The Association of Triton X Surfactants with β-Cyclodextrin. An Isothermal Titration Calorimetry Study

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Abstract. The association with β-cyclodextrin of a series of Triton X surfactants with different ethylene oxide (EO) chain lengths was studied by isothermal titration calorimetry at 298.15 K. The results agree with a 1:1 association model. Association constants and changes in Gibbs free energies, enthalpies and entropies were derived for the association process. Association of these surfactants with β-cyclodextrin have favorable enthalpy changes and unfavorable entropy changes. The shorter the EO chain of the surfactant, the greater the association constant with β-cyclodextrin.

Key words: Association constant, β-cyclodextrin, Triton X surfactants, isothermal titration calorimetry.

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides with 6, 7, or 8 glucose units, called α-, β-, and γ-CD, respectively. One of their most important properties is the ability to form inclusion complexes with various lipophilic compounds [1–4]. The inclusion complexes of nonionic surfactants and cyclodextrins have been studied by a number of physical methods, including UV-visible spectroscopy, fluorescence spectroscopy, NMR, and surface tension [5–7]. Unfortunately, the association constants reported in the literature differ widely [5-7]. In this study, isothermal titration calorimetry [8] was used to determine the stoichiometry, association constants, and enthalpy changes for the reaction of a series of Triton X surfactants (Triton X-114, Triton X-100, Triton X-102 and Triton X-405) with β-cyclodextrin. The results provide information about the effects of the EO chain length of the surfactants on the thermodynamic quantities measured.

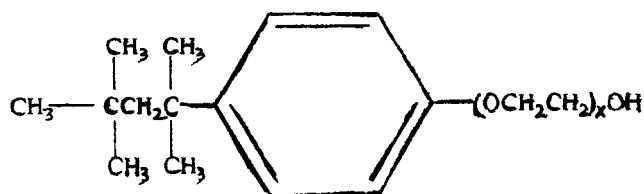[*] Author for correspondence.

Figure 1. The structure of Triton X surfactants, $x = 7.5$ for Triton X-114, $x = 9.5$ for Triton X-100, $x = 12.5$ for Triton X-102, and $x = 40$ for Triton X-405.

2. Experimental

2.1. REAGENTS

β-CD was obtained from Aldrich and dried at 86°C in vacuo for 24 h before use. Triton X-114, Triton X-100, Triton X-102 and Triton X-405 were purchased from Fluka and used without further purification. The structure of these surfactants is shown in Figure 1. Twice-distilled water was used in the experiments.

2.2. ISOTHERMAL TITRATION CALORIMETER (ITC) MEASUREMENTS

The experiments were performed in a Model 4200 isothermal titration calorimeter (Calorimetry Sciences Corporation, U.S.A). All solutions were degassed by water aspiration prior to loading. The sample cell (750 μL) was filled with surfactant solution at approximately 0.1 mmol/L and the 250 μL buret syringe with β-CD solution of approximately 1.5 mmol/L. The titration consisted of 25 injections of 10 μL each at 300 second intervals. The ITC uses proprietary software to set up experiments, control the calorimeter, and collect the raw heat rate data. ITC Dataworks is provided to integrate the heat pulses and make baseline and blank corrections. The thermodynamic parameters (enthalpy change ΔH^0, association constant K_a, and stoichiometry n) were calculated with the Bindworks program [9, 10].

The binding of Ba^{2+} to 18-crown-6 was used to verify the performance of the calorimeter, the values for the binding constant and the binding enthalpy have been very precisely determined [11]. We did a single determination under conditions very similar to those of Wadsö *et al.*, and obtained n, K_a and ΔH^0 values of 1, 5754 $\pm$ 200, and -31.25 ± 0.40 kJ/mol. The published values are $n = 1$, $K_a = 5900 \pm 200$, and $\Delta = -31.42 \pm 0.20$ kJ/mol [11].

The enthalpies of dilution of the titrant and surfactants were determined in separate experiments by titrating water into surfactant solution and β-CD solution into water. No significant effect was found for β-CD. The calorimeter was frequently calibrated electrically during the course of the study [8]. The calorimetric measurements were carried out at 298.15 K.

