group. Therefore, the attachment of nucleophiles or electrophiles to cyclodextrins is expected to affect the inclusion behavior of these modified cyclodextrins. From the ICD spectra, it is deduced that some functional groups, attached to the edge of cyclodextrin cavity, are embedded into the cavity of cyclodextrin, preventing the guest inclusion at least in part. On the other hand, the hydrophilic functional groups situated just above the cavity may increase the host hydration and therefore decrease the microenvironmental hydrophobicity to a great extent.[32a] As can be seen from Table 1, the complex stability constants, relative selectivity, and thermodynamic parameters for the inclusion complexation of the guest molecules (Chart 2) with modified cyclodextrins (**1**−**20**) are influenced by several factors: relative size between the cyclodextrin's cavity to the guest molecule, induced dipole of functional side arm attached to the edge of cyclodextrin cavity, spatial conformation, microenvironmental hydrophobicity, van der Waals, hydrogen-bonding interactions, and so on. To visualized the molecule-binding behavior of cyclodextrins (**1**−**20**) from the thermodynamic point of view, the free energy ($-\Delta G$), enthalpy ($-\Delta H$), and entropy changes ($T\Delta S$) for the inclusion complexation of L-tryptophan and the naphthalene derivatives are plotted for the host cyclodextrins (**1**−**20**) in Figures 3a−d.

As can be recognized more easily from Figures 3a−d, the ΔH values for the inclusion complexation of cyclodextrins (**1**−**20**) with the guests are all negative and stabilizing, whereas the $T\Delta S$ values are either negative or slightly positive. This means that these inclusion reactions are primarily enthalpy-driven processes, although some host−guest combinations, including **2**, **5**, **8**, and **13** as hosts, are evidently assisted by the entropy term to a great extent. For the inclusion complexation of L-tryptophan, 3-hydroxy-2-naphthoate, 2-naphthalenesulfonate, and 2,7-naphthalenedisulfonate with cyclodextrins, the enthalpic ($-\Delta H$) and entropic ($T\Delta S$) contributions to the complex stability ($-\Delta G$) are discussed below.

Complexation of L-Tryptophan. As can be seen from Table 1 and Figure 3a, the size-fitted combination of L-tryptophan with β-cyclodextrin (**2**) gives the strongest

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Table 1. Complex Stability Constant (*K*) and Thermodynamic Parameters (in kcal/mol) for 1:1 Host−Guest Complexation of Some Aromatic Guest Molecules with Cyclodextrins and Modified Cyclodextrins (1−20) in Aqueous Solution (*T* = 298 K)

