Calorimetric Titration of Inclusion Complexation with Modified β-Cyclodextrins.[1] Enthalpy–Entropy Compensation in Host–Guest Complexation: From Ionophore to Cyclodextrin and Cyclophane

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Abstract: Calorimetric titrations have been performed at 25 °C in an aqueous solution (pH 7.20) to give the complex stability constants and thermodynamic parameters for the 1:1 complexation of 2-naphthalenesulfonate with various β-cyclodextrin (CD) derivatives **1–15**. All of the derivatizations examined led to substantial decreases in complex stability, which are discussed from the thermodynamic point of view. Except for methylated CD **2** and bridged CDs **14** and **15**, the marked stability drops caused by derivatizations are solely 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 CDs. The copper chelation in **4**, **6**, **8**, and **10** did not improve the complex stability, in spite of the presumed ion pairing of Cu^{2+} with the naphthalenesulfonate anion accommodated in the CD cavity. This is probably rationalized by the decreased hydrophobicity of the CD cavity caused by the closely located ionic species (Cu^{2+}). Contrary to the pronounced enhancement reported for 1-anilino-8-naphthalenesulfonate (ANS) as a guest, the capped CDs **14** and **15** did not promote the binding of 2-naphthalenesulfonate, but rather reduced the binding constants by 2–3 orders of magnitude, as compared with the parent CD **1**. Thermodynamically, the reduced complex stabilities for **14** and **15** are mainly attributed to the decreased enthalpic gain, while the entropic gain is kept unchanged for **15** or becomes more positive for **14**. As was the case with the parent CDs, the ΔH–$T\Delta S$ plot for modified CDs **2-16** shows an excellent linear relationship, affording a very large slope (α 1.07) and intercept ($T\Delta S_0$ 5.0). Interestingly, similar analyses of the thermodynamic parameters reported for quinone-receptor porphyrin **17**, metalloporphyrins **18–29**, and cyclophanes/calixarenes **30–43** also afford compensatory ΔH–$T\Delta S$ relationships with distinctly different slopes α and intercepts $T\Delta S_0$. As proposed previously for the host–guest complexations with various ionophores and CDs, the α and $T\Delta S_0$ values nicely interpret the complexation behavior of all host categories as measures of the conformational changes and the extent of desolvation caused upon complexation, respectively. Thus, the enthalpy–entropy compensation effect is demonstrated to be a convenient, versatile tool for analyzing a wide variety of host–guest complexations involving weak forces such as dipole–dipole, ion–dipole, van der Waals, and hydrogen-bonding interactions.

Cyclodextrins (CDs) have been subjected to diverse modifications to give a wide variety of CD derivatives,[2-13] which have been applied successfully to enzyme-mimetic chemistry[3-10] and separation science and technology.[11-13] Nevertheless, the thermodynamics of inclusion complexation by these modified CDs have scarcely been investigated so far, and therefore, the nature of the weak interactions operative in the host–guest complexation by modified CDs and the thermodynamic consequence of the modifications remain unknown.

Our recent study[1] on the complexation thermodynamics of some naphthalene derivatives with natural α-, β-, and γ-CDs has shown that the thermodynamic parameters obtained are sensitive functions of the position, number, and type of anionic substituent(s) introduced in the guest molecule. Using the compiled thermodynamic parameters reported for the inclusion complexation of various guests with the natural CDs, it was further demonstrated that the enthalpy (ΔH) and entropy (ΔS) changes of complexation are compensatory to each other, displaying a good linear relationship between ΔH and $T\Delta S$ with a slope of 0.90 and an intercept of 3.1. This means that the enthalpic gain/loss from any changes in host, guest, or solvent is almost canceled out by the entropic loss/gain arising from the structural freezing/loosening in the inclusion compound produced, probably due to the global reorganization of the original hydrogen-bond network in CD upon complexation; only 10% of the enthalpic gain is reflected in the free energy change or complex stability.[1] It was thus shown that the enthalpy–entropy compensation effect, which

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(2) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer Verlag: Berlin, 1978.
(3) Tabushi, I. *Inclusion Compounds*; Atwood, J. L., Davies, J. E., MacNicol, D. Nd., Eds.; Academic: London, 1984; Vol. 3, Chapter 13.
(4) Breslow, R. *Inclusion Compounds*; Atwood, J. L., Davies, J. E., MacNicol, D. Nd., Eds.; Academic: London, 1984; Vol. 3, Chapter 14.
(5) Tabushi, I. *Tetrahedron* **1984**, *40*, 269.
(6) Tabushi, I.; Kuroda, Y. *Adv. Catal.* **1984**, *32*, 417.
(7) D'Souza, V. T.; Lu, X. L.; Ginger, R. D.; Bender, M. L. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 673.
(8) Akkaya, E. V.; Czarnik, A. W. *J. Am. Chem. Soc.* **1988**, *110*, 8553.
(9) Szejtli, J. *Cyclodextrin Technology*; Kluwer-Academic: Dordrecht, 1988.
(10) Ougar, H. *Bioorganic Chemistry*, 2nd ed.; Springer: New York, 1989.
(11) Sybilska, D.; Smolkova-Keulemansova, E. *Inclusion Compounds*; Atwood, J. L., Davies, J. E., MacNicol, D. Nd., Eds.; Academic: London, 1984; Vol. 3, Chapter 6.
(12) Szejtli, J. *Starch/Staerke* **1987**, *39*, 357.
(13) Schurig V.; Nowotny, H.-P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 939.