2.3. MATHEMATICAL TREATMENT

Assuming that β-CD forms a 1:1 inclusion complex with surfactant,

$$\beta - CD + S = \beta - CD \cdot S, \tag{1}$$

the association constant of the complex (K_a) is defined by

$$K_a = \frac{\Theta}{[1 - \Theta][S]} \quad \text{and} \quad \Theta = \frac{\beta - CD \cdot S]}{[\beta - CD]_0} \tag{2}$$

where $[S]$, $[\beta - CD]$, and $[\beta - CD \cdot S]$ are the equilibrium concentrations of surfactant, β-CD and the complex, respectively. $[\beta - CD]_0$ and $[S]_0$ are the total concentrations of β-CD and surfactant, respectively. Therefore the heat of association is

$$Q = \Theta[CD]_0 \Delta H^0 V_0 \tag{3}$$

where ΔH^0 is the enthalpy change, and V_0 is the total volume of the solution. Combining Equation (2) and (3), we arrive at

$$\begin{aligned}
Q = {} & \frac{[\beta - CD]_0 \Delta H^0 V_0}{2} \left[1 + \frac{[S]_0}{[\beta - CD]_0} + \frac{1}{K_a[\beta - CD]_0} \right. \\
& \left. \times \left(\left(1 + \frac{1}{K_a[\beta - CD]_0} \right)^2 - \frac{4[S]_0}{[\beta - CD]_0} \right)^{1/2} \right]
\end{aligned} \tag{4}$$

An algorithm based on the Marquardt method [12, 13], is used to get K_a and ΔH^0 [12] from Equation (4).

The entropy change, ΔS^0, and free energy change, ΔG^0, of association are calculated by the equation:

$$\Delta G^0 = -RT Ln K_a = \Delta H^0 - T \Delta S^0 \tag{5}$$

3. Results

Data from a representative titration experiment are given in Figure 2. The area under each peak in Figure 2 gives the heat, Q, for that injection. Table I lists the thermodynamic data obtained. For all four surfactants investigated, 1:1 complexes were formed, consistent with the literature [5–7]. The stoichiometric ratio for the complexes can also be obtained from the endpoints of plots as shown in Figure 3.

Table I shows that $-\Delta G^0$, $-\Delta H^0$ and $-\Delta S^0$ decrease with an increasing EO chain length of the surfactants. ΔH^0 is negative, indicating that it is energetically favorable for the weakly polar surfactants to be included in the β-CD cavity. The
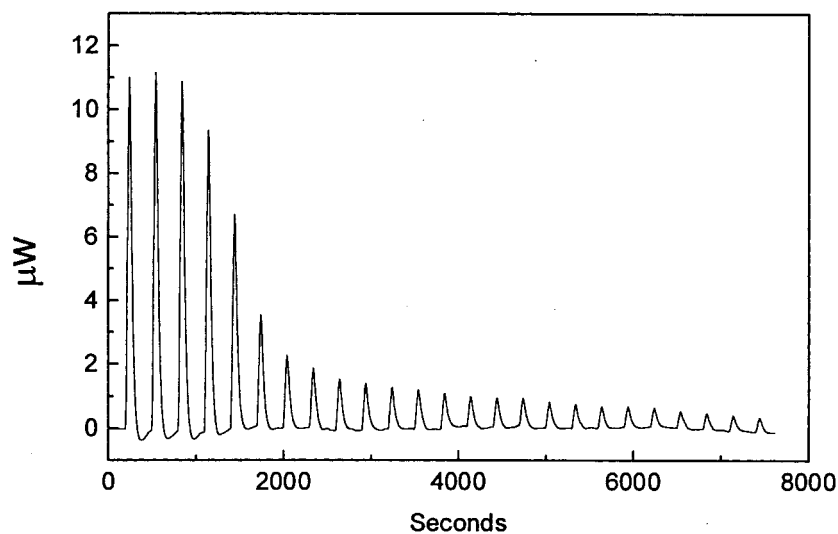
Figure 2. Plot of heat rate versus time. The raw data obtained for 25 automatic injections, each of 10 μL of 1.5 mM β-CD solution into the sample cell containing 750 μL of 0.1 mM Triton X-100 solution.