host	guest	log *K*	$-\Delta G°$	$-\Delta H°$	$T\Delta S°$	ref
1	L-tryptophan	1.79 ± 0.03	2.44	2.32 ± 0.07	0.12	*a*
2		3.26 ± 0.04	4.45	1.11 ± 0.06	3.34	*a*
3		1.95 ± 0.07	2.66	5.18 ± 0.11	−2.52	*a*
4		2.39 ± 0.05	3.26	2.64 ± 0.12	0.62	*a*
5		3.71 ± 0.03	5.06	1.06 ± 0.05	4.00	*a*
6		2.22 ± 0.01	3.02	5.71 ± 0.05	−2.69	*a*
7		1.98 ± 0.08	2.70	7.61 ± 0.07	−4.91	*a*
8		3.36 ± 0.06	4.58	1.47 ± 0.09	3.11	*a*
9		2.07 ± 0.03	2.82	8.20 ± 0.13	−5.38	*a*
10		2.24 ± 0.04	3.06	2.68 ± 0.11	0.38	*a*
11		2.02 ± 0.02	2.76	2.40 ± 0.05	0.36	*a*
2	sodium 3-hydroxy-2-naphthoate	2.15 ± 0.02	2.93	10.45 ± 0.12	−7.52	*a*
5		2.88 ± 0.08	3.92	10.90 ± 0.13	−6.98	*a*
7		2.34 ± 0.02	3.19	7.46 ± 0.06	−4.27	*a*
1	disodium 2,7-naphthalenedisulfonate	0.98 ± 0.06	1.34	5.99 ± 0.05	−4.65	*b*
2		2.44 ± 0.02	3.33	6.75 ± 0.08	−3.42	*b*
3		2.58 ± 0.02	3.52	0.86 ± 0.01	2.66	*b*
4		2.56 ± 0.07	3.49	1.87 ± 0.08	1.62	*a*
5		2.01 ± 0.04	2.74	9.23 ± 0.05	−6.49	*a*
6		1.92 ± 0.06	2.69	4.42 ± 0.04	−1.73	*a*
12		3.68 ± 0.03	5.02	2.62 ± 0.05	2.40	*a*
13		3.86 ± 0.06	5.27	1.98 ± 0.06	3.29	*a*
14		1.92 ± 0.05	2.62	7.54 ± 0.02	−4.92	*a*
15		2.42 ± 0.11	3.30	6.89 ± 0.09	−3.59	*a*
17		2.54 ± 0.05	3.47	6.35 ± 0.07	−2.88	*a*
19		2.64 ± 0.04	3.60	6.34 ± 0.12	−2.74	*a*
20		2.69 ± 0.08	3.67	4.47 ± 0.09	−0.80	*a*
2	sodium 2-naphthalenesulfonate	5.37 ± 0.07	7.33	7.01 ± 0.06	0.32	*b*
5		3.04 ± 0.03	4.15	8.20 ± 0.11	−4.05	*a*
12		2.78 ± 0.01	3.79	9.61 ± 0.08	−5.82	*a*
13		2.84 ± 0.01	3.88	9.07 ± 0.07	−5.19	*a*
14		2.03 ± 0.05	2.77	6.31 ± 0.09	−3.54	*a*
15		2.56 ± 0.01	3.49	4.52 ± 0.13	−1.03	*a*
16		3.51 ± 0.08	4.79	4.07 ± 0.09	0.72	*a*
17		2.58 ± 0.06	3.52	3.08 ± 0.09	0.44	*a*
18		2.14 ± 0.04	2.92	10.05 ± 0.06	−7.13	*a*
19		2.53 ± 0.07	3.45	4.60 ± 0.13	−1.15	*a*
20		3.61 ± 0.08	4.93	3.46 ± 0.05	1.47	*a*
21		2.94 ± 0.03	4.01	2.89 ± 0.08	1.12	*c*
22		3.13 ± 0.02	4.27	13.75 ± 0.09	−9.48	*c*
23		2.50 ± 0.03	3.41	10.30 ± 0.10	−6.89	*c*
24		3.13 ± 0.10	4.27	7.19 ± 0.08	−2.92	*c*
25		3.42 ± 0.02	4.67	4.00 ± 0.09	0.67	*c*
26		3.21 ± 0.03	4.38	8.01 ± 0.08	−3.63	*c*
27		3.81 ± 0.06	5.20	3.29 ± 0.04	1.91	*c*
28		3.93 ± 0.05	5.36	6.63 ± 0.04	−1.27	*c*
29		2.95 ± 0.02	4.02	6.75 ± 0.06	−2.73	*c*
30		3.58 ± 0.05	4.88	10.90 ± 0.06	−6.02	*c*
31		3.62 ± 0.02	4.94	10.72 ± 0.06	−5.78	*c*
32		1.85 ± 0.04	2.52	20.39 ± 0.25	−17.87	*c*
33		3.94 ± 0.02	5.37	2.99 ± 0.07	2.38	*c*
34		2.74 ± 0.06	3.74	3.88 ± 0.08	−0.14	*c*
35	benzoic acid	2.74	3.73	16.4	−12.8	*d*
	m-hydroxybenzoic acid	3.06	4.17	17.3	−13.1	*d*
	p-hydroxybenzoic acid	2.98	4.07	14.4	−10.1	*d*
35	*m*-nitrophenol	2.82	3.85	10.2	−6.3	*d*
	p-nitrophenol	2.87	3.91	14.9	−11.0	*d*
	m-nitroaniline	3.05	4.16	11.5	−8.1	*d*,*e*
	p-nitroaniline	3.48	4.74	14.4	−9.8	*d*
4	L-alanine	3.37	4.60	5.88	−1.30	*f*
	D-alanine	3.19	4.35	3.92	0.44	*f*
	L-valine	3.56	4.86	−4.23	9.09	*f*
	D-valine	3.33	4.54	2.42	2.12	*f*
	L-isoleucine	3.72	5.08	17.52	−12.40	*f*
	L-proline	3.34	4.55	−3.07	7.62	*f*
	L-serine	3.15	4.30	6.08	−1.76	*f*
	D-serine	2.92	3.98	6.62	−2.63	*f*
	L-cysteine	2.99	4.08	7.28	−3.19	*f*
	L-aspartic acid	3.65	4.97	−1.25	6.23	*f*
	L-leucine	3.60	4.91	1.28	3.63	*f*
	D-leucine	3.35	4.57	8.85	−4.26	*f*
5	L-alanine	3.14	4.28	8.49	−4.21	*g*
	D-alanine	3.06	4.17	4.89	−0.72	*g*
	L-valine	3.65	4.99	0.92	4.07	*g*

