

Thermodynamic and Kinetic Characterization of Host–Guest Association between Bolaform Surfactants and α - and β -Cyclodextrins

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The thermodynamics and kinetics of formation of host–guest complexes between a series of bolaform surfactants of type $C_nMe_6^{2+}2Br^-$ ($n = 8, 10$, and 12) and α -cyclodextrin and β -cyclodextrin were studied with the aid of isothermal titration calorimetry (ITC) at 298.15 and 308.20 K. The association constant, the enthalpy, and the entropy of formation were determined. The obtained thermodynamic parameters are compared with parameters for the micelle formation of a related cationic surfactant. The difference in magnitude and sign between the parameters of the α -CD and β -CD complexes is discussed based on the curvature of the cavity of the CD. We suggest that the water molecules inside the α -CD cavity are not able to maintain their hydrogen bond network. Upon complex formation these water molecules are expelled and reform their hydrogen bond network. The situation is different in the larger β -CD cavity where water has the possibility of a more extensive hydrogen bonding. The kinetics for α -CD is slow, associated with high activation energies for both association and dissociation of the complex. The rates increased with a decrease in the number of methylene groups in the hydrocarbon chain. The slow kinetics is argued to originate from the fact that the charged headgroup needs to be pushed through a relative nonpolar cavity. A comparison is made with the Born energy.

Introduction

Bolaform amphiphilic molecules contain two hydrophilic head groups joined by a hydrophobic hydrocarbon chain.¹ Compared to conventional surfactants (with just one hydrophilic head-group), bolaform surfactants have a lower propensity to form micelles; the critical micelle concentration (cmc) of these surfactants is generally high and the size of the micelles is relatively small.² These properties, among others, indicate novel and useful applications for these surfactants. Thus, bolaform amphiphile molecules can be used as coatings on smooth solid materials, where one end is attached to the surface of electrodes, polyelectrolyte, or nanoparticles, whereas the other headgroup is used for solubilization in water and for interactions with solutes.³ The self-assembly of these molecules at the solid–liquid interfaces has been suggested as a novel way to obtain mesoporous structures.⁴ Furthermore, bolaform surfactants have also been studied for possible use in the extraction of metal ions⁵ and as photosensitive molecules^{6,7} and to induce ion-pair formation of electrolytes in aqueous solutions.⁸

Cyclodextrins (CD) are cyclic oligosaccharides formed through $\alpha(1-4)$ ether linkages of glucopyranose units.⁹ The most commonly used CDs are the α -, β -, and γ -cyclodextrins, having six, seven, or eight glucoside units, respectively. CD has the shape of a truncated cone, where the cavity is lined by the glucosidic oxygen bridges. On each end of the cone there is a belt of hydrogen bonds. This molecular arrangement gives

a hydrophobic character to the CD cavities relative to the external surface which is hydrophilic.

Cyclodextrin host–guest complexes may impart beneficial modifications of guest molecules such as enhancement of solubility, stabilization of labile guests, physical isolation of incompatible compounds and control of volatility and sublimation. Furthermore, the chemical reactivity of the guest is often changed by the incorporation into the CD cavity.¹⁰ Because of the relative nonpolar character of the cavity in comparison to the polar exterior, cyclodextrins can form inclusion complexes with a wide variety of guest molecules, predominantly due to hydrophobic interactions.¹¹ However, we note that it is reported that some inorganic salts, such as, $NaClO_4$, $KSCN$, $Pb(OH)_2$, NH_4VO_3 , etc.,¹² form complexes, although with low equilibrium constants. On the other hand, the inorganic salt tetramethylammonium bromide $(NCH_3)_4Br$ does not interact with CD as investigated by Cabaleiro-Lago et al. (self-diffusion NMR)¹³ and Lyon et al. (chemical shift NMR).¹⁴

Surfactants are ideal guests that allow for a systematic study of CD complexation, since both hydrophobic and hydrophilic moieties can be systematically varied. Recently, many studies covering different types of surfactants and cyclodextrins have been reported.^{13,15–17} Bolaform surfactants are of special interest as guest molecules due to the balance of several intermolecular forces: the hydrophobic effect which tends to protect the alkyl chain from the aqueous environment, the requirement of dehydration of the head groups during complex formation, as well as effects due to steric hindrances.¹⁸ Bolaform amphiphiles also show inclusion dynamics significantly different from those of homologous univalent surfactants.¹⁴ This is due to the fact that a charged headgroup has to pass through the hydrophobic CD cavity. The dynamic properties will depend on the size of cyclodextrin cavity, the surfactant end-groups and the size of