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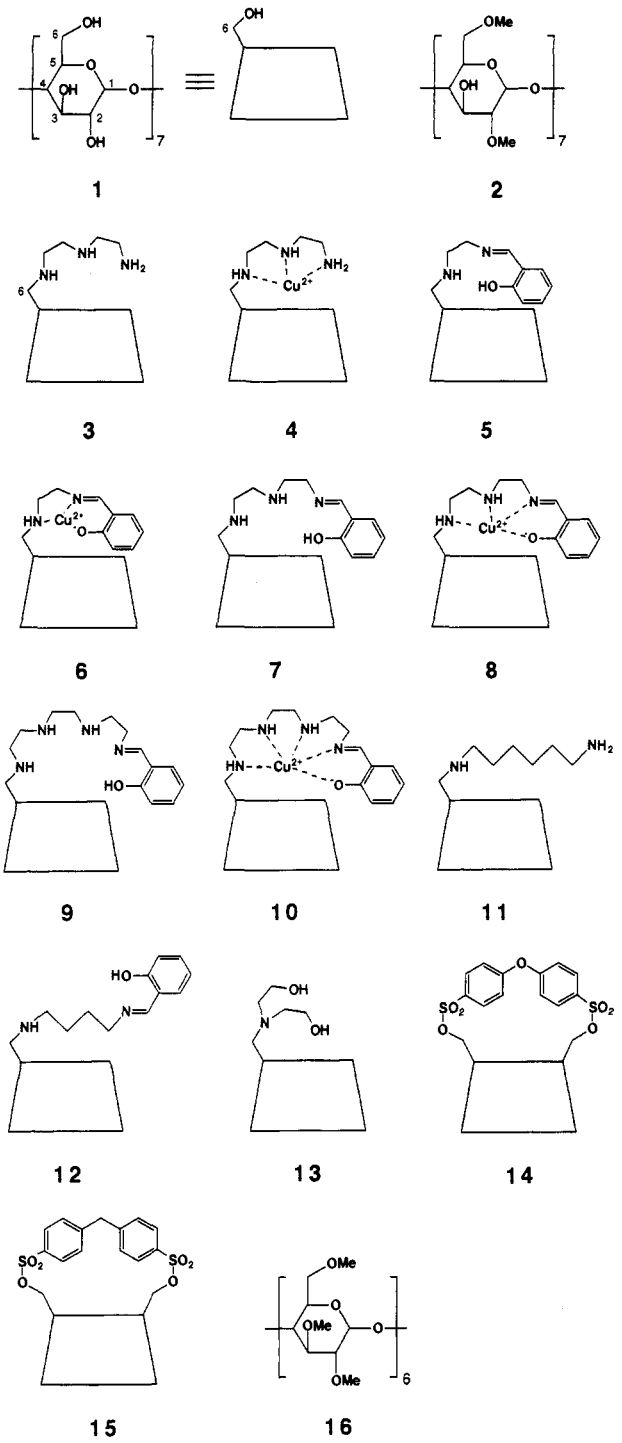
Chart I. Cyclodextrins



was originally proposed as an effective tool for understanding quantitatively the cation-binding behavior of acyclic and macro(bi)cyclic ionophores,[14-17] can be extended to inclusion complexation by natural CDs in aqueous solution, in spite of the apparent differences in the species and forces involved in these two complexation processes.

In this study, we synthesized a series of β-CD derivatives and their copper(II) chelates, shown in Chart I, and the host–guest complexation behavior of these β-CD derivatives was investigated by using calorimetric titration in order to discuss the role of modifications upon complexation from the thermodynamic point of view. Another intention of this study is to discuss the general validity and significance of the compensatory enthalpy–entropy relationship observed for the host–guest complexations of diverse host molecules from ionophores to cyclodextrins and even to cyclophanes/calixarenes through weak forces such as dipole–dipole, ion–dipole, van der Waals, and/or hydrogen-bonding interactions. Eventually, we wish to propose a unified interpretation of the whole host–guest chemistry from the viewpoint of the enthalpy–entropy compensation effect.

Experimental Section

Materials. β-Cyclodextrin (**1**) and sodium 2-naphthalenesulfonate, both purchased from Nakarai, were dried under a reduced pressure prior to use. Heptakis(2,6-*O*-dimethyl)-β-cyclodextrin (**2**) was prepared, according to the procedures reported by Casu et al.[18] Amino β-CDs **3**, **11**, and **13** were synthesized as reported recently.[19] Cyclodextrin Schiff bases **5**, **7**, **9**, and **12** were prepared in the reactions of the respective amino β-CDs with salicylaldehyde.[20] Bridged β-CDs **14** and **15** were synthesized by the reported procedures.[21,22]

The copper(II) chelates **4**, **6**, **8**, and **10** were prepared by the reaction of the corresponding CD derivatives **3**, **5**, **7**, and **9** with slightly excess amounts of copper perchlorate, according to similar procedures reported earlier.[20] The other materials used were purified as previously.[1]

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 calorimetric titration.

Apparatus and Procedures. 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 an LKB 8721-2 precision calorimeter connected to a microcomputer for automated titration and subsequent data processing.[23] The principle of the measurement and the detailed experimental procedures were reported elsewhere.[24-27] In a typical run, a solution of 2-naphthalenesulfonate was continuously introduced at a rate of 0.43 mL/min into a solution of CD derivative **1**–**15** (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 simultaneously by computer simulation. The heat of dilution of the guest was measured separately, for which appropriate corrections were made throughout the work. The reliability of the whole system and the calculation procedures were doubly checked by comparison of the obtained thermodynamic data with the reported values;[28,29] the results were satisfactory within experimental error.

Results

Assuming a 1:1 stoichiometry for the complexation of 2-naphthalenesulfonate (G) with CD derivatives **1**–**15**, the complex stability constant (K) and the enthalpy change (ΔH) were determined calorimetrically by using the least-squares method to

(14) Inoue, Y.; Hakushi, T.; Liu, Y. *Cation Binding by Macrocycles*; Inoue, Y., Gokel, G. W., Eds.; Marcel Dekker: New York, 1990; Chapter 1.
(15) Inoue, Y.; Hakushi, T. *J. Chem. Soc., Perkin Trans. 2* **1985**, 935.
(16) 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.
(17) Liu, Y.; Tong, L.-H.; Huang, S.; Tian, B.-Z.; Inoue, Y.; Hakushi, T. *J. Phys. Chem.* **1990**, *94*, 2666.
(18) Casu, B.; Reggiani, M.; Gallo, G. G.; Vigevani, A. *Tetrahedron* **1968**, *24*, 803.
(19) Shen, B.-J.; Tong, L.-H.; Jin, D.-S. *Chin. Chem. Lett.* **1991**, *2*, 205.
(20) Shen, B.-J.; Tong, L.-H.; Jin, D.-S. *Synth. Commun.* **1991**, *21*, 635.
(21) Tabushi, I.; Shimokawa, K.; Shimizu, N.; Shirakata, H.; Fujita, K. *J. Am. Chem. Soc.* **1976**, *98*, 7855.
(22) Breslow, R.; Bory, P.; Hersh, C. L. *J. Am. Chem. Soc.* **1980**, *102*, 2115.
(23) Shi, J.-P.; Liu, Yu.; Sun, L.-C. *Fenxi Yiqi (Anal. Instrum.)* **1988**, *2*, 42.
(24) Wadsö, I. *Sci. Tools* **1966**, *13*, 33.
(25) Liu, Y.; Hu, J. *Wuli Huaxue Xuebao (Acta Phys. Chim. Sin.)* **1987**, *2*, 11.
(26) Liu, Y.; Wang, Y.; Guo, Z.-Q.; Yang, S.-Y.; Jin, D.-S. *Huaxue Xuebao (Acta Chim. Sin.)* **1986**, *44*, 22.
(27) Liu, Y.; Tong, L.-H.; Sun, X.-Q.; Wang, D.-F.; Hu, H.-W. *Huaxue Xuebao (Acta Chim. Sin.)* **1991**, *49*, 220.
(28) Hansen, L. D.; Lewis, E. R. *J. Chem. Thermodyn.* **1971**, *3*, 35.
(29) 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.

