and Siebrand[30] in their treatment of the second excited singlet state of anthracene. However, due to the necessary assumption of the magnitude of k_{PYR} in our analysis, we believe that a more complex analysis of our data is not warranted at this time.

IV. Conclusion

Laser flash photolysis of methyldiazirine-d_4 generates ethylidene-d_4, which can be intercepted with pyridine to form an ylide (λ_{max} = 365 nm). A double-reciprocal plot of the yield of ylide versus the concentration of pyridine is linear. Assuming that k_{PYR} is 1×10^9 M^{-1}, the lifetime (τ) of singlet ethylidene-d_4 is calculated to be 500 ps in pentane at ambient temperature and the activation barrier to its isomerization is less than 2.3 kcal/mol. Photolysis of methyldiazirine also leads to ethylene formation concerted with nitrogen extrusion in competition with carbene formation.

V. Experimental Section

Product Analysis. Methyldiazirine and methyldiazirine-d_4 were prepared by the method of Schmitz.[31] The fluorescence[10] and LFP[32]

techniques used in this work have been described previously.

The yields of methylcarbene-d_4 and methylcarbene have been measured by analyzing methanolic solutions of the parent diazirines by NMR. The deuterio and protio diazirines were prepared in methanol and methanol-d_4, respectively; a small amount of benzene-d_6 (or benzene) was added as an internal standard. Three peaks were found in the initial ^{2}H NMR spectrum of methyldiazirine-d_4: benzene-d_6 (δ 7.15) and methyldiazirine-d_4 (CD$_3$, δ 0.6899; D, δ 0.6531). Several additional peaks were observed for 12-h photolysis with 350-nm light (Rayonet reactor) at 4 °C. These were assigned to the insertion product (CD$_3$, δ 0.9175, doublet; D, δ 3.1869, doublet) and ethylene-d_4 (δ 5.1664). When these peaks are integrated against the benzene standard, we find ~30% yield of carbene insertion product (ethyl-d_4 methyl ether) and 28% ethylene-d_4. The spectra for methyldiazirine can be analyzed in the same manner, showing 22% yield of carbene insertion product (ethyl methyl-d_3 ether) and 18% ethylene. The ratio (yield of **5**-d_4/yield of **6**-d_4 = 1.36) obtained from this experiment is consistent within experimental error with our earlier findings concerning the yield of carbene obtained from photolysis of dimethyldiazirine-d_6 and dimethyldiazirine.[10]

(30) (a) Andre, J. C.; Niclause, M.; Ware, W. R. *Chem. Phys.* **1978**, *28*, 371. (b) Bohne, C.; Kennedy, S. R.; Boch, R.; Negri, F.; Orlandi, G.; Siebrand, W.; Scaiano, J. C. *J. Phys. Chem.* **1991**, *94*, 10, 300.
(31) Schmitz, E. *Chem. Ber.* **1962**, *95*, 688.

(32) Soundararajan, N.; Platz, M. S.; Jackson, J. E.; Doyle, M. P.; Oon, S.-M.; Liu, M. T. H.; Anand, S. M. *J. Am. Chem. Soc.* **1988**, *110*, 7143.

Thermodynamics of Molecular Recognition by Cyclodextrins. 1. Calorimetric Titration of Inclusion Complexation of Naphthalenesulfonates with α-, β-, and γ-Cyclodextrins: Enthalpy–Entropy Compensation

Yoshihisa Inoue,[*,†,‡] **Tadao Hakushi,**[⊥] **Yu Liu,**[*,§] **Lin-Hui Tong,**[§] **Bao-Jian Shen,**[§] **and Dao-Sen Jin**[§]

Contribution from the Department of Material Science, Himeji Institute of Technology, Kamigori, Hyogo 678-12, Japan, Department of Applied Chemistry, Himeji Institute of Technology, Himeji, Hyogo 671-22, Japan, and Lanzhou Institute of Chemical Physics, Academia Sinica, Lanzhou 730000, China. Received June 3, 1992

Abstract: Calorimetric titrations have been performed at 25 °C in buffered aqueous solution (pH 7.20) to give the complex stability constants and the thermodynamic parameters for the inclusion complexation of naphthalenesulfonates **1–6** and naphthaleneacetate **7** with α-, β-, and γ-cyclodextrins (CDs). Data analyses assuming 1:1 stoichiometry were successfully applied to all of the host–guest combinations employed, except for the inclusion of 2-naphthalenesulfonate **2** with γ-CD, where both 1:1 and 1:2 host–guest complex formations were observed. The thermodynamic parameters obtained are critical functions of the position, number, and type of the anionic substituent(s) introduced to the guest molecule. The inclusion complexation is mostly enthalpy-driven with a minor or major positive entropic contribution, but in some cases a substantial positive entropic contribution determines the complex stability. Furthermore, the general validity of the enthalpy–entropy compensation effect, originally proposed for the cation binding by acyclic and macro(bi)cyclic ligands, was tested for the inclusion complexation by CD. Using all the thermodynamic data obtained here and reported elsewhere, the ΔH–$T\Delta S$ plot for CD gave a good straight line. On the basis of our explanation proposed previously, the slope very close to unity (α 0.90) indicates that, despite the apparently rigid skeleton of CD, the inclusion complexation causes substantial conformational changes involving the reorganization of the original hydrogen bond network, while the intermediate intercept ($T\Delta S_0$ 3.1) means fairly extensive dehydration occurring upon inclusion. It is thus demonstrated that, beyond the major driving forces operating in both types of complexation, i.e., ion–dipole and van der Waals interaction, the host–guest complexation phenomena involving the weak interactions may be understood in the general context of the enthalpy–entropy compensation effect.

Natural and chemically modified cyclodextrins (CDs) are known to recognize a wide variety of organic, as well as inorganic, guest molecules, forming host–guest inclusion complexes in

aqueous solution.[1] They also provide an excellent model system mimicking the substrate-specific interaction of enzymes; some of them are successful enzyme models,[2–9] while the others are applied

† JRDC research fellow 1992–1994.
‡ Department of Material Science, Himeji Institute of Technology.
⊥ Department of Applied Chemistry, Himeji Institute of Technology.
§ Lanzhou Institute of Chemical Physics.

(1) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer Verlag: Berlin, 1978.
(2) Tabushi, I. *Inclusion Compounds*; Atwood, J. L., Davies, J. E., MacNicol, D. D., Eds.; Academic Press: London, 1984; Vol. 3, Chapter 13.

476 *J. Am. Chem. Soc., Vol. 115, No. 2, 1993*

Inoue et al.