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alkyl chain.¹⁹ In a previous paper,²⁰ we have reported that dodecane-1,12-bis(trimethylammonium bromide) in aqueous solution binds with β -cyclodextrin in a 1:1 complex, with an association constant of around 2500–3000 M⁻¹, as measured by electrical conductivity and ¹H NMR self-diffusion techniques. The stability of the 1:1 complex is lower than for the analogous monohead surfactant, on account of the requirement to have two charges close to the CD-molecule in the bolaform/CD complex. Finally, we note that bolaform surfactant/CD complexes belong to the general class of so-called pseudorotaxanes, which are presently of considerable interest to the scientific community.²¹

In this work, we report on the complex formation between short chain bolaform amphiphiles: octane-1,8-bis(trimethylammonium bromide), decane-1,10-bis(trimethylammonium bromide), and dodecane-1,12-bis(trimethylammonium bromide) and α - and β -CD. We have used isothermal titration calorimetry (ITC) to determine thermodynamic parameters (stoichiometry, association constant, enthalpy) of those systems. In addition, time-resolved ITC data were used to obtain kinetic parameters for the association between bolaform surfactants and α -CD. We used NMR data to support and corroborate the findings from the ITC experiments.

Materials and Methods

Materials. β -cyclodextrin (β -CD) was purchased from Aldrich ($\geq 99\%$ purity, according to the manufacturer). α -cyclodextrin (α -CD) and γ -cyclodextrin (γ -CD) were from Fluka both with a purity of 98%. The concentrations of cyclodextrins were corrected for the amount of hydration water according to the manufacturer. The bolaform surfactants octane-1,8-bis(trimethylammonium bromide), C₈Me₆, decane-1,10-bis(trimethylammonium bromide), C₁₀Me₆, and dodecane-1,12-bis(trimethylammonium bromide), C₁₂Me₆ were a kind gift from Prof. Piero Baglioni (Florence University) and they were used without further purification. All samples for ¹H NMR measurements were prepared in heavy water (isotope substitution $> 99.8\%$) from Dr Glaser AG, Basel while all samples for ITC were prepared with Millipore-Q water. High quality propan-1-ol for ITC calibration purposes was purchased from BDH.

The concentration of samples for ITC experiments was expressed in mol/kg. The concentrations of the bolaform surfactants are lower than the cmc in all samples; i.e., micelles are not present in the investigated solutions.

Isothermal Titration Calorimetry. The titration calorimetric measurements were performed using the 2277 TAM Thermal Activity Monitor system (Thermometric AB, Järfälla, Sweden).²² The experiments consisted of series of consecutive additions of concentrated bolaform amphiphile solution to the calorimeter vessel, containing initially 0.900 g of CD solution or pure water, at 298.15 and 308.20 K. The surfactant solution was added in aliquots of 4.16 to 9.98 μ L from a gastight Hamilton syringe through a thin stainless steel capillary tube. A microprocessor-controlled motor-driven syringe was used for injections. The time interval between injections was chosen according to the systems and varied from 900 s for β -CD and γ -CD, to 5100 s for α -CD-containing systems, where a slow reaction was observed. For each bolaform surfactant/CD system, experiments were repeated at least twice with different initial conditions (e.g., injection volume, CD or bolaform concentration). The recorded calorimetric signals were deconvoluted using the Tian equation with a time constant of 180 s to correct for the time delay of the calorimeter.²² Figure 1 illustrates a calorimetric titration curve resulting from the addition of C₁₂Me₆ into a β -CD

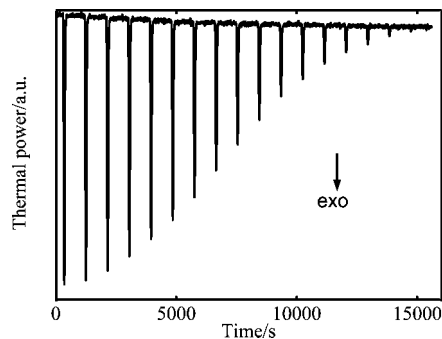


Figure 1. Thermal power as a function of time for sequential 4.16 μ L injections of 0.1116 mol/kg dodecane-1,12-bis(trimethylammonium bromide) into 4.746 mmol/kg β -CD aqueous solution at 308.20 K.

solution. Control experiments were performed to determine the heat of dilution by injecting the surfactant solutions into water, everything else being kept constant. The dilution heats determined in the control experiments were subtracted from the experimental heat measured in the titration experiments.