Table I. Thermodynamic parameters for the association of Triton X surfactants with β-CD at 298.15 K[a]

Surfactants[b]	X^c	$K_a{}^d$	n	$\dfrac{-\Delta H^0}{\text{kJ·mol}^{-1}}$	$\dfrac{-\Delta G^0}{\text{kJ·mol}^{-1}}$	$\dfrac{-\Delta S^0}{\text{J·}K^{-1}\text{·mol}^{-1}}$
Triton X-114	7.5	11051 ± 310	1	38.69 ± 0.5	23.08 ± 0.07	52.39 ± 1.9
Triton X-100	9.5	9100 ± 260	1	35.81 ± 0.3	22.60 ± 0.08	44.27 ± 1.2
Triton X-102	12.5	7590 ± 200	1	30.10 ± 0.6	22.15 ± 0.06	26.67 ± 2.2
Triton X-405	40	4856 ± 150	1	26.20 ± 0.7	21.04 ± 0.12	17.31 ± 2.8

[a]Experimental values for the association constants, heat of binding and stoichiometric ratios from nonlinear least-squares minimization. The values are the averages of three determinations. Error limits are 0.077%.
[b]The critical micelle of concentrations of Triton X-114, Triton X-100, Triton X-102, and Triton X-405 are 0.26 mmol/L, 0.31 mmol/L, 0.40 mmol/L, and 1.10 mmol/L, respectively.
[c]The average numbers of EO units of Triton X surfactants.
[d]The standard state is 1 mol/L.

largest changes in enthalpy occur with Triton X-114 which has the shortest EO chain length. The entropy changes were negative. The association constant for β-CD and Triton X-102, $K_a = 7600$ obtained from this experiment is consistent with that reported for β-CD and Igepal CA720 of 7700 determined from fluorescence measurements [6]. The structure of Igepal CA720 is similar to Triton X-102. But the value is large compared to those reported for Triton X-102 and β-CD determined from UV-Vis, $K_a = 1500$ and induced circular dichroism, $K_a = 500$, measurements [6].
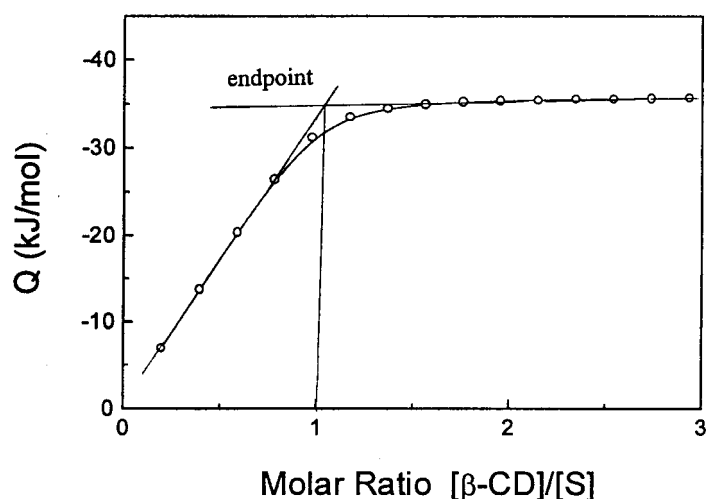
Figure 3. The heat of association versus molar ratio [β-CD]/[Triton X-100]. The curve is the best-fit to the 1:1 association model by the software supplied with the calorimeter.

4. Discussion

On the basis of molecular size, the phenyl ring of Triton X-100 (3.0 Å wide and 5.0 Å long) [6] is small enough to fit inside the β-CD cavity (inner diameter of 7.8 Å wide and a length of 7.8 Å) [14]. NMR results show that part of the hydrocarbon chain, phenyl group, and probably part of the EO chain adjacent to the phenyl group come into close proximity with the H-3 and H-5 protons of the β-CD [6].