Chart I. Guest Molecules
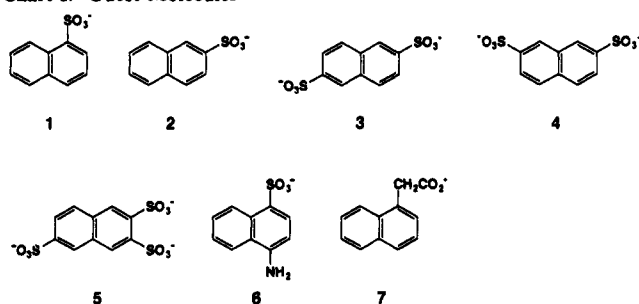
to several areas of science and technology.[1,10–12] For more comprehensive understanding of the nature of the noncovalent interaction operating between host CD and guest molecules and also of the factors governing the host–guest complexation by CDs, a good deal of effort has been devoted to the investigation of the complexation thermodynamics of several types of guest molecules with CDs.[1,13–34] In this context, it seems rather curious that little

attention has been paid to the effect of the guest's substitution upon complexation behavior from the thermodynamic point of view.

In a series of the thermodynamic studies on cation binding by macrocyclic and the related ligands,[35–38] we have demonstrated that good-to-excellent linear relationships are found between the enthalpy (ΔH) and entropy changes (ΔS) in the homogeneous-phase complexation of cationic species with different categories of synthetic and natural ligands like glyme/podand, crown ether, cryptand, bis(crown ethers), and ionophore antiobiotic. This compensatory enthalpy–entropy relationship holds also in the solvent extraction of aqueous metal picrates by crown ethers with 1:1 and 1:2 cation–ligand stoichiometries.[39,40] Importantly, this extrathermodynamic relationship serves our understanding of the nature of the cation–ligand complexation through ion–dipole interaction.[35,36,39,40] Thus, the slope (α) and the intercept ($T\Delta S_o$) of the ΔH–$T\Delta S$ plot are characteristic of the ligand topology and the complex stoichiometry and can be used as the quantitative measures of ligand's conformational change and of the extent of cation/ligand desolvation caused upon complex formation. This unique compensation effect holds in general as far as the cation–ligand complexation involves the weak ion–dipole interaction.[35] By contrast, the thermodynamic parameters for covalently interacting complexes of heavy and transition metal ions with nitrogen or sulfur ligands never display such a compensation effect, the complex stability being determined solely by the enthalpic change.[35] In this context, the inclusion complexation by CD is of our special interest, since it occurs mostly through the weak interactions, i.e., van der Waals, hydrogen bonding, and/or dipole–dipole interactions.

In this study, a series of naphthalene derivatives possessing hydrophilic sulfonate or carboxylate group(s) at different position(s) were chosen as the guest molecules, since they have a rigid rectangular shape in common and are suitable for examining the effects of position, number, and type of the substituent on the thermodynamic properties. We first report the thermodynamic parameters for the inclusion complexation of the naphthalene-(poly)sulfonates 1–6 and naphthaleneacetate 7 with α-, β-, and γ-CDs and discuss the factors controlling the complex stability from the thermodynamic point of view. We also wish to demonstrate that, as is the case with the host–guest complexation of cationic species with acyclic and macro(bi)cyclic ligands,[35–38] the compiled thermodynamic parameters hitherto reported for the inclusion complexation by CDs also give a good linear ΔH–$T\Delta S$ plot, whose slope α and intercept $T\Delta S_o$ disclose a detailed profile of the molecular recognition by CDs.

Experimental Section

Materials. α-, β-, and γ-cyclodextrins purchased from Nakarai were used without further purification. Commercially available sodium salts of 1- and 2-naphthalenesulfonates (1 and 2), 2,6- and 2,7-naphthalenedisulfonates (3 and 4), 2,3,6-naphthalenetrisulfonate (5), 4-amino-1-naphthalenesulfonate (6), and 1-naphthaleneacetate (7) were dried in vacuo prior to use. Distilled, deionized water of (1.0–1.2) × 10⁻⁶ S/cm was used throughout the work.

Disodium hydrogen phosphate and sodium dihydrogen phosphate were dissolved in distilled, deionized water to make a 0.1 M phosphate buffer solution of pH 7.20 for calorimetry.

Apparatus and Procedures. Calorimetric titrations were performed at pH 7.20 and in a thermostated water bath at 25 °C, by using an LKB 8721-2 precision calorimeter, which was connected to a microcomputer for the automated titration and data processing.[41] The principle of the

(3) Breslow, R. *Inclusion Compounds*; Atwood, J. L., Davis, J. E., Mac-Nicol, D. D., Eds.; Academic Press: London, 1984; Vol. 3, Chapter 14.

(4) Tabushi, I. *Tetrahedron* **1984**, *40*, 269.

(5) Tabushi, I.; Kuroda, Y. *Adv. Catal.* **1984**, *32*, 417.

(6) D'Souza, V. T.; Lu, X. L.; Ginger, R. D.; Bender, M. L. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 673.

(7) Akkaya, E. V.; Czarnik, A. W. *J. Am. Chem. Soc.* **1988**, *110*, 8553.

(8) Szejtli, J. *Cyclodextrin Technology*; Kluwer-Academic: Dordrecht, 1988.

(9) Ouger, H. *Bioorganic Chemistry*, 2nd. ed.; Springer: New York, 1989.

(10) Sybilska, D.; Smolkova-Keulemansova, E. *Inclusion Compounds*; Atwood, J. L., Davies, J. E., MacNicol, D. D., Eds.; Academic: London, 1984; Vol. 3, Chapter 6.

(11) Szejtli, J. *Starch* **1987**, *39*, 357.

(12) Schurig, V.; Nowotny, H.-P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 939.

(13) Lewis, E. A.; Hansen, L. D. *J. Chem. Soc., Perkin Trans. 2* **1973**, 2081.

(14) Ikeda, K.; Uekama, K.; Otagiri, M. *Chem. Pharm. Bull.* **1975**, *23*, 201.

(15) Otagiri, M.; Miyaji, T.; Uekama, K.; Ikeda, K. *Chem. Pharm. Bull.* **1976**, *24*, 1146.

(16) Tabushi, I.; Kiyosuke, Y.; Sugimoto, T.; Yamamura, K. *J. Am. Chem. Soc.* **1978**, *100*, 916.

(17) Michon, J.; Rassat, A. *J. Am. Chem. Soc.* **1979**, *101*, 4337.

(18) Matsui, Y.; Mochida, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2808.

(19) Eftink, M. R.; Harrison, J. C. *Bioorg. Chem.* **1981**, *10*, 388.

(20) Turro, N. J.; Okubo, T.; Chung, C.-J. *J. Am. Chem. Soc.* **1982**, *104*, 1789.

(21) Tucker, E. E.; Christian, S. D. *J. Am. Chem. Soc.* **1984**, *106*, 1942.

(22) Hersey, A.; Robinson, B. H. *J. Chem. Soc., Faraday Trans. 1* **1984**, *80*, 2039; **1986**, *82*, 1271.