Dilution of 10 wt% propan-1-ol solution in water was used to calibrate the titration microcalorimetric setup as described in ref.²³

¹H NMR Studies. ¹H NMR spectra were recorded at 298.15 \pm 0.1 K on a Bruker 500 MHz spectrometer. The NMR spectra were acquired without solvent presaturation. Acquisition parameters consisted of 65k points covering a sweep width of 6 kHz, a pulse width of 6.35 μ s and a total repetition time of approximately 15 s. A stock solution containing 1 mmol/kg of surfactant and 10 mmol/kg of α -CD in heavy water was prepared and stirred for approximately 24 h at room temperature. This solution was diluted with a solution containing 1 mmol/kg of surfactant in heavy water to the desired α -CD concentration and transferred into a 5 mm NMR tube. The samples were prepared at least 36 h prior to measurements and kept in a water bath at the desired temperature before measurements.

Model Used To Evaluate ITC Results. The heat produced in an experiment in which n_{CD-S} moles of complex are formed is given by

$$Q = n_{CD-S} \Delta H_{assn} \quad (1)$$

where ΔH_{assn} is the molar enthalpy of association and n_{CD-S} is the amount of complex. In an ITC experiment, the heat generated by the i -th injection is:

$$Q_i = (n_{CD-S,i} - n_{CD-S,i-1}) \Delta H_{assn} = (V_i[CD-S]_i - V_{i-1}[CD-S]_{i-1}) \Delta H_{assn} \quad (2)$$

where $[CD-S]_i$ is the concentration of the complex and V_i is the total volume of solution after injection i , respectively.

As previously reported,²⁰ β -CD forms a 1:1 inclusion compound with C₁₂Me₆. Therefore, it can be assumed that if the C₈ and C₁₀ analogues form complexes, their stoichiometry will be 1:1. Consequently, on the assumption that a 1:1 complex $CD-S$ is formed, the concentration of the complex can be calculated from²⁰

$$[CD-S]^2 - \left([CD]_0 + [S]_0 + \frac{1}{K}\right)[CD-S] + [CD]_0[S]_0 = 0 \quad (3)$$

where K is the equilibrium constant, and $[CD]_0$ and $[S]_0$ represent the total (initial) concentration of cyclodextrin and surfactant, respectively.

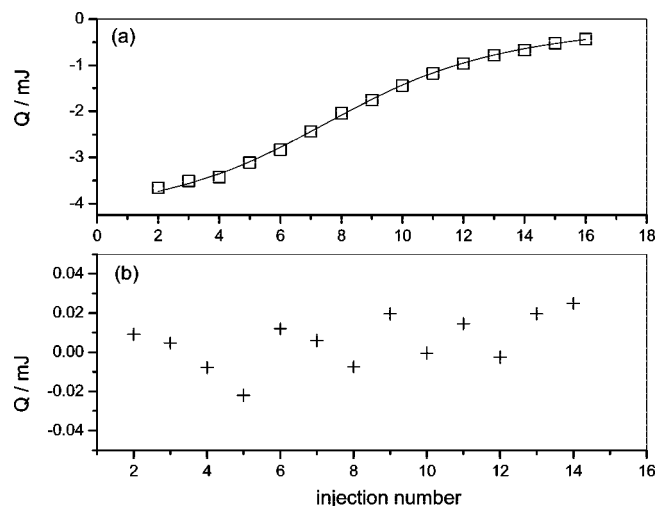


Figure 2. Heat ($Q = Q_{\text{obs}} - Q_{\text{dil}}$) per injection versus injection number at 308.20 K. (\square , $+$) are experimental points and (—) fitted line predicted by eqs 2 and 3. (a) Injections of 4.16 μL of C_{12}Me_6 at 0.1116 mol/kg in 0.900 g of a solution of β -CD at 4.746 mmol/kg. (b) Injections of 4.99 μL of C_8Me_6 at 0.204 mol/kg in 0.900 g of a solution of β -CD at 14.54 mmol/kg.

Equilibrium constants and enthalpy values were calculated from a least-squares fitting procedure (eqs 2 and 3) using in-house developed software. An example of the fit is given in Figure 2a.

