Journal of Inclusion Phenomena and Molecular Recognition in Chemistry **26:** 175–183, 1996.

Substituent Effect and Enthalpy–Entropy Compensation on the Inclusion of β-Cyclodextrin with 1-Substituted Naphthalenes

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(Received: 7 November 1995; in final form: 25 June 1996)

Abstract. The inclusion complexation of β-CD with 1-substituted naphthalenes has been investigated by fluorescence spectroscopy. It was observed that the association constants were influenced by the molar refraction (R_m), hydrophobic constant (π_x), and Hammett constant (σ_x) of substituents in the guest compounds. The thermodynamic parameters ΔG^0, ΔH^0, and ΔS^0 determined by measuring the temperature-dependent K_a values shows that inclusion complex formation is enthalpy driven. The results are discussed in terms of enthalpy–entropy compensation.

Key words: β-CD, enthalpy–entropy compensation, inclusion complex, naphthalene derivatives, substituent effect.

1. Introduction

Cyclodextrin (CD), an ideal natural miniature of an enzyme, can recognize a variety of organic molecules in aqueous solution, since it has a hydrophobic cavity of appropriate dimension and a hydrophilic exterior. The molecular recognition properties of CD have therefore been a subject of special interest in recent years as models for enzyme-substrate binding processes [1–4]. High binding affinity to CD generally requires a good spatial complementarity in the host–guest complex. β-CD, with a cavity diameter of 6.5 Å, allows the best spatial fit for many common guest moieties such as benzene and naphthalene.

It has been reported that naphthalene can be included by β-CD to form a 1 : 1 complex [5]. The association constant for the naphthalene complex with β-CD is larger than that with γ-CD [6]; the cavity of β-CD is thus considered to be suitable to include the naphthalene moiety. There are two possible orientations of 1-substituted naphthalenes in β-CD inclusion complexes [6,7]. According to the host–guest space-fitting model, 1-substituted naphthalenes prefer the axial over

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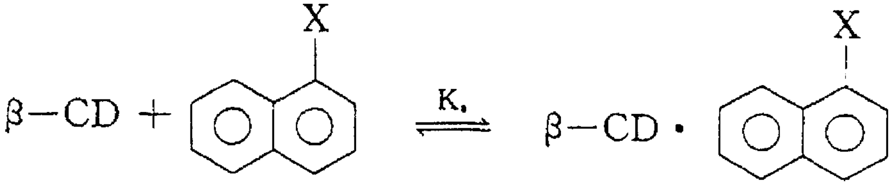
the equatorial orientation in the cavity of β-CD [6]. Apparently, inclusion of 1-substituted naphthalene into β-CD is highly regioselective. It has also been noted that the association constants of inclusion complexation of naphthalene derivatives with β-CD are more sensitive to the position and number of substituents but less sensitive to the type of substituents [8].

Thermodynamic studies indicated that the inclusion of β-CD with 1-naphthalenesulphonate and 1-naphthaleneacetate ions is entropy driven [8]. However, very few examples were reported of the driving force for β-CD-1-substituted naphthalene complex formation in the literature.

In the present study we have determined the association constants K_a, and thermodynamic parameters ΔG^0, ΔH^0, and ΔS^0 for inclusion complexation of β-CD with a series of 1-substituted naphthalenes. The substituent effect and enthalpy–entropy compensation on the inclusion complexation is discussed.



(X = H, OH, OCH_3, $OCOCH_3$, NH_2, $NHCH_3$, $NHCOCH_3$, Cl, CH_3, CH_2Br,
CH_2OH, CHO, COOH, $COOC_2H_5$, $CONH_2$, CN)

2. Experimental

2.1. INSTRUMENTATION

The fluorescence spectra of 1-substituted naphthalene derivatives in water were measured with a Hitachi FM 850 spectrofluorimeter. The cell compartments were connected to an external thermostat to control the temperature.

2.2. REAGENTS

1-Substituted naphthalenes, obtained commercially, were purified by distillation (for liquids) and recrystallization or sublimation (for solid samples), respectively. The purity of guest compounds was checked using melting point and chromatographic methods. β-CD (97%, Suzhou Weijing Plant) was recrystallized three times from distilled water and dried at 90 °C *in vacuo* for 24 h before use. Triply distilled water was employed.