Table I. Complex Stability Constant (K) and Thermodynamic Parameters (in kcal/mol) for 1:1 Host–Guest Complexation of Some Aromatic Guest Molecules with Modified Cyclodextrins **1–16** in Aqueous Solution (T = 298 K)

host	guest	log K	$-\Delta G$	$-\Delta H$	$T\Delta S$	ref
1	2-naphthalene-sulfonate	5.37 ± 0.07	7.33	7.01 ± 0.06	0.32	*a*
2		2.94 ± 0.03	4.01	2.89 ± 0.08	1.12	*a*
3		3.13 ± 0.02	4.27	13.75 ± 0.09	−9.48	*a*
4		2.50 ± 0.03	3.41	10.30 ± 0.10	−6.89	*a*
5		3.13 ± 0.10	4.27	7.19 ± 0.08	−2.92	*a*
6		3.42 ± 0.02	4.67	4.00 ± 0.09	0.67	*a*
7		3.21 ± 0.03	4.38	8.01 ± 0.08	−3.63	*a*
8		3.81 ± 0.06	5.20	3.29 ± 0.04	1.91	*a*
9		3.93 ± 0.05	5.36	6.63 ± 0.04	−1.27	*a*
10		2.95 ± 0.02	4.02	6.75 ± 0.06	−2.73	*a*
11		3.58 ± 0.05	4.88	10.90 ± 0.06	−6.02	*a*
12		3.62 ± 0.02	4.94	10.72 ± 0.06	−5.78	*a*
13		1.85 ± 0.04	2.52	20.39 ± 0.25	−17.87	*a*
14[b]		3.94 ± 0.02	5.37	2.99 ± 0.07	2.38	*a*
15[c]		2.74 ± 0.06	3.74	3.88 ± 0.08	−0.14	*a*
16	benzoic acid	2.74	3.73	16.4	−12.8	*d*
	m-hydroxy-benzoic acid	3.06	4.17	17.3	−13.1	*d*
	p-hydroxy-benzoic acid	2.98	4.07	14.4	−10.1	*d*
	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*

[a] This work; calorimetric titrations performed at 25 °C in a buffered aqueous solution at pH 7.20. [b] A,D-bridged cyclodextrin. [c] Mixture of 40% A,C- and 60% A,D-bridged cyclodextrins. [d] Reference 30; thermodynamic parameters determined by variable-temperature circular dichroism spectrometry 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.

minimize the error square sum (U):[25-27]

$$G + CD \overset{K}{\rightleftarrows} G\cdot CD \tag{1}$$

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

where Q_t refers to the net heat of complexation measured at time t in minutes, while 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 ΔH for complexation with **1–15** were determined by computer simulation with continuously changing K, i.e. N_t, to minimize the U value. For all the host–guest combinations examined, the U values were minimized satisfactorily to give the optimized sets of K and ΔH listed in Table I. No serious deviation was found in the fitting process, verifying the 1:1 stoichiometry of complexation as assumed above.

Discussion

Modified Cyclodextrins. In the present study, β-cyclodextrin (CD) was subjected to several types of peripheral modifications affording a wide variety of cyclodextrin derivatives: heptakis-(2,6-*O*-dimethyl)-CD **2**, diethylenetriamino-CD **3**, oligoethyleneamine Schiff bases **5**, **7**, and **9**, the reference amino compounds **11** and **13**, and bridging disulfonates **14** and **15**.

As can be seen from Table I, the thermodynamic parameters obtained reveal that all the modifications applied to CD lead to the substantially reduced complex stabilities for the inclusion complexation of 2-naphthalenesulfonate, although the thermodynamic quantities for each CD derivative behave quite differently. Except for the methylated CD **2** and the bridged CDs **14** and **15**, the marked drops in stability constant (K) caused by the modifications are mostly attributable to the highly negative entropy changes ($T\Delta S$), whereas the enthalpy changes (ΔH) are comparable to or much greater than that for the parent CD **1**.

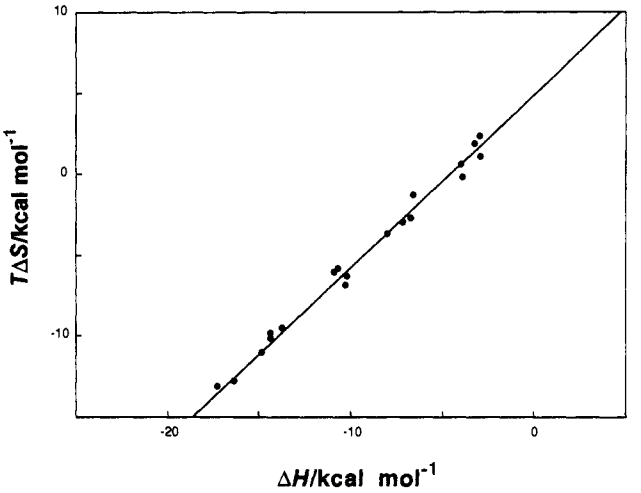


Figure 1. Enthalpy–entropy compensation plot for inclusion complexation of 2-naphthalenesulfonate with β-cyclodextrin derivatives **2–16** (correlation coefficient (r), 0.994; number of data set (n), 22); see Table I for the original data.

Table II. Slope (α) and Intercept ($T\Delta S_0$) of the ΔH–$T\Delta S$ Plots for 1:1 Host–Guest Complexation in Homogeneous Solution

host	α	$T\Delta S_0$	ref
glyme/podand	0.86	2.3	*a*
crown ether	0.76	2.4	*a*
cryptand	0.51	4.0	*a*
cyclodextrin	0.90	3.1	*b*
modified cyclodextrin (**2–16**)	1.07	5.0	*c*
quinone-receptor porphyrin (**17**)	0.60	0.0	*c, d*
metalloporphyrin (**18–29**)	0.61	1.6	*c*
cyclophane/calixarene (**30–43**)	0.78	3.4	*c*

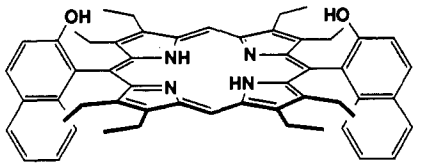
[a] Reference 15. [b] Reference 1 [c] This work. [d] Reference 31.