Table 1 (Continued)

host	guest	log K	$-\Delta G°$	$-\Delta H°$	$T\Delta S°$	ref
	D-valine	3.34	4.56	−10.19	14.76	*g*
	L-isoleucine	3.90	5.33	1.52	3.73	*g*
	L-proline	3.08	4.19	−1.15	5.34	*g*
	L-serine	3.07	4.18	9.38	−5.17	*g*
	D-serine	2.82	3.85	12.74	−8.34	*g*
	L-cysteine	2.43	3.31	−2.29	5.61	*g*
	L-aspartic acid	3.61	4.92	−2.21	7.73	*g*
	L-leucine	3.69	5.03	1.67	3.36	*g*
	D-leucine	3.46	4.72	−5.02	9.68	*g*
	L-lysine	2.31	3.15	−4.88	8.03	*g*
	L-methionine	2.52	3.80	−9.50	13.20	*g*
	L-glutamic acid	2.88	3.92	−3.18	7.10	*g*
6	L-alanine	3.03	4.13	10.49	−6.22	*f*
	D-alanine	2.96	4.03	3.46	0.58	*f*
	L-valine	3.46	4.72	4.25	0.42	*f*
	L-isoleucine	3.65	4.98	−3.74	8.72	*f*
	L-proline	3.06	4.18	−6.70	11.18	*f*
	L-serine	3.00	4.09	5.60	−1.50	*f*
	D-serine	2.77	3.78	4.88	−1.10	*f*
	L-cysteine	2.69	3.67	−4.52	8.19	*f*
	L-aspartic acid	3.58	4.89	−2.64	7.53	*f*
	L-leucine	3.50	4.77	1.84	2.93	*f*
	D-leucine	3.22	4.40	3.84	0.57	*f*
14	L-alanine	3.62	4.93	−8.02	12.98	*g*
	D-alanine	3.52	4.80	7.27	−2.48	*g*
	L-valine	3.82	5.21	9.59	−4.38	*g*
	L-isoleucine	3.79	5.17	11.38	−6.17	*g*
	L-proline	3.64	4.96	4.02	0.95	*g*
	L-serine	3.49	4.74	−6.28	11.02	*g*
	D-serine	3.43	4.67	−5.14	10.03	*g*
	L-cysteine	2.65	3.61	15.75	−12.08	*g*
	L-glutamic acid	4.17	5.69	17.06	−11.31	*g*
	L-lysine	2.57	3.49	−7.17	10.66	*g*
	L-aspartic acid	4.04	5.47	7.21	−1.70	*g*
	L-leucine	3.70	5.05	−7.16	12.21	*g*
	D-leucine	3.67	5.01	3.18	1.83	*g*

[a] This work; calorimetric titrations performed at 25.0 °C in a buffered aqueous solution at pH 7.20. [b] Reference 31. [c] Reference 32a. [d] Reference 32c, thermodynamic parameters determined by variable-temperature circular dichroism spectrometer at 20−60 °C. [e] Data not used in the plot, since $\Delta G \neq \Delta H - T\Delta S$ within an error limit of 0.2 kcal/mol. [f] Reference 32d (VT UV−vis). [g] Reference 32b (VT UV−vis).

inclusion complex (log $K = 3.26$) among the native α- to γ-cyclodextrins and forms a typical entropy-driven complex. Thus, the complex is inferred to be stabilized by the entropic gain arising from the desolvation of the host and guest molecules upon complexation, as well as the release of water molecules trapped originally in the cavity. Both the smaller α-cyclodextrin and larger γ-cyclodextrin give the poor inclusion abilities forming enthalpy-driven complexes with accompanying negligible or negative entropic contribution. The decreases in the complex stability constants for hosts **1** and **3** (log $K =$ 1.79 and 1.95) are mainly attributable to the reduced or negative entropic contribution, probably due to the less extensive desolvation. Although α- and γ-cyclodextrins incidentally afford comparable K values, their thermodynamic profiles are completely different.