(23) Takagi, S.; Maeda, M. *J. Incl. Phenom.* **1984**, *2*, 775.

(24) Yoshida, N.; Seiyama, A.; Fujimoto, M. *Chem. Lett.* **1984**, 703.

(25) Herkstroeter, W. G.; Martic, P. A.; Farid, S. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1453.

(26) Sanemasa, I.; Kobayashi, T.; Deguchi, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1033.

(27) Cromwell, W. C.; Byström, K.; Eftink, M. R. *J. Phys. Chem.* **1985**, *89*, 326.

(28) Barone, G.; Castronuovo, G.; Del Vecchio, P.; Elia, V.; Muscetta, M. *J. Chem. Soc., Faraday Trans. 1* **1986**, *82*, 2089.

(29) Eastman, M. P.; Freiha, B.; Hsu, C. C.; Lum, K. C.; Chang, C. A. *J. Phys. Chem.* **1987**, *91*, 1953.

(30) Fujiwara, H.; Arakawa, H.; Murata, S.; Sasaki, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3891.

(31) Eftink, M. R.; Andy, M. L.; Byström, K.; Perlmutter, H. D.; Kristol, D. S. *J. Am. Chem. Soc.* **1989**, *111*, 6765.

(32) Yoshida, N.; Seiyama, A.; Fujimoto, M. *J. Phys. Chem.* **1990**, *94*, 4246.

(33) Huang, J.; Bright, F. V. *J. Phys. Chem.* **1990**, *94*, 8457.

(34) Tong, L.-H.; Liu, Y.; *Youji Huaxue (Org. Chem.)* **1990**, *10*, 432.

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

(36) Inoue, Y.; Hakushi, T. *J. Chem. Soc., Perkin Trans. 2* **1985**, 935.

(37) 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.

(38) Liu, Y.; Tong, L.-H.; Huang, S.; Tian, B.-Z.; Inoue, Y.; Hakushi, T. *J. Phys. Chem.* **1990**, *94*, 2666.

(39) Inoue, Y.; Amano, F.; Okada, N.; Inada, H.; Ouchi, M.; Tai, A.; Hakushi, T.; Liu, Y.; Tong, L.-H. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1239.

(40) Liu, Y.; Tong, L.-H.; Inoue, Y.; Hakushi, T. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1247.

Table I. Complex Stability Constant (K) and Thermodynamic Parameters in kcal/mol for 1:1 and/or 1:2 Inclusion Complex Formation of Naphthalene Derivatives with α-, β-, and γ-Cyclodextrins in Water at 25 °C[a]

host	guest	stoichiometry (n)[b]	log K_n	$-\Delta G$	$-\Delta H$	$T\Delta S$
α	2-naphthalenesulfonate (**2**)	1	2.56 ± 0.01	3.49	0.78 ± 0.07	2.71
α	2,7-naphthalenedisulfonate (**4**)	1	0.98 ± 0.06	1.34	5.99 ± 0.05	−4.65
α	1-naphthaleneacetate (**7**)	1	2.94 ± 0.04	4.01	0.74 ± 0.01	3.27
β	1-naphthalenesulfonate (**1**)	1	3.40 ± 0.06	4.64	1.49 ± 0.05	3.15
β	2-naphthalenesulfonate (**2**)	1	5.37 ± 0.07	7.33	7.01 ± 0.06	0.32
β	2,6-naphthalenedisulfonate (**3**)	1	3.29 ± 0.05	4.49	2.79 ± 0.07	1.70
β	2,7-naphthalenedisulfonate (**4**)	1	2.44 ± 0.02	3.33	6.75 ± 0.08	−3.42
β	2,3,6-naphthalenetrisulfonate (**5**)	1	2.22 ± 0.03	3.03	3.09 ± 0.15	−0.06
β	4-amino-1-naphthalenesulfonate (**6**)	1	1.70 ± 0.03	2.32	2.38 ± 0.04	0.06
β	1-naphthaleneacetate (**7**)	1	4.35 ± 0.05	5.93	1.11 ± 0.06	4.82
γ	2-naphthalenesulfonate (**2**)	1	1.58 ± 0.03	1.58	4.18 ± 0.07	−2.60
		2	2.59 ± 0.07	4.11	5.73 ± 0.06	−1.62
γ	2,7-naphthalenedisulfonate (**4**)	1	2.58 ± 0.02	3.52	0.86 ± 0.01	2.66
γ	4-amino-1-naphthalenesulfonate (**6**)	1	1.31 ± 0.08	1.79	6.70 ± 0.13	−4.91

[a] Determined calorimetrically in buffered aqueous solution at pH 7.20 (0.1 M sodium phosphate); average of more than three independent runs. [b] Guest/host ratio.

measurement and the detailed experiment procedures were reported elsewhere.[42-45] In a typical run, a solution of naphthalene derivative **1–7** was continuously introduced at a rate of 0.43 mL/min into a cyclodextrin solution (3–5 mM) placed in the calorimeter. A titration curve was obtained by plotting the temperature change (measured by ΔE/mV) against the amount of the guest added, from which the complex stability constant (K) and the enthalpy change (ΔH) were calculated. The heats of dilution of the guest naphthalenes were measured separately, for which appropriate corrections were made. Representative results and calculations for the successive 1:1 and 1:2 complexation of **2** with γ-CD are included in the supplementary material. The reliability of the whole system and the calculation procedures was doubly checked by comparison of the obtained thermodynamic data with the reported values;[46,47] the results were satisfactory within the experimental error.

Results

Cyclodextrin (CD) and guest molecule(s) are known to form the 1:1 and/or 1:2 host–guest inclusion complexes successively in aqueous solution.[1] The successive 1:1 and 1:2 inclusions of a guest (G) with a host CD is expressed by the following equilibria.
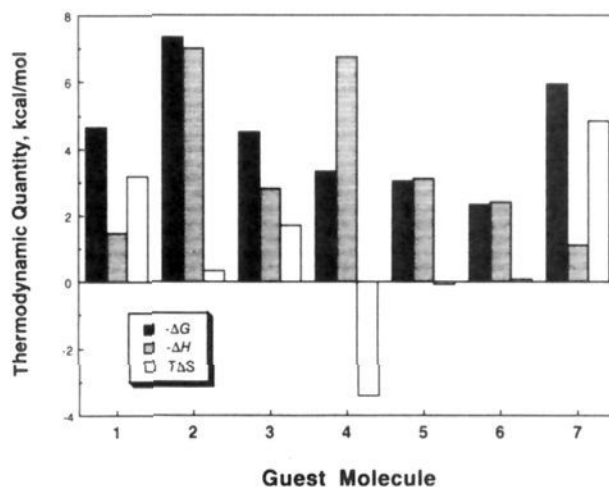
$$G + CD \underset{}{\overset{K_1}{\rightleftharpoons}} G{\cdot}CD \tag{1}$$

$$G{\cdot}CD + G \underset{}{\overset{K_2}{\rightleftharpoons}} G_2{\cdot}CD \tag{2}$$

For the inclusion complexation of naphthalene derivatives **1–7** by a CD with 1:1 and/or 1:2 stoichiometry, the stepwise complex stability constant(s) (K_n; $n = 1$ or 2) and the enthalpy change(s) (ΔH_n), where applicable, were determined calorimetrically by using the least-squares method to minimize the U value:[43-45]

$$U(K_i, \Delta H_i) = \sum_{t=1}^{m} [Q_t - \sum_{i=1}^{n} (N_{i,t} \Delta H_i)]^2 \tag{3}$$

where Q_t refers to the net heat of complexation measured at time t in minute, while N_t denotes the amount in mole of the complex formed at time t and is therefore related directly to the stability constant K.