2.3. PREPARATION OF SAMPLES

Aqueous solutions were prepared of 1-substituted naphthalenes (8×10^{-6} to 4×10^{-5} mol/dm^3) containing β-CD in the range from 6×10^{-4} to 4×10^{-3} mol/dm^3. The buffer solutions were made up with HCl—KCl (pH = 1.5), Na_2HPO_4–

NaH_2PO_4 (pH = 6.9), and Na_2CO_3–$NaHCO_3$ (pH = 9.3) for 1-naphthoic acid, 1-aminonaphthalene and 1-naphthol. The solutions were degassed by purging with argon, ultrasonicated for 10 min at ambient temperature, then allowed to stand for several hours at the same temperature as the working conditions before measurements. The fluorescence spectra were recorded at 25, 30, 35 and 45 ± 0.1 °C, respectively.

3. Results and Discussion

3.1. INCLUSION COMPLEX FORMATION

The intensities of fluorescence spectra of 1-substituted naphthalenes in water were observed as a function of the concentration of β-CD added. Figure 1 shows the fluorescence intensity enhancement of 1-naphthol with the concentration of β-CD. According to the Benesi–Hildebrand equation [9] (1), plotting $1/\Delta I$ against 1/[CD] gives a straight line

$$1/\Delta I = 1/a[N] + 1/aK_\mathrm{a}[\mathrm{N}][\mathrm{CD}] \tag{1}$$

where ΔI is the difference of fluorescence intensities in the presence and absence of β-CD, a is a constant, [N] and [CD] are the concentrations of 1-substituted naphthalene and β-CD, respectively, and K_a is the association constant.

The association constants (K_a) were obtained from the ratio of the intercept $1/a$[N] to the slope $1/aK_\mathrm{a}$[N] of the straight line for the inclusion of β-CD with 1-substituted naphthalenes (Figure 2).

It is well known that the association constant is temperature dependent [1]. By measuring the K_a values at different temperatures and plotting $R \ln K_\mathrm{a}$ against $1/T$ according to Equation (2), ΔH and ΔS were obtained from the slope and intercept of the straight line, respectively.

$$R \ln K_\mathrm{a} = -\Delta H/T + \Delta S. \tag{2}$$

The association constant K_a, thermodynamic parameters ΔG^0, ΔH^0, and $T\Delta S^0$ at 298 K for the inclusion complexation of β-CD with 1-substituted naphthalenes are presented in Table I.

3.2. SUBSTITUENT EFFECT

For the inclusion of β-CD with 1-substituted naphthalenes the change in association constants may be caused only by the variation of substituents under the same conditions. It is noted that the stabilities of the inclusion complexes are related to the properties of the substituents of the guest compounds. The K_a values are influenced by the molar refraction (R_m), hydrophobic constant (π_x) and Hammett constant (σ_x) of the substituents of the 1-substituted naphthalene derivatives. A multiple regression model was established for the inclusion of β-CD with the guest