As compared with the thermodynamic quantities obtained with parent α-, β-, and γ-cyclodextrins (**1**−**3**), the modified α-, β-, and γ-cyclodextrins (**4**−**6**), bearing a positively charged pyridinio group, are expected to exhibit increased complex stability through the electrostatic interaction by ion-pairing between N^+ and the carboxylate of tryptophan accommodated in the cyclodextrin cavity. Indeed, the complex stability constants K for **4**−**6** are larger by roughly 0.3−0.6 order of magnitude than those for the parent cyclodextrins **1**−**3** as a consequence of the increased enthalpic and/or entropic gain.

Possessing the same host moiety and a similar phosphate group at the peripheral position, β-cyclodextrin phosphates **7** and **8** gave contrasting results. Although the thermodynamic parameters obtained for the hydrogen phosphate **8** are almost identical with those for the parent **2**, the introduction of a diphenyl phosphate group leads to much weaker complexation between tryptophan and **7**, which is evidently enthalpy-driven but the enthalpic gain ($-\Delta H°$ 4.61) is exceedingly canceled out by the accompanying entropic loss ($T\Delta S°$ −4.91). This large entropic loss may be attributable to the drastic conformational changes upon extrusion of one of the phosphate's phenyl groups originally perching just above the cavity, which is suggested by the ICD studies.

A series of structurally related arylseleno derivatives **9**−**11** showed quite interesting and contrasting complexation behavior and affords some insights into the structural requirements for self-inclusion and its thermodynamic consequences. As can be seen from Table 1, all the seleno derivatives give almost comparable complex stability constants around 2.0−2.2, but the thermodynamic profiles differ strikingly between the phenylseleno derivative **9** and the *p*-tolyl- or benzylseleno derivative (**10** or **11**). Beyond the apparent differences in structure, the thermodynamic behavior of **9** is similar to that of **7**, i.e., the large enthalpic gain accompanied by the similarly large entropic loss. This may be attributable to the fact that both modified cyclodextrins possess a phenyl group which is connected to the cyclodextrin through a short linkage and is perching just above the cavity. On the other hand, the tolyl and benzyl groups in **10** and **11** in