The stability constant K and the enthalpy change ΔH of complexation for each host–guest combination were calculated by the computer simulation with continuously changing K, i.e., N_t, to minimize U. Simply assuming the 1:1 complex stoichiometry, the U value was minimized satisfactorily for most host–guest combinations to give the optimized set of K and ΔH for 1:1 complexation. However, the heat development observed for the complexation of 2-naphthalenesulfonate **2** with γ-CD was analyzed successfully only by assuming the successive 1:1 and 1:2 com-

(41) Shi, J.-P.; Liu, Yu.; Sun, L.-C. *Fenxi Yiqi (Anal. Instrum.)* **1988**, *2*, 42.

(42) Wadsö, I. *Sci. Tools* **1966**, *13*, 33.

(43) Liu, Y.; Hu, J. *Wuli Huaxue Xuebao (Acta Phys. Chim. Sin.)* **1987**, *2*, 11.

(44) Liu, Y.; Wang, Y.; Guo, Z.-Q.; Yang, S.-Y.; Jin, D.-S. *Huaxue Xuebao (Acta Chim. Sin.)* **1986**, *44*, 22.

(45) Liu, Y.; Tong, L.-H.; Sun, X.-Q.; Wang, D.-F.; Hu, H.-W. *Huaxue Xuebao (Acta Chim. Sin.)* **1991**, *49*, 220.

Figure 1. Free energy ($-\Delta G$), enthalpy ($-\Delta H$), and entropy changes ($T\Delta S$) for the inclusion complexation of naphthalene derivatives **1–7** with β-cyclodextrin in a buffered aqueous solution (pH 7.20) at 25 °C.

plexation, affording the optimized sets of K_1 and ΔH_1 and K_2 and ΔH_2. The stability constants and the thermodynamic parameters obtained are listed in Table I; the experimental errors were well below the standard deviations calculated for K and ΔH from the data of more than three independent measurements.

Discussion

Complex Stability. As can be seen from Table I, the inclusion complexations of naphthalene derivatives **1–7** with CDs are exclusively exothermic and mostly enthalpy driven with varying positive or negative entropic contribution. In Figure 1, the enthalpic ($-\Delta H$) and entropic contributions ($T\Delta S$) to the complex stability ($-\Delta G$) are visualized for the complexation of naphthalene guests **1–7** with β-CD. Of these guest molecules, the 2-substituted and polysubstituted naphthalenesulfonates **2–6** form the typical enthalpy-driven complexes with minimal or negative entropic gains, whereas the 1-substituted naphthalenes **1** and **7** give entropy-driven complexes with minor positive enthalpic contributions, for which the substitution pattern may be responsible, as discussed below.

Guest Orientation. It is noted that the complex stability constants K as well as the thermodynamic quantities for the inclusion of naphthalene derivatives are highly sensitive to the position and number of the substituent introduced but less sensitive to the type of the substituent. Indeed, in the complexation of sulfonates **1–6** with β-CD, the stability constant varies over almost four orders of magnitude and a very high selectivity sequence is attained between these guest molecules. Thus, the stability constant for 1-naphthalenesulfonate **1** (log K 3.40) is two orders of magnitude smaller than that for 2-naphthalenesulfonate **2** (5.37) but is still fairly greater than those for the guests **3–6** (1.70–3.29). On the other hand, 1-naphthalenesulfonate **1** and 1-naphthaleneacetate

Table II. Reported Thermodynamic Parameters in kcal/mol for Inclusion of Various Guest Molecules with α-, β-, and γ-Cyclodextrins in Water at 25 °C