We consider the measured ΔH to represent ΔH° in the evaluation below. This approximation neglects any dependence in the measured ΔH values on the CD concentration.

Experimental Results and Discussion

Thermodynamic Properties of C_nMe_6 ($n = 8, 10, 12$)/ α - and β -CD Complexes at 308.20 K from ITC Measurements. At 298.15 K, the enthalpy of complex formation of β -CD was found to be small which makes the ITC measurements uncertain. For experiments with α -CD the kinetics is slow (see further below) which makes the experiments quite time-consuming and lowers the precision on account of problems in assessing whether the baseline is reached after each surfactant addition. Some preliminary experiments indicated that these problems could be handled if the experiments were carried out at 308.20 K. Consequently, the data shown and discussed in this section all refer to 308.20 K. Some additional data at 298.15 K will be presented below.

Figure 2a shows a typical calorimetric titration experiment ($\text{C}_{12}\text{Me}_6/\beta$ -CD) where the heat per injection as a function of the injection number shows a sigmoidal trend.²⁴ The heat of interaction, Q , was obtained from the difference between the experimental heat, Q_{obs} , and the heat of dilution, Q_{dil} , for each surfactant solution addition. Included in the graph is also the result of a fit of Eqs. 2 and 3 to the experimental data.

The dilution enthalpy, $\Delta H_{\text{dil}}^\circ$, of 0.1116 mol/kg C_{12}Me_6 to infinite dilution was 0.99 (± 0.10) kJ/mol. The measured Q_{dil} varied only slightly with concentration. The value of $\Delta H_{\text{dil}}^\circ$ for 0.1079 mol/kg C_{10}Me_6 was 1.84 (± 0.05) kJ/mol and for 0.204 mol/kg C_8Me_6 it was 2.36 (± 0.01) kJ/mol. For these more concentrated solutions Q_{dil} varied somewhat with concentration.

From ITC experiments, it was possible to observe complex formation between C_nMe_6 ($n = 8, 10, 12$) and α -CD and ($n = 10, 12$) and β -CD. No association was observed for C_8Me_6 with β -CD, as the addition of C_8Me_6 to β -CD solution does not produce any measurable heat (see Figure 2b).

TABLE 1: Values of Thermodynamic Parameters for the Association of C_nMe_6 with α - and β -CD at 308.20 K^c

CD	C_nMe_6	$K/(\text{kg mol}^{-1})$	$\Delta H_{\text{assn}}^\circ/(\text{kJ mol}^{-1})$	$\Delta G_{\text{assn}}^\circ/(\text{kJ mol}^{-1})$	$\Delta S_{\text{assn}}^\circ/(\text{J K}^{-1} \text{mol}^{-1})$
α -	$n = 8$	35 (± 1)	-16.8 (± 0.1)	-9.1 (± 0.1)	-25.0 (± 0.4)
	$n = 10$	764 (± 100)	-25 (± 1)	-17.0 (± 0.3)	-25 (± 3)
	$n = 12$	3817 (± 340)	-31 (± 2)	-21.2 (± 0.2)	-31 (± 2)
β -	$n = 8$				
	$n = 10$	137 (± 10)	-4.7 (± 0.1)	-12.6 (± 0.7)	25.6 (± 0.2)
	$n = 12$	1953 (± 100)	-9.7 (± 0.1)	-19.4 (± 0.1)	31.5 (± 0.5)

^a $\Delta G_{\text{assn}}^\circ = -RT \ln(K)$, R is the gas constant. ^b From $\Delta G_{\text{assn}}^\circ = \Delta H_{\text{assn}}^\circ - T\Delta S_{\text{assn}}^\circ$. ^c Each set of parameters are obtained from at least two (often more) data sets with different initial conditions. Errors quoted for K and $\Delta H_{\text{assn}}^\circ$ are obtained from the fittings. Errors for $\Delta G_{\text{assn}}^\circ$ and $\Delta S_{\text{assn}}^\circ$ are propagated errors.