From the entropic point of view alone, the host–guest complexation, accompanying inherently molecular association, is unfavorable, but the entropic loss arising from the host–guest association is often compensated by the gain from the release of water molecules bound originally in and around the CD cavity, giving rise to the almost 0 $T\Delta S$ value for the parent CD **1** (Table I).[1] The present results indicate that most modifications employed enhance the hydrophobic interaction between the host CD and the guest 2-naphthalenesulfonate to give much higher enthalpic gains ($-\Delta H$). This seems reasonable, since the substitution of any less-hydrophilic substituents for the 2- and/or 6-hydroxyl group(s) of CD should increase the hydrophobicity around the cavity.

On the other hand, the highly negative $T\Delta S$ values obtained for most modified CDs, which exceed the increased enthalpic gains and are responsible for the decreased complex stabilities, may be rationalized in terms of the decreased number of trapped water molecules that can be released upon complexation. When the long side chain is originally included in the cavity of the free host, the guest inclusion may take place but only a small amount of bound water is released upon complexation. In contrast, the short or bridging side chains in **2**, **14**, and **15** cannot completely substitute the bound water in the cavity, and therefore, these methylated and bridged CDs afford rather comparable entropic gains as **1** does.

Copper(II)-Bound Amino Cyclodextrins. As judged from the complex stabilities, no drastic changes appear to occur in the complexation behavior of the copper(II) chelates of amino CDs **4**, **6**, **8**, and **10**. Close examination of the thermodynamic quantities reveals, however, that the apparently trivial change in log K or ΔG is just a consequence of a critical balance between the deviations of ΔH and $T\Delta S$ in the opposite directions. Except for the case of **10**, the chelation of the copper(II) ion substantially

Chart II. Porphyrins



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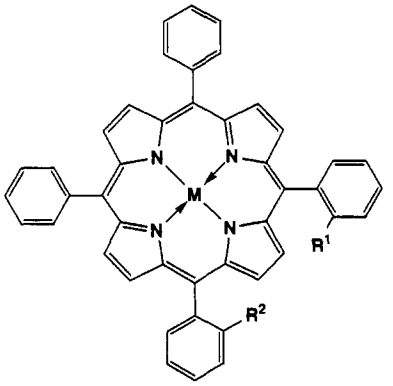
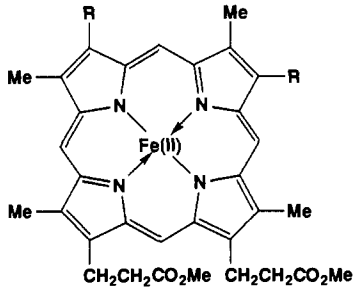
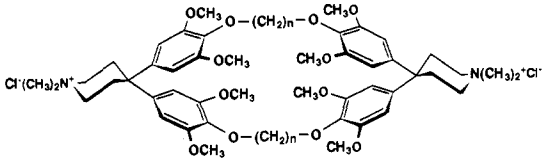


18 M = Fe(II), $R^1 = R^2 = H$
19 M = Zn(II), $R^1 = R^2 = H$
20 M = Zn(II), R^1 = 3-$PyCH_2CONH$, $R^2 = H$
21 M = Zn(II), R^1 = 3-$PyCH_2CH_2CH_2CONH$, $R^2 = H$
22 M = Zn(II), R^1 = 3-$PyCH_2CH_2CH_2CH_2CONH$, $R^2 = H$
23 M = Zn(II), $R^1 = CH_3CONH$, $R^2 = H$
24 M = Zn(II), $R^1 = PhCH_2CH_2CONH$, $R^2 = H$
25 M = Zn(II), $R^1 = R^2 = PhCH_2CH_2CH_2CH_2CONH$

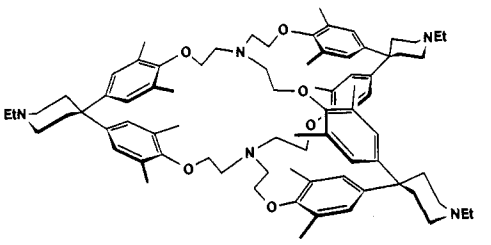


26 R = H
27 R = CH_3CH_2
28 R = CH_2=CH
29 R = CH_3CO

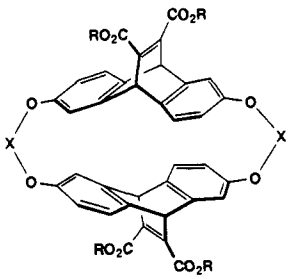
Chart III. Cyclophanes

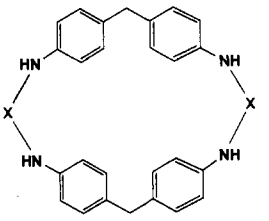


30 n = 4
32 n = 3



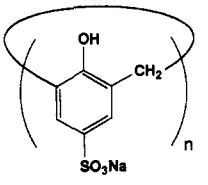
31

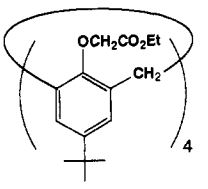




33 R = CH_3, X = CH_2–*p*-C_6H_4–CH_2
34 R = Cs, X = CH_2–*p*-C_6H_4–CH_2
35 R = Cs, X = CH_2–*m*-C_6H_4–CH_2
36 R = Cs, X = CH_2–*trans*-1,4-*c*-C_6H_{10}–CH_2
37 R = Cs, X = $(CH_2)_5$

38 X = $(CH_2)_4$
39 X = $(CH_2)_5$





40 n = 4
41 n = 6
42 n = 8

43

diminishes the enthalpic gain by 3.2–4.7 kcal/mol, which is (over)-compensated by the decreased entropic loss of 2.6–5.5 kcal/mol.

The copper chelation in **4**, **6**, **8**, and **10** might be expected to enhance the complex stability through the electrostatic interaction by ion-pairing between Cu^{2+} and the naphthalenesulfonate anion accommodated in the CD cavity. In fact, this is not the case: probably the presence of an ionic species (Cu^{2+}) situated just above the cavity may increase the host hydration and simultaneously decrease the microenvironmental hydrophobicity to a great extent, while the side-chain conformation fixed originally in the copper chelates does not accompany any further entropic loss upon complexation, affording less negative or slightly positive entropy changes.

Capped Cyclodextrins. The bridging disulfonylation of **1** has been demonstrated to enhance the complexing ability of the capped CD **15** (log K = 3.11) toward 1-anilino-8-naphthalenesulfonate (ANS) by a factor of 24, as compared with the parent CD **1** (log K = 1.75).[21] However, the present study demonstrates that the same capped CD **15**, or **14**, does not enhance the binding constant for 2-naphthalenesulfonate but rather reduces it by 2–3 orders of magnitude. This apparent discrepancy would be rationalized by the different sizes of the guest moiety accommodated actually in the CD cavity. Examinations with CPK molecular models indicate that most parts of 2-naphthalenesulfonate can be accommodated in the cavity in the longitudinal direction, while the naphthalene moiety of ANS cannot penetrate in the longitudinal or lateral direction and only the anilino group can be embedded into the cavity. The smaller anilino group, being less sensitive to the steric hindrance induced by capping, may enjoy the increased hydrophobicity of the capped CD to give the higher binding constant for ANS.