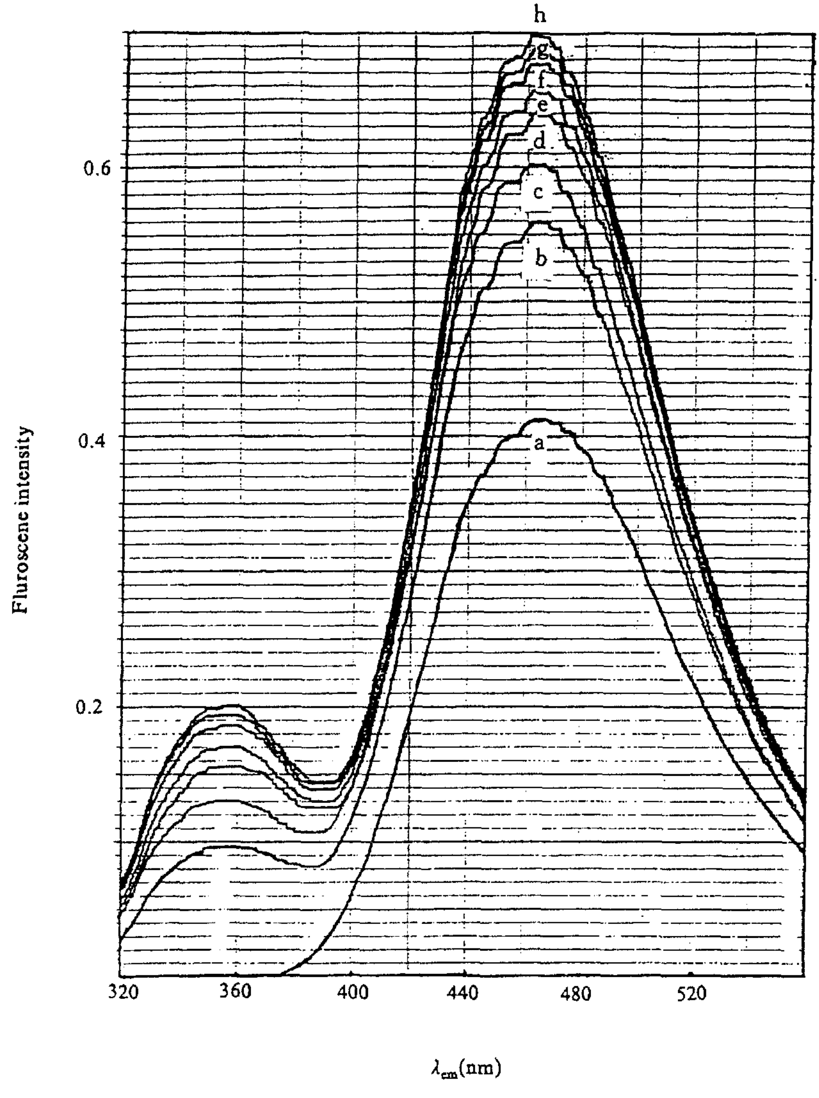


Figure 1. Fluorescence spectra of 1-naphthol in the presence of 0 (a), 6.0×10^{-4} (b), 1.0×10^{-3} (c), 1.5×10^{-3} (d), 2.0×10^{-3} (e), 2.8×10^{-3} (f), 3.7×10^{-3} (g), 4.0×10^{-3} (h) mol/dm^3 of β-CD in water.

compounds by using substituent constants taken from the compilation of Hansch and Leo [10] and the $\ln K_a$ values measured experimentally (3).

$$\ln K_a = 6.89(0.35) - 0.062R_m(0.04) - 0.46\sigma_x(0.35) + 0.60\pi_x(0.21). \quad (3)$$

The association constant K_a is negatively correlated with the molar refraction (R_m) [1,11] which reflects the volume of the substrate. It is clear that the association constant is affected by the size of the substituent of the substrate. The negative

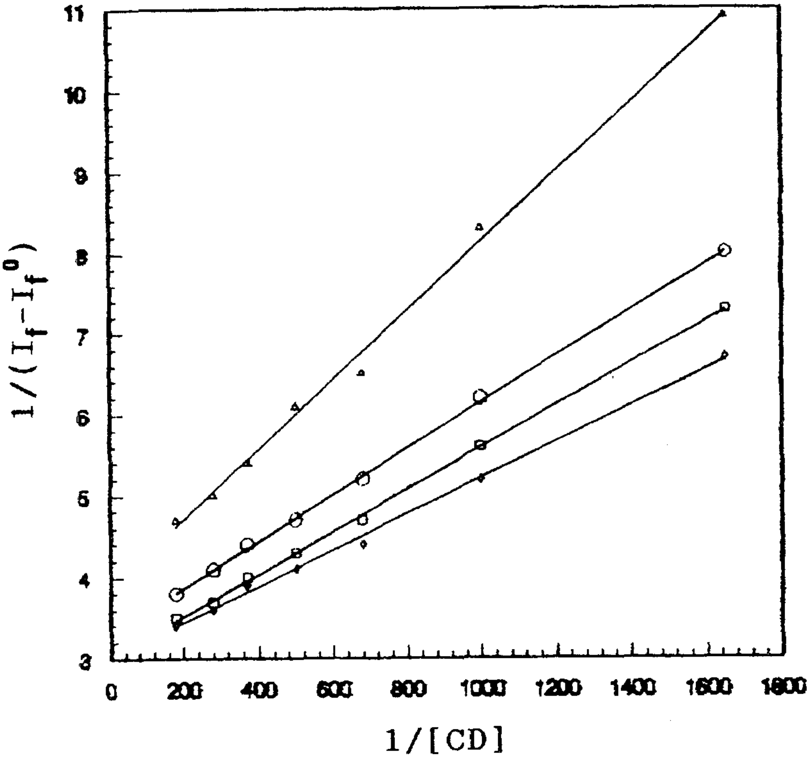


Figure 2. Plots of $1/\Delta I$ against 1/[CD] for the inclusion complexation of β-CD with 1-naphthol at 25 °C (◊), 30 °C (□), 35 °C (○) and 45 °C (△).

correlation of $\ln K_a$ with R_m reveals that the naphthalene moiety is included in the cavity of β-CD and the substituent located near the wider rim of the cavity [6]. When the naphthalene ring is embedded in an axial manner, the substituent at the α-position would interact slightly with the secondary hydroxyl group of β-CD.