TABLE 2: Effect of Time on the Composition of the System According to the Reaction Scheme in Equation 4

	$[S]/(\text{mol/kg})$	$[\alpha\text{-CD}]/(\text{mol/kg})$	$[\text{CD-S}]/(\text{mol/kg})$	heat/J
$t = 0$	a	b	0	0
$t = t$	$a - x$	$b - x$	x	Q_t
$t = \infty$	$a - x_{\text{eq}}$	$b - x_{\text{eq}}$	x_{eq}	Q_{eq}

We also investigated whether bolaform surfactants interact with γ -CD. The addition of C_{12}Me_6 to γ -CD gave a small enthalpy of 0.59 (± 0.02) kJ/mol, indicating that no complex was formed. Probably, the larger cavity of the γ -CD (7.9 Å internal diameter) does not favor hydrophobic interactions with the alkyl chain of C_{12}Me_6 , which presumably is the main driving-force for the inclusion process (see further below). The data obtained from the analysis of the ITC experiments are summarized in Table 1.

The main results of this study are the thermodynamic data presented in Table 1. The association is stronger between C_nMe_6 and α -CD than that found for the same bolaform surfactant and β -CD. The complex formation is exothermic, more so for α -CD than for β -CD and the process has a negative entropy change for the former and a positive for the latter. These trends appear to be general and are shown by many different guest molecules (see ref 25 and references therein). Thus, the strength of interaction depends on the width of the CD cavity. The cavity diameter of α -CD is reported to be 4.7–5.3 Å and of β -CD 6.0–6.5 Å.⁹ The volume of the α -CD cavity is 174 Å³ and the volume of the β -CD cavity is 262 Å³.⁹ Assuming that the volume of water is 30 Å³ the number of water molecules that α -CD and β -CD can accommodate is 6 and 9, respectively.

As always, it is not straightforward to interpret the thermodynamic parameters in terms of molecular quantities, but in the following we will suggest some possible reasons for the observations. As a starting point, we note that the enthalpy of formation for micelles of the surfactant dodecyltrimethylammonium bromide at 298 K is -2.1 kJ/mol.^{26–28} At 308.20 K, a value can be estimated to -6.5 kJ/mol.²⁷ These numbers implies a negative value of ΔC_p for the micellization, and for dodecyltrimethylammonium bromide, ΔC_p is -0.47 kJ/(K mol).²⁷ These features are typical for a process dominated by the hydrophobic effect, i.e. the disaffinity of oil for water, at room temperature.²⁹ Although our data at 298.15 K are uncertain, they indicate for the case of α -CD and C_{12}Me_6 a similar value of ΔC_p for the complexation process.

The formation of the inclusion complex involves the insertion of the (dehydrated) guest into the nonpolar cavity of the CD and the release of water from the CD cavity. Since the dehydration of the guest surfactant is similar in the micellization and inclusion processes, the difference must lie in the properties

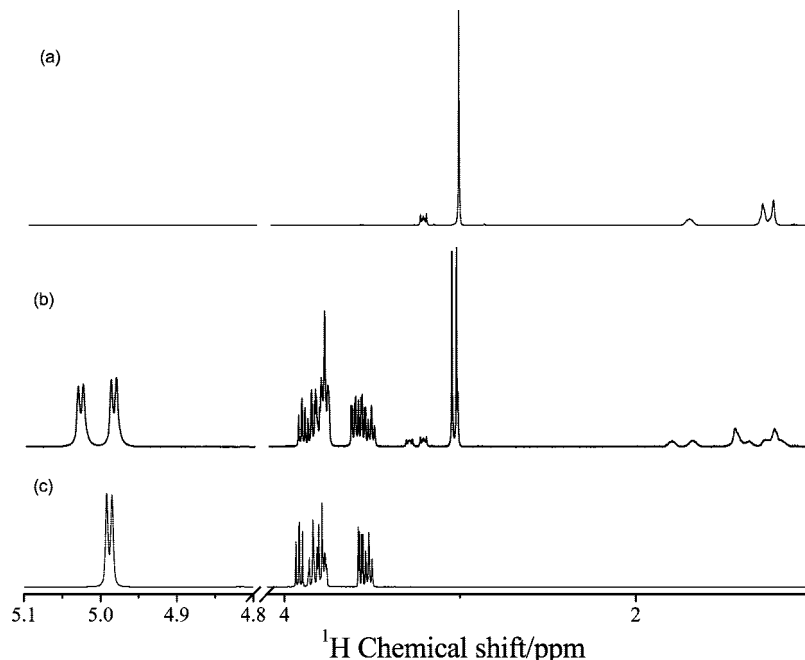


Figure 3. Proton spectra at 298 K: (A) bolaform surfactant $C_{12}Me_6$; (B) bolaform surfactant $C_{12}Me_6$ and α -CD with $[\alpha\text{-CD}]/[S] = 1.7$, (C) α -CD.