Thermodynamically, the reduced complex stabilities for **14** and **15** are mainly ascribable to the decreased enthalpic gain ($-\Delta H$), while the entropic gain ($T\Delta S$) is kept unchanged for **15** or becomes more positive for **14**. The bridging disulfonylation, which increases the hydrophobicity around the CD cavity,[21,22] does not contribute to the enhancement of the hydrophobic interaction with 2-naphthalenesulfonate but rather interferes with guest inclusion probably through steric hindrance. It is emphasized, therefore, that the frequently employed strategy to enhance the binding constant by creating an expanded hydrophobic pocket

Table III. Reported Thermodynamic Parameters (in kcal/mol) for Host–Guest Complexation of Various Guests with Quinone-Receptor Porphyrin **17**, Metalloporphyrins **18–29**, and Cyclophanes/Calixarenes **30–43**[a]

host	guest	solvent	$-\Delta G$	$-\Delta H$	$T\Delta S$	ref
		Quinone-Receptor Porphyrin				
17	1,4-benzoquinone	chloroform-*d*	2.4	5.6	−3.3	*b*
	chloranil		3.6	8.6	−5.1	*b*
	fluoranil		3.5	8.0	−4.5	*b*
	2,5-dichloro-1,4-benzoquinone		3.1	8.4	−5.3	*b*
	2-chloro-1,4-benzoquinone		2.8	6.5	−3.7	*b*
	2-methyl-1,4-benzoquinone		2.7	6.3	−3.6	*b*
	2,5-dimethyl-1,4-benzoquinone		2.8	6.8	−4.0	*b*
	duroquinone		3.6	9.0	−5.5	*b*
	2,3-dimethoxy-5-methyl-1,4-benzoquinone		2.1	6.0	−4.0	*b*
	tetramethoxy-1,4-benzoquinone		1.2	4.3	−3.1	*b*
	1,4-naphthoquinone		3.0	8.3	−5.3	*b*
	9,10-anthraquinone		3.2	7.9	−4.7	*b*
	1,4-cyclohexanedione		1.4	2.9	−1.5	*b*
		Metalloporphyrins				
18	3-cyanopyridine	*N,N*-dimethylformamide	5.6	12.3	−6.9	*c*
	3-chloropyridine		6.4	12.0	−5.7	*c*
	3-bromopyridine		6.4	12.9	−6.6	*c*
	pyridine		7.7	14.4	−6.9	*c*
	3-methylpyridine		7.3	15.7	−8.3	*c*
	4-methylpyridine		8.3	15.3	−7.2	*c*
19	pyridine	cyclohexane	6.0	10.0	−4.0	*d*
		chloroform	4.0	4.0	0.0	*e*
		benzene	4.9	8.8	−3.9	*e*
		benzene	5.0	9.2	−4.2	*f*
	3-picoline	toluene	5.0	8.7	−3.7	*g*
20	3-picoline	toluene-d_8	1.2	2.7	−1.5	*g*
21	3-picoline	toluene-d_8	0.4	1.1	−0.7	*g*
22	3-picoline	toluene-d_8	1.8	2.2	−0.4	*g*
23	3-picoline	toluene	5.4	9.3	−3.9	*g*
24	3-picoline	toluene	5.5	10.6	−5.1	*g*
25	3-picoline	toluene	6.1	11.3	−5.2	*g*
26	4-methylpyridine	benzene	3.3	−0.8	3.9	*h*
	4-vinylpyridine		3.9	1.6	2.4	*h*
	pyridine		3.5	2.4	1.2	*h*
	4-(butoxycarbonyl)pyridine		4.8	6.7	−2.1	*h*
	4-cyanopyridine		4.8	6.9	−2.1	*h*
27	4-methylpyridine	benzene	5.1	8.7	−3.6	*h*
	4-vinylpyridine		5.0	10.2	−4.8	*h, i*
	pyridine		3.3	5.2	−1.8	*h*
	4-(butoxycarbonyl)pyridine		4.3	8.9	−4.5	*h*
	4-cyanopyridine		3.8	11.7	−7.2	*h, i*
28	4-aminopyridine	benzene	7.7	16.1	−8.3	*h*
	4-methylpyridine		9.0	14.0	−4.8	*h*
	4-vinylpyridine		5.1	7.4	−2.4	*h*
	pyridine		1.8	3.3	−1.5	*h*
	4-(butoxycarbonyl)pyridine		4.0	10.1	−6.0	*h*
	4-cyanopyridine		4.1	9.0	−4.8	*h*
29	4-methylpyridine	benzene	1.5	2.6	−1.2	*h*
	4-vinylpyridine		3.6	3.6	0.0	*h*
	pyridine		1.8	7.5	9.5	*h, i*
	4-(butoxycarbonyl)pyridine		5.0	−7.0	12.5	*h, i*
	4-cyanopyridine		1.7	−7.5	9.5	*h*
		Cyclophanes/Calixarenes				
30	dimethyl *p*-benzenedicarboxylate	H_2O	6.81	11.8	−5.0	*j*
	p-nitrotoluene		6.01	8.1	−2.1	*j*
	p-tolunitrile		6.01	8.1	−2.1	*j*
	p-nitrophenol		5.86	10.5	−4.6	*j*
	p-dimethoxybenzene		5.38	10.0	−4.6	*j*
	p-xylene		5.33	7.2	−1.9	*j*
	p-dicyanobenzene		5.23	10.3	−5.1	*j*
	p-dinitrobenzene		5.22	9.8	−4.6	*j*
	p-cresol		4.71	10.6	−5.9	*j*
	hydroquinone		3.69	10.3	−6.6	*j*
	p-dimethoxybenzene	methanol	1.2	3.7	−2.5	*j*
30	dimethyl *p*-benzenedicarboxylate	D_2O (20 °C)	6.8	10.7	−4.0	*k*
	p-nitrotoluene		6.0	9.6	−3.6	*k*
	p-tolunitrile		6.0	9.8	−3.8	*k*
	p-nitrophenol		5.9	11.7	−5.8	*k*
	p-dimethoxybenzene		5.4	10.2	−4.8	*k*
	p-xylene		5.3	7.4	−2.1	*k*
	p-dicyanobenzene		5.2	9.5	−4.3	*k*
	p-dinitrobenzene		5.2	9.5	−4.3	*k*
	p-cresol		4.7	9.1	−4.4	*k*
	p-diaminobenzene		3.4	7.1	−3.7	*k*
	p-dicyanobenzene	methanol-d_4	1.8	4.2	−2.4	*k*
	p-dimethoxybenzene		1.2	4.4	−3.2	*k*