host	guest	$-\Delta G$	$-\Delta H$	$T\Delta S$	ref
α	ethanol	1.12	0.60	0.53	a
α	ethanol	1.36	0.57	0.80	b
α	1-propanol	1.96	1.46	0.50	a
α	1-propanol	2.72	1.62	1.10	c
α	1-propanol	2.00	1.45	0.55	b
α	2-propanol	7.32	0.13	7.19	c
α	1-butanol	2.72	2.37	0.36	a
α	1-butanol	2.65	2.87	−0.22	d
α	1-butanol	3.51	3.37	0.14	c
α	1-butanol	2.60	2.44	0.16	b
α	2-methyl-1-propanol	1.98	2.15	−0.17	a
α	2-methyl-2-propanol	1.84	2.25	−0.41	a
α	1-pentanol	3.42	3.82	−0.40	d
α	1-pentanol	3.43	3.53	−0.10	b
α	2,2-dimethyl-1-propanol	2.01	2.87	−0.86	d
α	1-hexanol	3.96	4.11	−0.15	b
α	1-hexanol	4.01	4.54	−0.43	d
α	cyclohexanol	2.39	2.91	−0.52	b
α	cyclohexanol	2.07	1.93	0.14	c
α	cyclohexanol	2.46	3.34	−0.88	d
α	benzene	2.05	3.14	−1.09	e
α	benzene	2.7	−0.6	3.3	e, f, g
α	benzene	3.43	3.9	−0.5	e, g, h
α	benzene	4.5	3.99	0.51	i
α	pyridine	3.0	2.5	0.6	j
α	4-iodoaniline	8.99	7.35	1.64	g, i, k
α	indole	10.6	0.8	9.8	g, j, k
α	phenol	5.7	1.8	3.9	j
α	2-nitrophenol	5.0	0.5	4.5	j
α	4-nitrophenol (pH 3.0)	3.0	4.6	−1.6	l
α	4-nitrophenolate (pH 9.5)	4.35	9.3	−4.95	l
α	4-nitrophenol (1 M NaCl; pH 4.0)	3.45	4.6	−1.15	l
α	4-nitrophenolate (1 M NaCl; pH 10.0)	4.45	9.6	−5.15	l
α	4-cyanophenol (pH 4.0)	2.7	4.6	−1.9	l
α	4-cyanophenolate (pH 10.0)	3.8	6.0	−2.2	l
α	L-phenylalanine	5.6	1.1	4.5	j
α	L-tyrosine	4.0	1.0	3.0	j
α	L-tryprophan	2.0	1.8	0.3	j
α	anilinium perchlorate	2.0	12.3	−10.4	j
α	perchloric acid	2.2	7.5	−5.1	j
α	sodium perchlorate	1.8	9.7	−6.9	j
α	acetic acid	5.2	1.2	3.9	j
α	benzoic acid	4.1	9.6	−5.4	j
α	2-aminobenzoic acid	6.8	0.3	6.3	j
α	4-aminobenzoic acid	3.8	11.6	−7.8	j
α	3-methylbenzoic acid	3.3	11.6	−8.3	j
α	hydrocinnamic acid	4.2	7.5	−3.3	j
α	L-mandelic acid	3.1	4.9	−1.8	j
α	4-nitrobenzoic acid (pH 2.0)	3.1	9.2	−6.1	l
α	4-nitrobenzoate (pH 5.5)	2.2	4.8	−2.6	l
α	4-nitrophenylacetic acid (pH 2.0)	2.3	9.6	−7.3	l
α	4-nitrophenylacetate (pH 7.0)	2.5	5.0	−2.5	l
α	4-(3-Pr-4-OH-phenylazo)benzenesulfonate	5.38	7.96	−2.56	m
α	4-(3-Pr-4-O⁻-phenylazo)benzenesulfonate	5.31	7.60	−2.28	m
α	4-(3,5-iPr$_2$-4-OH-phenylazo)benzenesulfonate	3.92	4.68	−0.77	m
α	4-(3,5-iPr$_2$-4-O⁻-phenylazo)benzenesulfonate	3.97	5.23	−1.27	m
α	4-(3-Me-4-OH-5-CO$_2$⁻-phenylazo)benzenesulfonate	3.6	5.2	−1.6	n, o
α	4-(3-Me-4-OH-5-CO$_2$⁻-phenylazo)benzenesulfonate	0.9	3.3	−2.4	n, p
α	4-(2-pyridylazo)-N,N-dimethylaniline	3.8	7.9	−4.1	n, o
α	4-(2-pyridylazo)-N,N-dimethylaniline	0.6	−1.0	1.6	n, p
α	1-adamantanecarboxylic acid (pH 4.08)	2.9	3.2	−0.3	q
α	1-adamantanecarboxylic acid (pH 4.08)	3.6	8.8	−5.1	g, q
α	1-adamantanecarboxylate (pH 7.22)	3.22	3.1	0.12	q
α	1-adamantanecarboxylate (pH 8.50)	2.94	3.22	−0.09	q
α	1-adamantanecarboxylate (pH 8.5)	2.9	3.2	−0.3	r
α	3-noradamantanecarboxylate (pH 8.5)	2.7	3.4	−0.7	r
α	1-bicyclo[2.2.2]octanecarboxylate (pH 8.5)	2.0	3.4	−1.4	r
α	1-bicyclo[2.2.1]heptanecarboxylate (pH 8.5)	1.8	3.1	−1.3	r
α	1-bicyclo[2.2.1]heptenecarboxylate (pH 8.5)	1.9	2.4	−0.1	r
α	1-homoadamantanecarboxylate (pH 7.2)	3.9	5.3	−1.4	r
α	3-homoadamantanecarboxylate (pH 7.2)	3.5	4.6	−1.1	r
α	1-adamantaneacetate (pH 7.2)	3.1	3.0	0.1	r
α	1-adamantanecarboxylate (pH 7.2)	3.2	3.1	0.1	r
α	3-noradamantanecarboxylate (pH 7.2)	2.8	3.25	−0.4	r
α	2-norbornaneacetate (pH 7.2)	3.0	6.5	−3.5	r
α	1-bicyclo[2.2.2]octanecarboxylate (pH 7.2)	2.3	2.8	−0.6	r

Table II (Continued)