The most likely mode of complexation of ligands to cyclodextrins consists of insertion of the hydrophobic portion of the ligand into the cyclodextrin cavity with the polar group of the ligand remaining solvent exposed at the wide top end of the cavity [1–4]. Three types of interactions are usually considered to be responsible for the association of guest molecules with β-CD: van der Waals interactions, hydrogen bonds, and hydrophobic interactions [15, 16]. The resultant of all these interactions is measured by the thermodynamic quantities in this study. The following qualitative picture is useful for understanding these complexation reactions.

As can be seen from Table I, formation of the inclusion complexes of surfactants with β-CD is exothermic enthalpy driven, with negative entropic contributions. The interaction is characterized by a large and negative standard enthalpy change, even though one would expect, by consideration of the chemical nature of the surfactant and the β-CD cavity, that the association would be hydrophobically driven. From studies of the solvent dependence of the thermodynamics of the β-CD/surfactant interaction, we conclude that there is a significant contribution from the classical hydrophobic effect (i.e. a positive ΔS^0 contribution) but that this contribution is masked by predominant binding forces characterized by negative enthalpy and negative entropy changes. We speculate that the latter forces may be due to van der
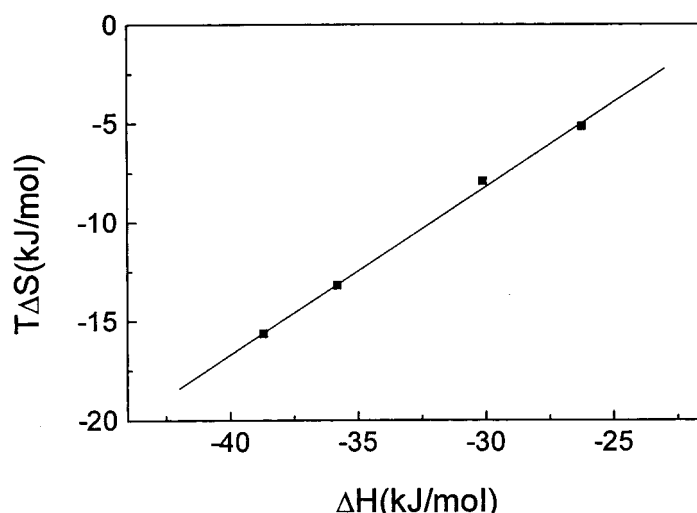
Figure 4. Enthalpy-entropy compensation plot for complexation of Triton X surfactants with β-CD (see Table I for the data).

Waals interaction and hydrogen bonding between the surfactant and β-CD pocket, which is particularly strong in this case due to the deep penetration and snug fit between the reactants. In addition, using the simple qualitative argument that a surfactant that is strongly bound within the β-CD cavity has lost some freedom of motion, one expects it to have a lower entropy than if it were weakly bound within the cavity. However, due to the stronger hydrogen bonding between the nonionic surfactant and solvent (water), the interaction of surfactant and water becomes stronger with an increasing EO chain length of the surfactant [17] (this conclusion also can be obtained from the critical concentrations of the surfactants, see Table I). The surfactant that interacts weakly with water forms the stronger inclusion complex.

Plotting the entropy changes ($T\Delta S^0$) against the enthalpy changes (ΔH^0) gives a straight line with a coefficient of 0.99, as shown in Figure 4. As has been proposed previously [16, 19, 20], the empirical linear relationship between ΔH^0 and ΔS^0, whatever the cause leads to Equation (6), where α and $T\Delta S_0$ refer to the slope and intercept of Figure 5. Equation (6) 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 (6) in the differential form of the Gibbs–Helmholtz Equation (7), we obtain Equation (8).

$$T\Delta S^0 = \alpha(\Delta H) + T\Delta S_0 \tag{6}$$

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

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

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^0 contributes toward raising the complex stability $(-\Delta G^0)$. The positive intercept $(T \Delta S_0)$ indicates the entropic contribution arises primarily from the desolvation process during host–guest complexation. The relative larger values of α (0.85) and the intermediate intercept values of $T \Delta S_0$ (17.3) indicate extensive dehydration occurring upon inclusion.

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