Table III (Continued)

host	guest	solvent	$-\Delta G$	$-\Delta H$	$T\Delta S$	ref
		Quinone-Receptor Porphyrin				
31	pyrene	2,2,2-trifluoroethanol	7.8	20.0	−12.2	*j*
		methanol	6.4	12.0	−5.6	*j*
		ethanol	6.1	11.0	−4.9	*j*
		N-methylacetamide	5.8	9.0	−3.2	*j*
		N-methylformamide	5.1	5.6	−0.5	*j*
		N,*N*-dimethylacetamide	4.4	2.0	2.4	*j*
		acetone	4.3	6.6	−2.3	*j*
		dimethyl sulfoxide	3.9	6.4	−2.5	*j*
		N,*N*-dimethylformamide	2.9	3.7	−0.8	*j*
		tetrahydrofuran	2.7	3.0	−0.3	*j*
		chloroform	2.3	3.1	−0.8	*j*
		benzene	1.5	0.8	0.7	*j*
32	*p*-nitrophenol	D_2O	4.5	10.1	−5.6	*k*
	p-nitrotoluene		4.5	8.5	−4.0	*k*
	dimethyl *p*-benzenedicarboxylate		4.5	8.0	−3.5	*k*
	p-xylene		4.2	6.4	−2.2	*k*
	p-dicyanobenzene		4.0	7.3	−3.3	*k*
	p-dimethoxybenzene		3.5	5.7	−2.2	*k*
33	1-adamantyltrimethylammonium iodide	chloroform-*d*	2.1	1.5	0.5	*l*
	N-methylquinolinium iodide		3.5	3.3	0.1	*l*
	N-ethylquinolinium iodide		2.5	3.6	−1.1	*l*
	N-methylisoquinolinium iodide		2.4	2.4	0.0	*l*
34	1-adamantyltrimethylammonium iodide	D_2O (pD 9)	7.3	4.7	2.6	*l*
	quinoline		6.0	11.0	−5.1	*l*
	isoquinoline		6.4	9.8	−3.3	*l*
	4-methylquinoline		7.1	9.8	−2.7	*l*
	N-methylindole		4.0	1.6	2.4	*l*
35	1-adamantyltrimethylammonium iodide	D_2O (pD 9)	6.4	3.4	3.0	*l*
36	1-adamantyltrimethylammonium iodide	D_2O (pD 9)	5.6	1.3	4.2	*l*
	quinoline		6.4	7.5	−1.1	*l*
	isoquinoline		6.3	2.9	3.3	*l*
	4-methylquinoline		6.3	−1.0	7.2	*l*
	N-methylindole		5.0	−0.3	5.4	*l*
37	1-adamantyltrimethylammonium iodide	D_2O (pD 9)	5.5	4.9	0.7	*l*
38	1-anilino-8-naphthalenesulfonate (ANS)	H_2O (pH 1.95)	5.2	3.6	1.6	*m*
	2-*p*-toluidinyl-6-naphthalenesulfonate (TNS)		7.0	6.4	0.6	*m*
39	ANS	H_2O (pH 1.95)	5.3	5.5	−0.2	*m*
	TNS		5.7	3.2	2.5	*m*
40	trimethylphenylanilinium chloride	D_2O (pD 7.3)	5.1	6.2	−1.1	*n*
41	trimethylphenylanilinium chloride	D_2O (pD 7.3)	3.7	0.3	3.5	*n*
42	trimethylphenylanilinium chloride (1:1 host–guest complex)	D_2O (pD 7.3)	5.1	0.0	5.1	*n*
	trimethylphenylanilinium chloride (1:2 host–guest complex)		5.0	0.0	5.0	*n*
43	Li^+	acetonitrile	8.73	11.66	−2.93	*o*
	Na^+		7.91	14.71	−6.79	*o*
	K^+		6.14	10.48	−4.34	*o*
	Rb^+		2.59	4.46	−1.89	*o*
	Cs^+		3.82	2.74	1.08	*o*
	Li^+	methanol	3.55	−1.21	4.75	*o*
	Na^+		6.82	10.90	−4.07	*o*
	K^+		3.27	3.40	−0.12	*o*

[a] Determined directly by calorimetric titration or indirectly by van't Hoff analysis of equilibrium constants obtained by variable-temperature (VT) polarography, NMR, UV–vis, or fluorescence spectrometry; $T = 298$ K, unless stated otherwise. [b] Reference 31 (thermodynamic parameters determined by VT NMR). [c] Reference 32 (VT polarography). [d] Reference 33 (VT UV–vis). [e] Reference 34 (VT UV–vis). [f] Reference 35 (VT UV–vis). [g] Reference 36 (VT NMR). [h] Reference 37 (VT UV–vis). [i] Data not used in plot, since $\Delta G \neq \Delta H - T\Delta S$ within an error limit of ±0.2 kcal/mol. [j] Reference 38 (calorimetry). [k] Reference 39 (VT NMR). [l] Reference 40 (VT NMR). [m] Reference 41 (VT fluorescence). [n] Reference 42 (VT NMR). [o] Reference 43 (calorimetry).

around the CD cavity does not always work well and lacks general thermodynamic verification, especially when the guest molecules are bulky.

Enthalpy–Entropy Compensation. As has been demonstrated recently for complexation with natural CDs,[1] an evident compensatory relationship between enthalpy and entropy changes is found also for the complexations of 2-naphthalenesulfonate by modified β-CDs **2-15** and of various guests by per-*O*-methylated α-CD **16**.[30] As shown in Figure 1, the ΔH–$T\Delta S$ plot gives an excellent straight line with a correlation coefficient of 0.99, although the available data points are fairly limited ($n = 22$). The slope α and the intercept $T\Delta S_0$ of the plot are distinctly different from those reported for the cation binding by ionophores of different topologies[14-17] and for the inclusion complexation by natural CDs.[1] The values obtained are compared with the relevant data in Table II.