host	guest	$-\Delta G$	$-\Delta H$	$T\Delta S$	ref
α	1-bicyclo[2.2.1]heptanecarboxylate (pH 7.2)	1.9	3.1	-1.2	r
α	1-bicyclo[2.2.1]heptenecarboxylate (pH 7.2)	2.0	2.0	0.0	r
α	1-adamantanecarboxylic acid (pH 4.05)	2.9	3.2	-0.3	r
α	3-noradamantanecarboxylic acid (pH 4.05)	3.1	3.1	0.0	r
α	2-norbornaneacetic acid (pH 4.05)	3.8	2.8	1.0	r
α	1-bicyclo[2.2.1]heptanecarboxylic acid (pH 4.05)	2.0	3.1	-1.1	r
α	1-bicyclo[2.2.1]heptenecarboxylic acid (pH 4.05)	3.1	2.4	0.7	r
α	1-adamantanecarboxylic acid (pH 4.05)	3.6	8.8	-5.2	g, h, r
α	3-noradamantanecarboxylic acid (pH 4.05)	3.5	11.9	-8.5	g, h, r
α	2-norbornaneacetic acid (pH 4.05)	4.5	5.8	-2.3	g, h, r
α	1-bicyclo[2.2.1]heptanecarboxylic acid (pH 4.05)	3.0	7.0	-4.0	g, h, r
α	1-bicyclo[2.2.1]heptenecarboxylic acid (pH 4.05)	3.0	5.0	-2.1	g, h, r
α	4-(3-Me-4-OH-phenylazo)benzenesulfonate	5.43	8.41	-2.98	s
α	4-(3-Et-4-OH-phenylazo)benzenesulfonate	4.76	4.80	-0.04	s
α	4-(3-Pr-4-OH-phenylazo)benzenesulfonate	5.38	7.96	-2.58	o, s
α	4-(3-Pr-4-OH-phenylazo)benzenesulfonate	0.41	2.10	-1.86	p, s
α	4-(3,5-iPr$_2$-4-OH-phenylazo)benzenesulfonate	3.92	4.68	-0.76	s
α	4-(3-Me-4-O$^-$-phenylazo)benzenesulfonate	4.85	4.18	0.67	s
α	4-(3-Et-4-O$^-$-phenylazo)benzenesulfonate	4.83	7.22	-2.39	s
α	4-(3-Pr-4-O$^-$-phenylazo)benzenesulfonate	5.31	7.58	-2.27	o, s
α	4-(3-Pr-4-O$^-$-phenylazo)benzenesulfonate	0.84	2.63	-1.82	p, s
α	4-(3,5-iPr$_2$-4-O$^-$-phenylazo)benzenesulfonate	3.97	5.23	-1.26	s
α	methyl orange	6.2	6.53	-0.33	i
α	Biebricht Scarlet	4.1	4.5	-0.4	n, o
α	Biebricht scarlet	0.1	0.2	-0.1	n, p
α	di-*tert*-butyl nitroxide	1.2	7.9	-6.7	t
α	3-carbamoylproxyl	0.7	5.3	-4.6	t
α	3-(aminomethyl)proxyl	1.0	7.9	-6.9	t
α	iodine	5.35	-2.28	7.62	u
β	1-butanol	1.67	0.69	0.98	c
β	1-butanol	1.67	-0.69	2.36	d
β	1-pentanol	2.39	1.10	1.29	c
β	1-pentanol	2.46	-1.10	3.56	d
β	2,2-dimethyl-1-propanol	3.70	2.10	1.60	d
β	1-hexanol	3.18	0.10	3.09	c
β	1-hexanol	3.18	-0.10	3.28	d
β	cyclohexanol	3.65	2.39	1.26	d
β	benzene	3.04	0.45	2.59	e
β	benzene	4.58	4.0	0.6	e, f, g
β	phenol	4.6	2.6	2.1	j
β	4-nitrophenol	4.1	10.5	-6.3	j
β	benzoic acid	2.9	7.6	-4.8	j
β	3-methylbenzoic acid	9.6	11.7	-2.1	g, j, k
β	1-adamantanecarboxylate (pH 8.5)	5.8	4.85	0.9	q, r
β	3-noradamantanecarboxylate (pH 8.5)	5.0	3.75	1.3	r
β	2-norbornaneacetate (pH 8.5)	5.2	1.95	3.2	r
β	1-bicyclo[2.2.2]octanecarboxylate (pH 8.5)	5.2	3.8	1.4	r
β	1-bicyclo[2.2.1]heptanecarboxylate (pH 8.5)	4.0	1.9	2.1	r
β	1-bicyclo[2.2.1]heptenecarboxylate (pH 8.5)	3.7	1.8	1.9	r
β	1-homoadamantanecarboxylate (pH 7.2)	5.7	7.8	-2.1	r
β	3-homoadamantanecarboxylate (pH 7.2)	5.7	7.5	-1.9	r
β	1-adamantaneacetate (pH 7.2)	5.9	5.3	0.5	q, r
β	1-adamantanecarboxylate (pH 7.2)	6.3	5.4	0.9	r
β	3-noradamantanecarboxylate (pH 7.2)	5.1	3.6	1.5	r
β	2-norbornaneacetate (pH 7.2)	4.9	2.5	2.4	r
β	1-bicyclo[2.2.2]octanecarboxylate (pH 7.2)	5.2	3.1	2.1	r
β	1-bicyclo[2.2.1]heptanecarboxylate (pH 7.2)	4.1	1.9	2.2	r
β	1-bicyclo[2.2.1]heptenecarboxylate (pH 7.2)	3.6	1.8	2.5	r
β	1-adamantanecarboxylic acid (pH 4.05)	7.5	7.53	-0.1	q, r
β	3-noradamantanecarboxylic acid (pH 4.05)	6.6	5.8	0.8	r
β	2-norbornaneacetic acid (pH 4.05)	6.4	6.2	0.2	r
β	1-bicyclo[2.2.1]heptanecarboxylic acid (pH 4.05)	5.2	5.5	-0.3	r
β	1-bicyclo[2.2.1]heptenecarboxylic acid (pH 4.05)	4.8	5.0	-0.2	r
β	2-anilinonaphthalene-6-sulfonic acid (Ic 0.0)	4.45	4.57	-0.12	v
β	2-anilinonaphthalene-6-sulfonic acid (Ic 0.2)	4.49	4.61	-0.12	v
β	2-anilinonaphthalene-6-sulfonic acid (Ic 0.3)	4.52	4.57	-0.05	v
β	2-anilinonaphthalene-6-sulfonic acid (Ic 0.5)	4.59	5.02	-0.43	v
β	2-anilinonaphthalene-6-sulfonic acid (Ic 1.0)	4.73	4.37	0.36	v
β	*N*-phenylanthranilic acid	3.95	2.08	1.87	w
β	flufenamic acid	4.23	3.48	0.72	w
β	mefenamic acid	3.80	5.77	-1.98	w
β	meclofenamic acid	3.65	10.00	-6.41	w
β	propylbarbituric acid	3.07	2.77	0.32	x
β	butylbarbituric acid	3.53	3.77	-0.23	x
β	pentylbarbituric acid	4.20	5.02	-0.87	x
β	hexylbarbituric acid	4.58	6.18	-1.62	x
β	heptylbarbituric acid	4.23	7.65	-2.91	x

Table II (Continued)

host	guest	$-\Delta G$	$-\Delta H$	$T\Delta S$	ref
β	pentobarbital	4.11	4.84	-0.72	x
β	amobarbital	4.19	6.31	-1.86	x
β	cyclobarbital	4.29	4.83	-1.13	x
β	phenobarbital	4.39	10.3	-5.93	x
β	mephobarbital	4.33	9.48	-5.16	x
β	hexobarbital	4.22	5.61	-1.40	x
β	ethylthiobarbituric acid	3.35	3.71	-0.07	x
β	propylthiobarbituric acid	3.38	3.93	-0.53	x
β	butylthiobarbituric acid	3.93	4.87	-0.94	x
β	pentylthiobarbituric acid	4.60	5.64	-1.60	x
β	hexylthiobarbituric acid	4.77	7.07	-2.44	x
β	thiopental	4.68	6.15	-1.50	x
β	thiophenobarbital	4.89	8.22	-3.34	x
β	phenolphthalein^{2-} (pH 10.0)	1.46	13.91	-12.45	y
β	d-N-oxide^z	1.6	8.5	-6.9	aa
β	l-N-oxide^{bb}	1.7	5.0	-3.3	aa
β	iodine	1.1	3.90	-2.8	y
γ	benzene	1.3	3.4	-2.1	e
γ	adamantanecarboxylic acid (pH 4.08)	5.9	0.1	6.6	g, q, cc
γ	adamantanecarboxylate (pH 7.22)	5.05	-1.26	6.32	q
γ	adamantanecarboxylate (pH 8.50)	4.81	-1.2	6.02	q
γ	BNK-10$^+$(type I)^{dd}	4.3	9.0	-4.8	ee
γ	BNK-10$^+$(type II)^{dd}	5.8	9.0	-3.3	ee
γ	pyrenylbutyrate	4.28	4.4	-0.12	ff