of the included water and interactions between surfactant and water with the interior of the cavity. For α -CD, the contribution to ΔH_{assn}^0 is approximately -2.5 kJ/mol per CH_2 (one kT per CH_2 group) at 308 K and, if one water molecule is displaced per CH_2 , approximately -2.5 kJ/mol (one kT) per expelled water molecule (probably higher since some methylene groups will reside outside the cavity). The general picture of hydrophobic hydration is that the introduction of a hydrocarbon into water gives rise to a structural rearrangement with increased order of the water close to the solute. The entropy increases when the water is released upon removal of the solute, while the enthalpy change is small (at room temperature). The negative entropy change for α -CD complex formation indicates that the situation for water molecules inside the cavity is different. We propose that they are not able to develop a full hydrogen bonded network inside the cavity leading to an increased disorder, probably due to the high curvature of the inside of the cavity. When the water molecules are released, the hydrogen bonds reform, which leads to an increased order and release of heat.

It is interesting to note that Briggner and Wadsö³⁰ observed a significantly lower heat capacity C_p of water in α -CD hydrates than for water in the β -CD and γ -CD hydrates. Accurate heat capacity measurements were performed on α -CD samples containing 0.58 and 6.12 mol H_2O , β -CD samples containing 0.42 and 10.66 mol H_2O and γ -CD samples containing 0.43 and 7.44 mol H_2O , respectively. C_p values for the bound water that were estimated from the difference in heat-capacity values for the dried and undried samples were 327 ± 7 J/(K mol), 732 ± 5 J/(K mol), and 493 ± 10 J/(K mol) for the α -, β - and γ -CD hydrates. Thus, the C_p per H_2O is 59 ± 1 J/(K mol) in α -CD hydrate while it is 71 ± 1 and 70 ± 1 J/(K mol) for the β - and γ -CD hydrates, respectively. The two latter values are close to C_p for liquid water (75 J/(K mol)). The location of the water molecules in α -CD with 6.12 water molecules is not known but some will reside in the cavity while others will stay on the outside. The close to normal C_p values for the hydration water in the β - and γ -CDs indicate that water molecules on the outside of α -CD will have C_p values close to the C_p for water. This follows since C_p for water in the hydrates cannot exceed C_p for

liquid water. The low average C_p value shows that the heat capacity for water inside the cavity of α -CD has a significantly lower C_p which agrees with the suggestion that these water molecules are less hydrogen-bonded.

Another effect that may contribute is the van der Waals interaction between the guest and the inside of the cavity, which may differ from that between hydrocarbon chains in a micelle.

As noted earlier ΔH_{assn}^0 is less exothermic for the inclusion compounds formed with β -CD, everything else being equal. In the scenario discussed above, this would be caused by the smaller curvature inside the β -CD cavity, which the water molecules can better adapt to. All water molecules are expected to be expelled upon complexation of both α -CD and β -CD (the volume of a CH_2 group is 27 \AA^3 and 8 CH_2 groups occupy a volume of 216 \AA^3).

Finally, we note that one possible contribution to the entropy change is the conformational entropy of the hydrocarbon chain in the cavity. The two charges at the ends must reside outside the cavity and this leads to a stretching of the hydrocarbon chain when it enters the cavity, which leads to a lowering of the conformational entropy. This effect is expected to be larger for the narrower cavity of α -CD compared to β -CD.

Thermodynamic Properties from 1H NMR for C_nMe_6 ($n = 8, 10, 12$)/ α -CD. Before discussing the time-resolved ITC-data, we will digress slightly and discuss some proton NMR data for the C_nMe_6/α -CD systems. As noted above, it is difficult to obtain the thermodynamic properties from ITC experiments at 298.15 K because of the slow kinetics of the process. In order to perform a full analysis of the kinetic data in terms of activation energies, we need values of the equilibrium constant K at 298.15 K. We have used proton NMR to obtain such data. On account of the slow exchange between bound and unbound species on the NMR time scale, the equilibrium concentrations can be directly obtained from the spectra. Figure 3 shows the proton spectra of α -CD and $C_{12}Me_6$ alone and of the α -CD- $C_{12}Me_6$ mixture. Clearly, the resonances for both CD and the surfactant are split in the mixture, and a straightforward integration of the peaks yields the equilibrium concentration

TABLE 3: Kinetic Parameters for the Formation of α -CD- C_n Me₆ ($n = 8, 10, 12$) Host–Guest Complexes