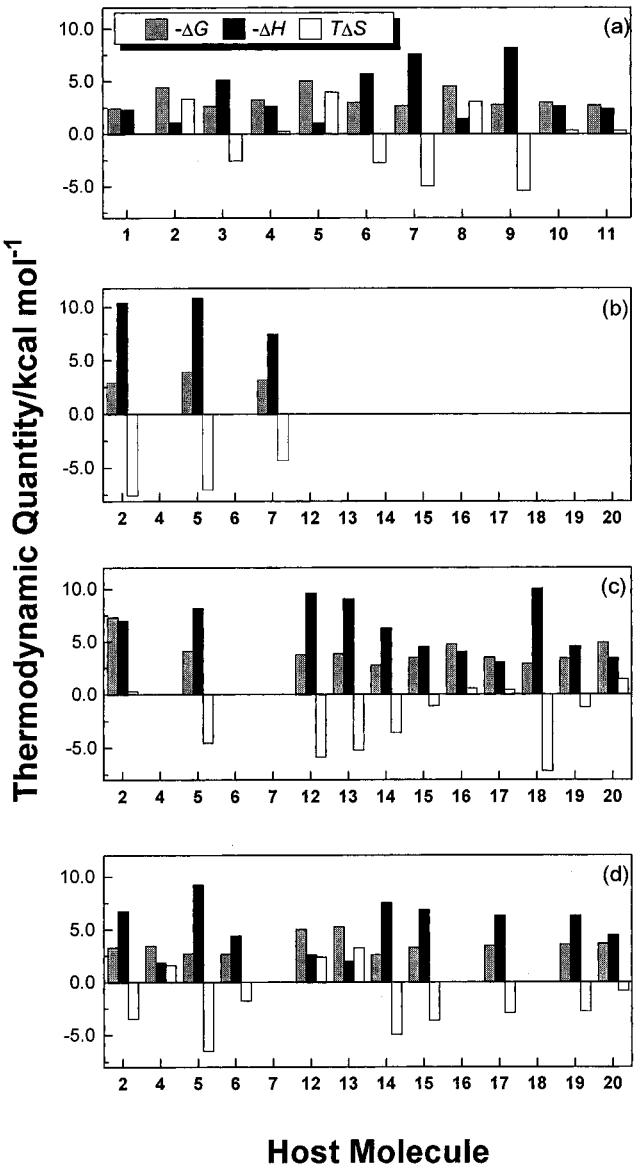

Figure 3. Free energy ($-\Delta G$), enthalpy ($-\Delta H$), and entropy changes ($T\Delta S$) for the inclusion complexation of L-tryptophan (a), 3-hydroxy-2-naphthoate (b), 2-naphthalenesulfonate (c), and 2,7-naphthalenedisulfonate (d) with cyclodextrins (**1**−**20**) in a buffered aqueous solution (pH 7.20) at 25 °C.

conjunction with the much longer C−Se bonds would lead to their tighter self-inclusion, which discourages the replacing inclusion of the guest tryptophan.

Complexation of 3-Hydroxy-2-naphthoate. Possessing a more rigid planar structure as compared with that of L-tryptophan, 3-hydroxy-2-naphthoate as a guest gave stronger hydrophobic and hydrogen-bonding interactions upon complexation with **2**, **5**, and **7**, forming typical enthalpy-driven complexes with the large negative entropy changes. However, as can be seen from Table 1 and Figure 3b, the larger enthalpic gains ($-\Delta H°$) do not immediately mean high complex stabilities and are canceled out by the large entropic loss arising from the structural freezing. It is noted that the modified β-cyclodextrins **5** and **7** show higher complex stabilities (log K = 2.88 and 2.34) than the parent β-cyclodextrin (log K = 2.15), probably through the extra electrostatic and/or hydrogen-bonding interactions.

Complexation of 2,7-Naphthalenedisulfonate. As shown in Table 1, the effects of cyclodextrin's cavity size on the thermodynamic parameters are best illustrated by the complexation of 2,7-naphthalenedisulfonate with the parent α-, β-, and γ-cyclodextrins.[31] In sharp contrast to this seeming reasonable result, the pyridinio cyclodextrins **4**−**6** show an opposite profile of the complex stability sequence which decreases monotonically with increasing cavity size.

Although the pyridinio β-cyclodextrin **5** gives the largest enthalpic gain ($-\Delta H°$) in the series as is the case with the parent **2**, very drastic changes in the thermodynamic parameters are induced by appending a pyridinio group to α- and γ-cyclodextrins yielding **4** and **6**. The enthalpic gain for **4** ($-\Delta H°$ 1.87) is much smaller than that for **1** (5.99), but the increased entropic gain ($T\Delta S°$) from −4.65 to 1.62 exceeds the loss in enthalpy, affording a higher complex stability for **4**. The small negative $\Delta H°$ and positive $T\Delta S°$ values for **4** jointly suggest that the inclusion interaction is very weak but the desolvation is rather extensive. This kind of situation may be realized in the case of simple ion pairing without intimate inclusion of hydrophilic disulfonate with the positively charged guest like **4**. By contrast, γ-cyclodextrin derivative **6** affords more negative $\Delta H°$ and $T\Delta S°$ values than the parent **3**. This corresponds to stronger inclusion and structural freezing, probably arising from the through-cavity complexation with two sulfonate moieties interacting with the peripheral hydroxyl and positively charged pyridinio groups.

The introduction of a methyl group to the pyridinio moiety of **5** does enhance the original log K of 2.01 for **5** up to 3.7−3.9 for **12** and **13**, for which the dramatic increases of the $T\Delta S°$ value are responsible. Although the origin of the positive entropy changes are not necessarily clear, one possible rationalization for the enhanced stability for **12** and **13** is the intervention of CH−π interaction between the electron-deficient methyl group on the positively charged pyridinio group and the guest's naphthyl group accommodated in the cavity.[45] It is also totally unexpected that, irrespective of the diversity of the substituents introduced, the more sophisticated β-cyclodextrin derivatives **14**, **15**, **17**, and **20** show quite comparable thermodynamic quantities, which are incidentally fairly similar to those for the parent β-cyclodextrin **2**. Thus, thermodynamically these modifications do not very much affect the complexation behavior of β-cyclodextrin.