^{a} Reference 28. ^{b} Reference 30. ^{c} Reference 23. ^{d} Reference 18. ^{e} Reference 21. ^{f} Values for 1:2 host–guest complexation. ^{g} Not used in the plot/calculation. ^{h} Values for 2:1 host–guest complexation. ^{i} Reference 16. ^{j} Reference 13. ^{k} Large error. ^{l} Reference 19. ^{m} Reference 24. ^{n} Reference 22. ^{o} Values for encounter complex formation or fast preequilibrium step. ^{p} Values for relaxed complex formation or the second rate-determining step to final stable complex. ^{q} Reference 27. ^{r} Reference 31. ^{s} Reference 32. ^{t} Reference 29. ^{u} Reference 26. ^{v} Reference 33. ^{w} Reference 14. ^{x} Reference 15. ^{y} Reference 34. ^{z} Proxyl: 2,2,5,5-tetramethylpyrrolidinyl-1-oxy. ^{aa} Reference 17. ^{bb} d- or l-N-oxide: (1''R,3''R)- or (1''S,3''R)-disipro[2,2,6,6-tetramethylpiperidine-1-oxyl)-4,4'-(oxazolidine-3'-oxy)-2',1''-(3''-methylcyclohexane). ^{cc} Indirectly calculated ΔG and $T\Delta S$. ^{dd} BNK-10: [10-(4-bromonaphthoyl)decyl]trimethylammonium bromide; the naphthoyl group is buried deeply in the cavity or is close to the surface of the cavity in type I or II complex, respectively. ^{ee} Reference 20. ^{ff} Reference 25.
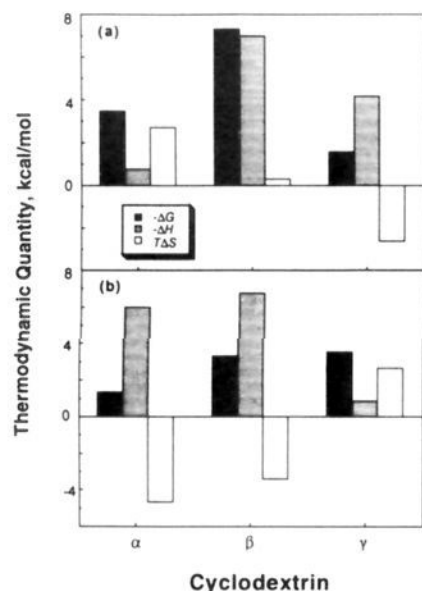

Figure 2. Free energy $(-\Delta G)$, enthalpy $(-\Delta H)$, and entropy changes $(T\Delta S)$ for the inclusion complexation of (a) 2-naphthalenesulfonate **2** and (b) 2,7-naphthalenesulfonate **4** with α-, β-, and γ-cyclodextrins in buffered aqueous solution (pH 7.20) at 25 °C.

Figure 3. Enthalpy–entropy compensation plot for the inclusion complexation of various guests with α- (O), β- (●), and γ-cyclodextrins (⊞); see Tables I and II for the original data.

7 show a smaller difference in K and a similar tendency in the thermodynamic parameters as shown in Figure 1. Certainly, the guest's hydrophilicity rationalizes at least in part the general tendency of K that decreases with increasing number of hydrophilic substituents from **1** to **5**, but the substantial difference in K between **1** and **2** or **3** and **4** clearly indicates that the cyclodextrin cavity recognizes the guest's orientation or has a preferred direction of inclusion.

Examinations with CPK molecular models indicate that the hydrophobic naphthalene part of **2** is embedded deeply into the cavity of β-CD in the longitudinal direction, leaving the sulfonate group in the hydrophilic aqueous outside region. By contrast,
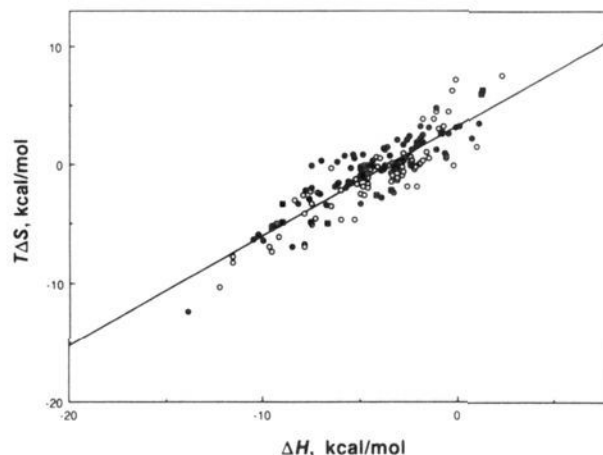
1-naphthalenesulfonate **1** can only form a shallowly penetrating longitudinal or weakly-interacting lateral inclusion complex due to the steric hindrance of the 1-sulfonyl group. A preliminary induced circular dichroism study of the inclusion complexation suggested the longitudinal rather than lateral inclusion for both isomers.[48] The thermodynamic consequences of these situations are the much greater enthalpic gain $(-\Delta H$ 7.01 kcal/mol), arising from the stronger hydrophobic interaction, and the much smaller entropic gain $(T\Delta S$ 0.32 kcal/mol), due to the less extensive dehydrogenation upon inclusion, for **2**, as compared with those for **1** $(-\Delta H$ 1.49 kcal/mol; $T\Delta S$ 3.15 kcal/mol).

The increased steric hindrance and hydrophilicity of other di- or trisubstituted naphthalenes **3–6** reduce both the hydrophobic

(46) Hansen, L. D.; Lewis, E. R. *J. Chem. Thermodyn.* **1971**, *3*, 35.
(47) Izatt, R. M.; Terry, R. E.; Haymore, B. L.; Hansen, L. D.; Dally, N. K.; Avondet, A. G.; Christensen, J. J. *J. Am. Chem. Soc.* **1976**, *98*, 7620.
(48) Hu, J.; Zhang, H.-W.; Liu, Y.; Inoue, Y. Unpublished results.

Complexation of Naphthalenesulfonates with Cyclodextrins

J. Am. Chem. Soc., Vol. 115, No. 2, 1993   481

host–guest interaction and the extent of desolvation, as indicated by the smaller enthalpic and entropic gains, respectively, although the latter is a critical function of the substitution pattern. The fact that the two 1-substituted naphthalenes **1** and **7** give quite comparable thermodynamic parameters provides us with a further support for the above discussion.

Size-Fit Concept. It is interesting to discuss the molecular recognition by CD from the viewpoint of the size relationship between the host cavity and the guest diameter, since the van der Waals, hydrogen bonding, and dipole–dipole interactions should depend on how the size and shape of a guest fit into the host cavity. It is known that the "size-matched" host–guest combination yields a 1:1 complex, while the mismatched combination gives a 2:1 sandwich or 1:2 termolecular host–guest complex.[1,21,25,31,49] In this study, only the 1:1 complex stoichiometry was confirmed to occur, except for the inclusion of **2** with γ-CD, for which the slim shape of **2** and the large cavity of γ-CD may be jointly responsible.