T/K	S	$K^a/(\text{kg mol}^{-1})$	$k_{\text{off}}^b/(10^{-4} \text{ s}^{-1})$	$k_{\text{on}}/(\text{mol}^{-1} \text{ kg s}^{-1})$	$\tau_{1/2}^c/\text{s}$
298.15	C ₈ Me ₆	44	37.3	0.16 (± 0.01)	180
298.15	C ₁₀ Me ₆	1121	1.276	0.143 (± 0.001)	5430
298.15	C ₁₂ Me ₆	6900	0.183	0.126 (± 0.001)	38000
308.20	C ₈ Me ₆	35	84.6	0.30 (± 0.02)	80
308.20	C ₁₀ Me ₆	764	4.215	0.322 (± 0.001)	1645
308.20	C ₁₂ Me ₆	3817	0.914	0.349 (± 0.001)	7580

^a Values obtained from Table 1 for $T = 308.20$ K, and from a combination of ITC and ¹H NMR at 298.15 K (where the values of K are obtained from NMR). ^b $k_{\text{off}} = k_{\text{on}}/K$. ^c $\tau_{1/2} = \ln(2)/k_{\text{off}}$ and represents the half-life of the complex.

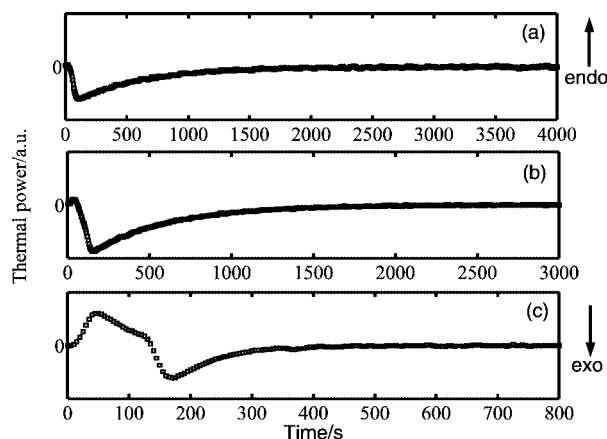


Figure 4. Thermal power as a function of time for the addition of bolaform surfactants to aqueous solutions of α -CD at 308.20 K: (a) [C₁₂Me₆] = 0.514 mmol/kg, [α -CD] = 4.97 mmol/kg; (b) [C₁₀Me₆] = 0.988 mmol/kg, [α -CD] = 5.30 mmol/kg; (c) [C₈Me₆] = 0.514 mmol/kg, [α -CD] = 4.97 mmol/kg.

from which values of the equilibrium constant for the complexation can be calculated. The results (using the anomeric proton peak of α -CD) are presented in column 3 in Table 3. For C₈Me₆ and C₁₀Me₆ the results are rather accurate and in agreement with predictions based on the data at 308.20 K and van't Hoff's equation. For C₁₂Me₆, the value is less precise because of the large value of K .

Kinetics of α -CD/ C_n Me₆ Association: ITC Measurements.

The kinetics of the complexation of some bolaform surfactants with quaternary ammonium and phosphonium head groups with α -CD have been shown to be slow.^{14,31} In our study, we have also observed slow reactions and have used time-resolved ITC data to obtain the kinetic parameters for bolaform surfactants with varying chain length. Figure 4 gives the time evolution of the thermal power after additions of a certain amount of surfactant to a solution of α -CD. The initial part of the curves shows the fast (endothermic) dilution effect. Clearly the kinetics of the complex formation is so slow that the ITC data can be used to obtain rate constants.

In analyzing the time-resolved ITC-data we consider the following process



where k_{on} and k_{off} are the rate constants for the “on” and “off” processes, respectively. As pointed out by Park³² the rate constants k_{on} and k_{off} in fact each depends on two microscopic rate constants. This follows since the CD molecule has the shape of a truncated cone with one opening smaller than the other, and threading and dethreading of the bolaform surfactant on

the CD will be different depending on which direction the process occurs. However, these microscopic rate constants cannot be determined separately.³² We also note that the bolaform surfactant is centrosymmetric meaning that there is only one complex formed.