Complexation of 2-Naphthalenesulfonate. As has been demonstrated previously for the inclusion complexation of 2-naphthalenesulfonate with the modified β-cyclodextrins **21**−**34**,[32a] all the present modifications applied to β-cyclodextrin lead to substantially reduced complex stabilities for **5** and **12**−**20**. Even pyridinio (**5**, **12**, **13**), quinolyl (**17**), and fluorenyl cyclodextrins (**19**, **20**), which give enhanced binding of L-tryptophan, 3-hydroxy-2-naphthoate, and 2,7-naphthalenedisulfonate, never promote the binding of 2-naphthalenesulfonate, but rather reduce the binding constant by 2−3 orders of magnitude, as compared with the parent cyclodextrin (**2**).

(43) Christensen, J. J.; Ruchman, J.; Eatough, D. J.; Izatt, R. M. *Thermochim. Acta* **1972**, *3*, 203.
(44) Eatough, D. J.; Christensen, J. J.; Izatt, R. M. *Thermochim. Acta* **1972**, *3*, 219.
(45) Nishio, M.; Umezawa, Y.; Hirata, M.; Takeuchi, Y. *Tetrahedron* **1995**, *51*, 8665.

Close examinations of the thermodynamic quantities, however, reveal some interesting features of the inclusion complexation of modified β-cyclodextrins with 2-naphthalenesulfonate as a guest molecule. Possessing a positively charged group linked to the edge of cyclodextrin cavity through a short chain, the host compounds **5**, **12**, and **13** appear to develop the hydrophobic and electrostatic interactions between cyclodextrin and 2-naphthalenesulfonate to give much higher enthalpic gains ($-\Delta H°$), which are however entirely canceled out by the entropic loss arising from the more rigid structural fixation in the inclusion complex produced, resulting in the much lower stability constants (log K = 2.78−3.04) than that for **2** (5.37). On the other hand, the anilino or quinolyl moiety in host cyclodextrins **14**−**17**, as revealed by the ICD study, is only shallowly accommodated in the cavity of free host and the thermodynamic parameters for these hosts resemble to those for the methylated cyclodextrin **21** and the bridged cyclodextrins **33** and **34** reported previously.[31] The mutually resembling thermodynamic parameters for these apparently very diverse types of modified cyclodextrins suggest some common behavior occurring upon their inclusion complexation. Linked with a short chain to cyclodextrin, the pendent or bridging group can exclude only partly the bound water molecules residing originally in the cavity and therefore the inclusion of guest by these hosts may become similar.

Enthalpy−Entropy Compensation. We have previously demonstrated that the thermodynamic parameters for the inclusion complexation of various neutral and charged organic guests with native α- to γ-cyclodextrins exhibit a compensatory relationship between ΔH and $T\Delta S$.[31] The slope (α) and intercept ($T\Delta S_0$) of the regression line of the $\Delta H - T\Delta S$ plot, as measures of the conformational changes and the extent of desolvation caused by inclusion,[46] are 0.90 and 3.1, respectively, which indicate fairly large conformational changes caused by the rearrangement of the hydrogen-bond network around the rim and the moderate dehydration mostly from the peripheral hydroxyl groups. More recently,[32a] we have studied the complexation thermodynamics of 2-naphthalenesulfonate with some cyclodextrin derivatives (**21**−**35**), the results of which afford an excellent $\Delta H - T\Delta S$ compensation plot of larger slope (α = 1.07) and intercept ($T\Delta S_0$ 5.0) than those for the native cyclodextrins.