The thermodynamic parameters obtained clearly indicate that the strongest binding occurs in general with β-CD, irrespective of the naphthalene guest employed, as can be seen from Table I. The use of the smaller host α-CD leads to a substantial decrease in complex stability, which is mostly attributable to the reduced enthalpic gain, probably due to the less extensive hydrophobic interactions with the smaller cavity of α-CD. The larger host γ-CD does not show straightforward behavior. As compared with the thermodynamic quantities obtained with β-CD, the slim guest **2** gives a substantially smaller K, arising from the reduced $T\Delta S$ probably owing to the less extensive desolvation. On the other hand, the more bulky guests **4** and **6** afford almost comparable K values for β- and γ-CD, although the thermodynamic profiles are completely different for **4** and **6**. The use of γ-CD causes a substantial decrease in $-\Delta H$ that is compensated by a large entropic gain from the extensive desolvation of the dianionic hydrophilic guest **4**, while an opposite behavior of the thermodynamic parameters is seen for the more lipophilic guest **6**, giving a high enthalpic gain from the size-matched interaction with the larger cavity.

The effects of cyclodextrin's cavity size on the thermodynamic parameters are best illustrated in the complexation of **2** and **4** with α-, β-, and γ-CD. In accord with the size-fit concept, the slim guest **2** forms a moderately stable complex with α-CD and a highly stable one with β-CD, and the more bulky guest **4** gives only moderately stable complexes with both β- and γ-CD. As can be seen from Figure 2, the changing profiles of the entropic term for these two guests are in sharp contrast with each other. As the cavity size increases, the entropic gain for the complexation of **2** decreases gradually from positive to negative, cancelling the moderate enthalpic gain obtained with γ-CD. By contrast, in the complexation of **4**, the entropic change behaves contrarily; the large enthalpic gain for α-CD is almost cancelled by the large entropic loss to give a poor stability, but the entropic contribution becomes less negative for β-CD and finally turns positive for γ-CD. Judging from these two extreme cases, we may conclude that the best size-fitted host–guest combination balances the entropic loss from molecular association and the entropic gain from desolvation, minimizing the net entropy change ($T\Delta S$).

Enthalpy–Entropy Compensation. In view of the good linear relationship between ΔH and ΔS observed for the cation binding by various acyclic and (bi)cyclic ligands,[35–40] it is our another intention of this study to test the general validity of the enthalpy–entropy compensation effect in the host–guest complexation by CDs. We therefore compiled the thermodynamic data reported hitherto for the inclusion complexation of a wide variety of guest molecules with α-, β-, and γ-CD in aqueous solution at 25 °C; the individual data are tabulated in Table II. Using these reported and present data sets in Tables I and II, the entropy changes ($T\Delta S$) are plotted against the enthalpy changes (ΔH) to give a good straight line with a correlation coefficient of 0.88, as shown in Figure 3. The slope and intercept obtained for CDs are listed in Table III, along with those for the cation binding by acyclic and (bi)cyclic ligands.

(49) Manka, J. S.; Lawrence, D. S. *J. Am. Chem. Soc.* **1990**, *112*, 2441.

Table III. The Slope (α) and Intercept ($T\Delta S_0$) of the ΔH–$T\Delta S$ Plots for 1:1 Host–Guest Complexations by Various Host Molecules in Homogeneous Solution and in Solvent Extraction

host	homogeneous phase		solvent extraction		ref
	α	$T\Delta S_0$	α	$T\Delta S_0$	
glyme/podand	0.86	2.3			a
crown ether	0.76	2.4	0.73	2.6	a, b
cryptand	0.51	4.0			a
cyclodextrin	0.90	3.1			c

a Reference 36. *b* Reference 39. *c* This work.

As has been proposed previously,[35–40] the empirical linear relationship between ΔH and ΔS means that, whatever the cause is, the resulting change in $T\Delta S$ is proportional to the accompanying change in ΔH, which leads to eq 4. Integration of eq 4 gives eq 5, where α and $T\Delta S_0$ refer to the slope and intercept of Figure 3. Equation 5 indicates that the entropy change consists of two terms, one of which is proportional to the enthalpy change and the other independent of it. Inserting eq 4 in the differential form of the Gibbs–Helmholtz eq 6, we obtain eq 7.

$$T\Delta(\Delta S) = \alpha\Delta(\Delta S) \qquad (4)$$

$$T\Delta S = \alpha\Delta H + T\Delta S_0 \qquad (5)$$

$$\Delta(\Delta G) = \Delta(\Delta H) - T\Delta(\Delta S) \qquad (6)$$

$$\Delta(\Delta G) = (1 - \alpha)\Delta(\Delta H) \qquad (7)$$

As can be seen from eq 4, the slope α is a quantitative measure of the entropic cancelling of the enthalpic gain from the host–guest complexation. In other words, only a proportion $(1 - \alpha)$ of the increment in ΔH contributes toward raising the complex stability $(-\Delta G)$. Equation 5 indicates that, as far as the intercept $(T\Delta S_0)$ is positive as is indeed the case with all the ligands and hosts examined, the complex formation can take place even in the absence of enthalpic gain $(-\Delta H)$. This situation is quite likely to occur, when the entropic contribution from the desolvation process is the major factor governing the host–guest complexation. From these considerations and the actual α and $T\Delta S_0$ values obtained for acyclic glymes/podands, cyclic crown ethers, and bicyclic cryptands, shown in Table III, we concluded that the α and $T\Delta S_0$ values can be used as quantitative measures of the conformational change and the extent of desolvation upon complex formation, respectively.[35–40] Thus, the flexible ligands like acyclic glymes/podands and cyclic crown ethers suffer substantial or moderate conformational change and less extensive desolvation upon cation binding, affording larger slopes (α 0.76–0.86) and smaller intercepts ($T\Delta S_0$ 2.3–2.4). By contrast, the bicyclic cryptands with a more rigid skeleton cannot greatly change the original conformation but undergo extensive desolvation of both cation and ligand, leading to the smallest slope (α 0.51) and the largest intercept ($T\Delta S_0$ 4.0). In this context, the large slope obtained for CDs (α 0.90), which is very close to unity, would be unexpected in view of the rigid skeleton of CD alone. However, this apparently surprising behavior may support the long-proposed global reorganization of the original hydrogen-bond network within the CD molecule upon inclusion complexation.

Finally, it is interesting to note that, beyond the apparent differences in the species and the forces involved, the cation–ligand complexation and the host–guest inclusion, both caused by the weak interactions, can be discussed as a unified general phenomenon in terms of the enthalpy–entropy compensation effect as a common language.

Supplementary Material Available: Calorimetric titration data and detailed calculation procedures for the successive 1:1 and 1:2 complexation of 2-naphthalenesulfonate (**2**) and γ-CD (11 pages). Ordering information is given on any current masthead page.