Of the host molecules examined thermodynamically, modified CDs **2–16** give the largest slope (α 1.07) and intercept ($T\Delta S_0$ 5.0). In our earlier works,[1,14-17] we have shown that the slope (α) and intercept ($T\Delta S_0$) of the ΔH–$T\Delta S$ plot can be related respectively to the degree of conformational change and the extent of desolvation induced upon complex formation. According to this theory, the unit slope α and the large intrinsic entropic gain $T\Delta S_0$ jointly indicate that the enthalpic gain from the inclusion complexation is completely canceled out by the entropic loss from the conformational changes caused upon guest inclusion. Nonetheless, the complexation by the modified CDs is still favored even in the absence of the enthalpic stabilization, exclusively due

(30) Harata, K.; Tsuda, K.; Uekama, K.; Otagiri, M.; Hirayama, F. *J. Inclusion Phenom.* **1988**, *6*, 135.

to the entropic gains from the discharge of the flexible side arm from the cavity in addition to the extensive desolvation of the host and guest molecules. This view derived from the thermodynamic data nicely coincides with the complexation mechanism of modified CDs, and therefore, the present result again supports our proposal that the complexation phenomenon can be understood in a general context of the enthalpy–entropy compensation effect as far as the weak interactions through the dipole–dipole, ion–dipole, hydrogen-bonding, and/or van der Waals forces are involved.[14]

Porphyrins, Cyclophanes, and Calixarenes. In this context, an intriguing logical extension of our previous and present work is to examine the general validity of the enthalpy–entropy compensation effect in other host–guest complexations that involve different sorts of weak interactions. In order to see the scope and limitations of this extrathermodynamic relationship, we surveyed all the available thermodynamic parameters reported for the host–guest complexations with quinone-receptor porphyrin **17**,[31] metalloporphyrins **18–29**,[32–37] and cyclophanes/calixarenes **30–43**[38–43] (Charts II and III), and the data compiled are tabulated in Table III. These molecules respectively represent typical host categories in which hydrogen-bonding, ion–dipole, and van der Waals interactions are the major driving force operative in their complexation processes. It should be noted that many of the thermodynamic parameters listed were determined indirectly through the van't Hoff analysis of the equilibrium constants obtained by the variable-temperature polarography, NMR, UV–vis, or fluorescence titration method.[31–37,39–42] The parameters thus obtained have been demonstrated by Diederich's[38] and Dougherty's[40] groups to be less accurate in general than those from the calorimetric titration, unless appropriate corrections for the heat capacity were made.[40]

Using most of these thermodynamic parameters that satisfy the equation $\Delta G = \Delta H - T\Delta S$ within an error limit of ±0.2 kcal/mol, the entropy change ($T\Delta S$) was plotted against the enthalpy change (ΔH) for each host category. As can be seen from Figures 2–4, the ΔH–$T\Delta S$ plots display good to excellent linear relationships with correlation coefficients of 0.95, 0.97, and 0.92, respectively, and give distinctly different slopes α and intercepts $T\Delta S_0$ for these three host categories, as shown in Table II.

The compensatory enthalpy–entropy relationship has already been observed in individual thermodynamic studies using some of these host–guest combinations.[31,37,38] In most cases, however, only the linear enthalpy–entropy relationship was reported and sometimes the isoequilibrium temperature was calculated, but the possible meanings of the slope and intercept obtained have not been discussed in further detail, except for the detailed discussion on the thermodynamics of the solvent effects in the cyclophane–arene inclusion complexation studied by Diederich's group.[38] This sort of discussion is quite useful indeed for the explanation of individual complexation behavior, but is not always applicable to different host–guest combinations and does not appear to lead to a global understanding of the host–guest complexation behavior. In this context, the classification of host–guest interaction through the host topology and the weak force

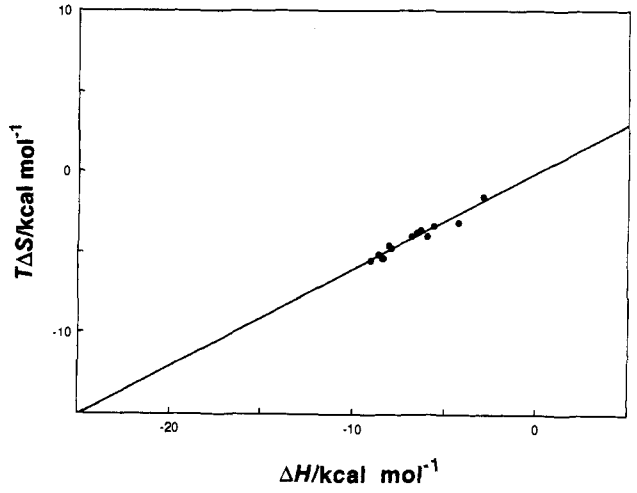


Figure 2. Enthalpy–entropy compensation plot for complexation of *p*-quinones and 1,4-cyclohexanedione with quinone-receptor porphyrin **17** ($r = 0.952$, $n = 13$); see Table III for the original data and references.

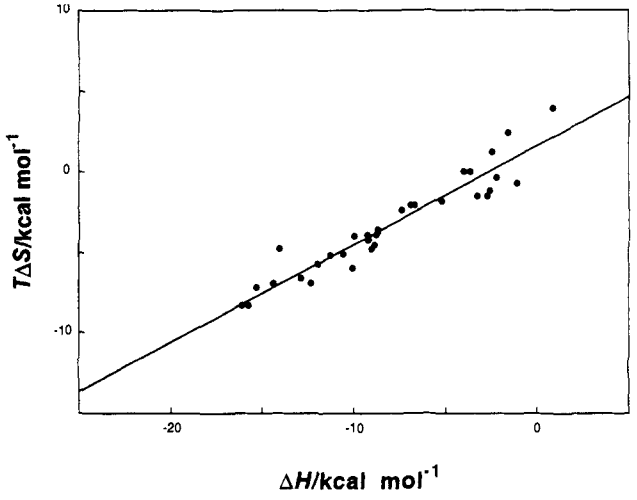


Figure 3. Enthalpy–entropy compensation plot for complexation of pyridines and picoline with metalloporphyrins **18–29** ($r = 0.972$, $n = 33$); see Table III for the original data and references.

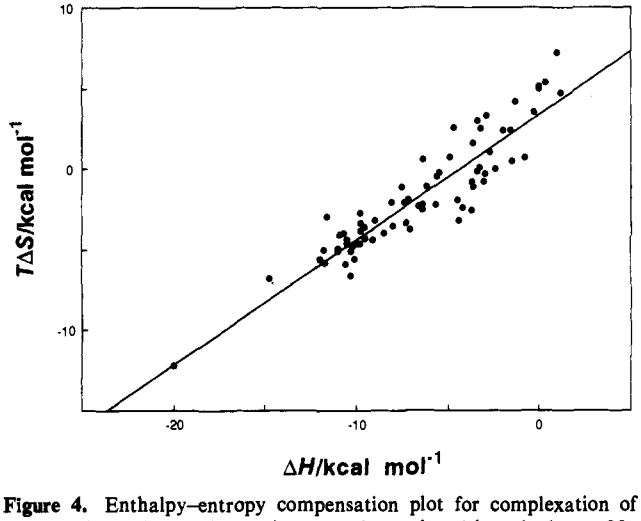


Figure 4. Enthalpy–entropy compensation plot for complexation of benzene derivatives and organic ammonium salts with cyclophanes **30–39** and calixarenes **40–43** ($r = 0.921$, $n = 75$); see Table III for the original data and references.