The present study enables us to examine more precisely and comprehensively the general validity of the enthalpy−entropy compensation effect in the complexation thermodynamics with a wider variety of both guests and modified cyclodextrins. Using the compiled thermodynamic quantities listed in Table 1 (number of data set (n) = 101), the entropy change ($T\Delta S$) was plotted against the enthalpy change (ΔH) to give an excellent regression line (correlation coefficient (r) = 0.993) of a large slope (α = 1.02) and intercept ($T\Delta S_0$ 4.3), Figure 4. The obtained extrathermodynamic parameters, α and $T\Delta S_0$, are in good agreement with the parameters calculated previously with a smaller sample size[32a] but are much larger than those for native cyclodextrins.[31] For comparison purpose, the slopes and intercepts are summarized in Table 2, along with those obtained for the

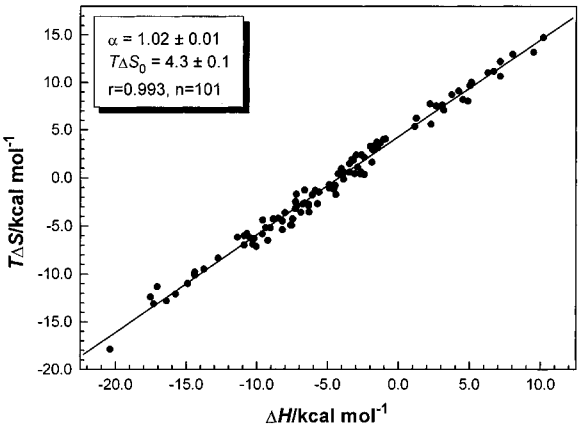

Figure 4. Enthalpy−entropy compensation plot for inclusion complexation with modified α-, β- and γ-cyclodextrins (**4**−**35**); see Table 1 for the original data.

Table 2. Slope (α) and Intercept ($T\Delta S_0$) of the $\Delta H - T\Delta S$ Plots for 1:1 Host−Guest Complexation in Homogeneous Solution

host	guest	a	$T\Delta S0$	ref
glyme/podand	cation	0.86	2.3	*a*
crown ether	cation	0.76	2.4	*a*
cryptand	cation	0.51	4.0	*a*
bis(crown ether)	cation	1.03	4.6	*a*
ionophore antibiotics	cation	0.95	5.6	*a*
cyclodextrin	molecule	0.90	3.1	*b*
modified cyclodextrin (**4**−**35**)	molecule	1.02	4.3	*c*

[a] Reference 37. [b] Reference 31. [c] This work.

representative cation binders such as glyme/podand, crown ether, bis(crown ether), cryptand, ionophore antibiotics, and the parent cyclodextrins.

For the series of acyclic, cyclic, and bicyclic cation binders, the slope (α) decreases with increasing host's dimensionality or structural rigidity from 0.86 (glyme/podand) to 0.76 (crown ether) and then to 0.51 (cryptand), while the intercept ($T\Delta S_0$) increases in this order from 2.3 to 4.0 with increasing coverage of the cation surface by ligand's donor. The bis(crown ethers) and ionophore antibiotics give much larger slope near unity and intercept around 5, indicating substantial conformatinal changes and extensive desolvation upon complexation. In this context, the slope of unity and the intercept of 4.3, which are incidentally very similar to those for bis(crown ethers) irrespective of the weak interaction involved, reveal that the inclusion complexation with modified cyclodextrins accompanies substantial changes in conformation and solvation. This seems reasonable, since the appended side arm, either self-included or excluded in the cavity, is considered to change its conformation upon guest inclusion.

On the other hand, the larger intercept ($T\Delta S_0$) indicates that the guest molecule accommodated in the cavity suffers extensive desolvation, which is characteristic of the three-dimensional complexation by cryptand, antibiotic, bis(crown ether),[37] and modified cyclodextrin, although the species and the weak interactions involved are completely different. Quantitatively, the unit slope (α) and the large intrinsic entropic gain ($T\Delta S_0$) indicate that the enthalpic gain from guest inclusion is completely canceled out by the entropic loss arising from the modi-

(46) Inoue, Y.; Hakushi, T.; Liu, Y. In *Cation Binding by Macrocycles*; Inoue, Y., Gokel, G. W., Eds.; Marcel Dekker: New York, 1990; Chapter 1.

fied cyclodextrin's conformational change required upon complexation, but the inclusion complexation is still favored even in the absence of enthalpic stabilization exclusively owing to the entropic gain originating from the extensive desolvation of both guest and host. Endeavors to measure and compile the thermodynamic quantities in the homogeneous phase for complexation of various guest molecules with hosts of other category with different topologies are currently in progress.

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