Similarly, a negative correlation between $\ln K_a$ and the Hammett σ-constant of the substituent was observed for the inclusion of β-CD with 1-substituted naphthalene. This fact indicates that the stabilities of the inclusion complexes are influenced by the electronic effect. The narrower rim of the CD cavity is the positive end and the wider rim is the negative end of the CD dipole [11]. As mentioned above, the naphthalene ring is included in the cavity and the α-substituent located in the wider rim of the β-CD cavity. The substituents with negative σ-values are electron donating and make the naphthalene ring electron richer, which favors the host–guest permanent dipole–induced dipole interaction; hence greater K_a values are obtained. On the other hand, electron-withdrawing substituents with large positive σ-values give the opposite results.

$\ln K_a$ was observed to be proportional to the hydrophobic constant (π_x) [12,13] of the substituent in the guest compounds. The π_x is defined as the logarithm of the

Table I. Association constants K_a (dm^3/mol), thermodynamic parameters ΔG^0, ΔH^0 and $T\Delta S^0$ (kJ mol^{-1}) for the inclusion complexation of β-CD with 1-substituted naphthalenes at 298 K.

X	K_a	ΔG^0	ΔH^0	$T\Delta S^0$
H	$6.78\ (0.41) \times 10^2$	−16.2	−11.4	4.7
OH	$1.22\ (0.08) \times 10^3$ $1.08\ (0.12) \times 10^3$ [a] $1.07\ (0.04) \times 10^3$ [b] $5.84\ (0.03) \times 10^2$ [c]	−17.6	−11.3	6.3
OCH_3	$1.38\ (0.07) \times 10^3$	−17.9	−17.6	0.3
$OCOCH_3$	$1.56\ (0.14) \times 10^2$	−12.5	−14.7	−2.2
NH_2	$2.50\ (0.22) \times 10^2$ $1.01\ (0.18) \times 10^2$ [a] $7.29\ (0.83) \times 10^2$ [b]	−14.1	−20.3	−6.2
$NHCH_3$	$4.09\ (0.50) \times 10^2$	−14.9	−28.4	−13.5
$NHCOCH_3$	$1.32\ (0.12) \times 10^2$	−12.1	−11.5	0.6
Cl	$1.21\ (0.10) \times 10^2$	−17.6	−71.7	−54.1
CH_3	$6.96\ (0.52) \times 10^2$	−16.2	−8.4	7.8
CH_2Br	$6.91\ (0.43) \times 10^2$	−16.6	−68.4	−51.8
CH_2OH	$3.99\ (0.32) \times 10^2$	−14.7	−43.6	−28.9
CHO	$3.98\ (0.36) \times 10^2$	−14.8	−42.5	−27.7
COOH	$3.47\ (0.31) \times 10^2$ [a]	−14.5	−11.2	3.3
$COOC_2H_5$	$4.58\ (0.26) \times 10^2$	−15.2	−32.3	−17.0
$CONH_2$	$4.31\ (0.33) \times 10^2$	−15.0	−79.1	−64.0
CN	$2.49\ (0.18) \times 10^2$	−13.7	−29.3	−15.7

[a] pH = 1.5.
[b] pH = 6.9.
[c] pH = 9.3.

partition ratio between an aqueous phase and a model lipid phase such as octanol [14,15]. The π_x value is a reasonable measure of hydrophobicity and is highly correlated with the bioconcentration of solutes in living tissues. It shows that a substituent of high hydrophobicity tends to push the naphthalene moiety into the apolar cavity of CD. It has also been noted that the influence of the hydrophobicity of the substituent on the inclusion complexation is not strong since the group is located near the wider rim of the cavity and is only partially hidden by CD.

3.3. ENTHALPY–ENTROPY COMPENSATION

The thermodynamic parameters ΔG^0, ΔH^0, and $T\Delta S^0$ for the inclusion complexation of β-CD with 1-substituted naphthalenes are summarized in Table I, from which it can be seen that the inclusion of naphthalene and 1-substituted naph-