(31) Aoyama, Y.; Asakawa, M.; Matsui, Y.; Ogoshi, H. *J. Am. Chem. Soc.* **1991**, *113*, 6233.
(32) Kadish, K. M.; Schaeper, D. *J. Chem. Soc., Chem. Commun.* **1980**, 1273.
(33) Vogel, G. C.; Stahlbush, J. R. *Inorg. Chem.* **1977**, *16*, 950.
(34) Cole, S. J.; Curthoys, G. C.; Magnusson, E. A.; Phillips, J. N. *Inorg. Chem.* **1972**, *11*, 1024.
(35) Miller, J. R.; Gorough, G. D. *J. Am. Chem. Soc.* **1952**, *74*, 3977.
(36) Walker, F. A.; Benson, M. *J. Am. Chem. Soc.* **1980**, *102*, 5530.
(37) Cole, S. J.; Curthoys, G. C.; Magnusson, E. A. *J. Am. Chem. Soc.* **1970**, *92*, 2991.
(38) Smithrud, D. B.; Wyman, T. B.; Diederich, F. *J. Am. Chem. Soc.* **1991**, *113*, 5420.
(39) Ferguson, S. B.; Seward, E. M.; Diederich, F.; Snaford, E. M.; Chou, A.; Inocencio-Szweda, P.; Knobler, C. B. *J. Org. Chem.* **1988**, *53*, 5593.
(40) Stauffer, D. A.; Barrans, R. E., Jr.; Dougherty, D. A. *J. Org. Chem.* **1990**, *55*, 2762.
(41) Chun, I. K.; Lee, M. W. *J. Korean Pharm. Sci.* **1989**, *19*, 71.
(42) Shinkai, S.; Araki, K.; Matsuda, T.; Manabe, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3856.
(43) Danil de Namor, A. F.; Apaza de Sueros, N.; McKervey, M. A.; Barrett, G.; Arnaud Neu, F.; Schwing-Weill, M. J. *J. Chem. Soc., Chem. Commun.* **1991**, 1546.

involved as well as the en bloc treatment of thermodynamic parameters are the basic conditions for a global discussion of host–guest complexation.

Quinone-receptor porphyrin **17**, carrying a very rigid porphyrin skeleton and two 2-naphthol substituents in cis configuration at the transannular positions, binds various *p*-quinones and diones fairly strongly in chloroform-*d*. As can be seen from Figure 2 and Table II, the linear ΔH–$T\Delta S$ plot gives a small slope (α 0.60) and 0 intercept ($T\Delta S_0$ 0.0). According to our theory,[1,14] the small slope for **17** indicates that the conformational changes upon complexation are minimal and up to 40% of the enthalpic gain ($-\Delta H$) arising from any change in guest is reflected on the complex stability ($-\Delta G$). The first conclusion is quite reasonable in view of the rigid skeleton and fairly restricted side arms in **17**, while the second one may promise that an *appropriate* variation/modification of the host/guest structures for higher complex stability could result in a 40% increase in stability. On the other hand, the 0 intercept means that the extent of desolvation upon complexation is minimal and the small entropic gain from desolvation, if any, is completely canceled out by the intrinsic entropic loss attributable to the molecular association. In other words, no complexation with **17** is expected to occur in the absence of enthalpic gain arising from the hydrogen-bonding interaction between the naphthol substituents and the *p*-quinone/dione guest. This sounds natural, since both the host and guest molecules are not heavily solvated in chloroform-*d* of low donor number.[44]

Interestingly, the ligation of various pyridines and picoline to metalloporphyrins **18–29** affords an almost comparable slope and a slightly larger intercept: $\alpha = 0.61$, $T\Delta S_0 = 1.6$; see Figure 3 and Table II. This may be somewhat surprising because the driving force involved here is completely different from that operative in the complexation of *p*-quinones with **17**. It is thus demonstrated that, in spite of the different binding forces involved, the complexations by quinone-receptor porphyrin **17** and metalloporphyrins **18–29** can be discussed on the same basis, i.e. the enthalpy–entropy compensation. For this host category too, the small slope and intercept indicate that the complexation causes only minimal conformational changes and less-extensive desolvation. This complexation profile for metalloporphyrins nicely coincides with the rigid structures of the host/guest molecules and the nature of the nondonating, low-polarity solvents employed.

(44) Marcus, Y. *Ion Solvation*; Wiley: Chichester, 1985.

By contrast, a much larger slope (α 0.78) and intercept ($T\Delta S_0$ 3.4) are obtained from the ΔH–$T\Delta S$ plot for the complexation of various organic guests with cyclophanes and calixarenes **30–43** in aqueous and methanolic solutions; see Figure 4 and Table II. From these values, fairly large conformational changes and a considerable degree of desolvation are inferred to occur upon complexation. Possessing flexible methylenes and/or ether oxygens connecting rigid aromatic moieties, these cyclophane hosts can more easily alter their conformations upon complexation than the porphyrin derivatives do. Furthermore, these cyclophanes with polar/charged groups must be heavily solvated through ion(dipole)–dipole and/or hydrogen-bonding interactions particularly in polar protic solvents such as water and methanol, and therefore, extensive desolvation is likely to occur upon complexation through hydrophobic interaction. Indeed, the reorganization of the hydrogen-bond network in the host–guest complex has recently been shown to play a significant role in the complexation of cyclophanes **30** and **32**.[45] Accordingly, the much larger intercept obtained for cyclophanes ($T\Delta S_0$ 3.4) is reasonably understood as a manifestation of the fairly extensive desolvation upon complexation.

It is interesting to note that the slope and, in particular, the intercept for cyclophanes are fairly close to those for cyclodextrins; see Table II. In view of the mechanism and weak interactions involved in the complexations by the hosts of these two categories, the similarity observed in the extrathermodynamic behavior of cyclophanes and cyclodextrins is not unexpected and may rather confirm the validity of the enthalpy–entropy compensation effect as a general tool for analyzing the profile of host–guest complexation involving any kinds of hosts, guests, and interactions working between them.

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(45) Jorgensen, W. L.; Nguyen, T. B.; Sanford, E. M.; Chao, I.; Houk, K. N.; Diederich, F. *J. Am. Chem. Soc.* **1992**, *114*, 4003.