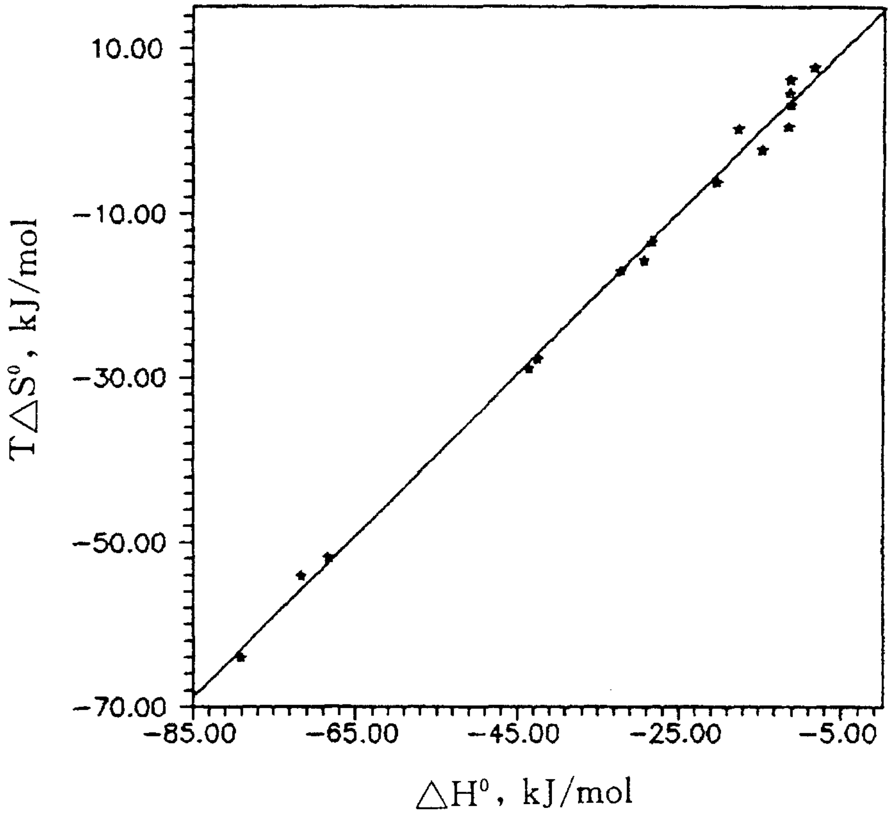


Figure 3. Enthalpy–entropy compensation plot for the inclusion complexation of β-CD with 1-substituted naphthalenes.

thalenes with β-CD is exclusively exothermic and largely driven by enthalpy, with varying positive or negative entropic contribution.

An empirical linear relationship between ΔH^0 and ΔS^0 [8,16–19] (Equation 4) was used for the analysis of the driving force. This means that the resulting change in $T\Delta S^0$ is proportional to the accompanying change in ΔH^0.

$$T\Delta(\Delta S^0) = \alpha\Delta(\Delta H^0). \tag{4}$$

Integrating Equation (4) gives Equation (5).

$$T\Delta S^0 = \alpha\Delta H^0 + T\Delta S_0^0. \tag{5}$$

Plotting $T\Delta S^0$ against ΔH^0 gives a straight line which fits Equation (6) (Figure 3).

$$\begin{gathered} T\Delta S^0 = 14.67 + 0.98\Delta H^0 \\ (n = 16, r = 0.997, \mathrm{sd} = 1.73) \end{gathered} \tag{6}$$

The changes in enthalpy (ΔH^0) and entropy (ΔS^0) upon inclusion complexation tend to compensate each other (Figure 3). The slope α is a quantitative measure of the entropic canceling of the enthalpic gain from the host–guest complexation. A slope of almost unity (0.98) and an intercept of 14.67 are obtained in the ΔH^0–$T\Delta S^0$ relationship.

Inserting Equation (4) in the differential Gibbs–Helmholtz equation (Equation 7) gives Equation (8).

$$\Delta(\Delta G^0) = \Delta(\Delta H^0) - T\Delta(\Delta S^0) \tag{7}$$

$$\Delta(\Delta G^0) = (1 - \alpha)\Delta(\Delta H^0). \tag{8}$$

According to Equation (8), only 2% of the enthalpic gain contributes to raising the driving force ($-\Delta G^0$), whereas 98% of the enthalpic gain is compensated by the entropic loss of the inclusion complexation of β-CD with 1-substituted naphthalenes.

It has been suggested that the slope (α) and intercept ($T\Delta S_0^0$) of the ΔH^0–$T\Delta S^0$ plot can be related to the degree of conformational change and the extent of desolvation induced upon complex formation, respectively [20,21]. The slope of near unity and the large intrinsic entropic gain (intercept) mean that the enthalpic gain from the inclusion complexation is almost canceled out by the entropic loss from the conformational changes caused by complex formation. In contrast to 1-naphthalenesulphonate and 1-naphthaleneacetate ions [8], the inclusion of 1-substituted naphthalenes used in this work is predominantly enthalpy driven.

In summary, the inclusion complexation of β-CD with 1-substituted naphthalenes is affected by the volume, hydrophobicity, and electronic properties of the substituents of the guests. The inclusion complex formation is mainly driven by enthalpy. Most of the enthalpy gain due to complex formation is canceled out by entropy loss caused by the conformational factor in the complexation process.

Acknowledgement

This work was supported by the National Natural Science Foundation of China. We are grateful to the referees, especially to one of them for the suggestion of regression analysis.

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