Using the nomenclature of Table 2, it is possible to write the differential rate law equation, where we have assumed that the “on” process is second-order while the “off” process is first order

$$\frac{dx}{dt} = k_{\text{on}}(a - x)(b - x) - k_{\text{off}}x \quad (5)$$

and at equilibrium

$$k_{\text{on}}(a - x_{\text{eq}})(b - x_{\text{eq}}) - k_{\text{off}}x_{\text{eq}} = 0 \quad (6)$$

From the equilibrium constant K and Eq. 5, it follows that $K = k_{\text{on}}/k_{\text{off}}$. Then

$$\frac{dx}{dt} = \frac{P(t)}{\Delta H} \quad (7)$$

with $P(t)$ the corrected thermal power at different times. This can be integrated to yield

$$x(t) = \int_0^{t=t} \frac{P(t)}{\Delta H} dt = \frac{Q(t)}{\Delta H} \quad (8)$$

The measured heat $Q(t)$ is directly proportional to the amount of the complex. We have used the integrated form of eq 5 in the analysis. The time-corrected thermal power data were first adjusted by subtracting the baseline which was assumed to be reached when the power signal become constant. Moreover, initial effects due to the heat of dilution must be corrected for. This was done by extrapolating the monotonously decreasing curves (see Figure 4) to zero time using higher order polynomials. The result was checked by comparing in an iterative fashion the degree of reaction at the peak of the power curves. This procedure is accurate for C₁₂Me₆ and C₁₀Me₆ and introduces a relatively small error for C₈Me₆. Since the equilibrium is strongly shifted to the complex, k_{off} was replaced with k_{on}/K and this parameter was held fixed in the nonlinear list square fit of the integrated rate law to $Q(t)$ at various times. An example of the fit is shown in Figure 5 and the obtained data are presented in Table 3.

It should be noted that the value of k_{on} is rather accurately determined since the “on” dominates on account of the large values of K . The value of k_{off} is considerably less accurate, since the values of K are associated with rather large errors, in particular at 298.15 K. From the data in Table 3 activation energies can be estimated and are presented in Table 4.

As for the rate constants the accuracies of the values for the “on” process are higher. We note that on account of van't Hoff's law, the difference between the two activation energies should be equal to the ΔH_{assn}^0 values of Table 1, if we take ΔH_{assn}^0 to be temperature independent in the interval 298.15 to 308.20 K. This indicates that the values of ΔE_{off} are overestimations, in particular for C₁₂Me₆.

The rates of formation of the complexes show only a weak dependence on the number of methylene groups in the surfactant. This is to some extent reflected in the activation energy for the “on” process, although it does show a larger relative variation. We note that the error in ΔE_{on} for C₈Me₆ is rather large.

The above results can be rationalized by the fact that the barrier presumably has a large contribution originating from the necessity to push a charge through the nonpolar cavity. In fact, the magnitude of this barrier can be estimated from the Born

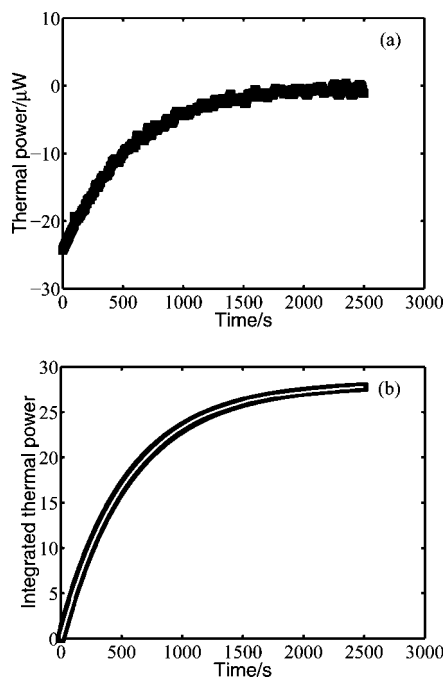


Figure 5. Illustration of the procedure used to treat the kinetic ITC data. The data correspond to those in Figure 4a corrected with the calibration constant, equal to 1.647×10^{-8} J/(au). In part a, the time-resolved data after correction for initial heat of dilution and baseline correction are shown. Part b shows the integrated heat obtained by fitting eq 5 to the experimental data (solid line through the points).

TABLE 4: Activation Energies Obtained from the Results in Table 3, Where Errors for ΔE_{on} are estimated from the Errors in k_{on} in Table 3

S	ΔE_{on}^a /(kJ mol ⁻¹)	ΔE_{off}^a /(kJ mol ⁻¹)
C ₈ Me ₆	55 (±10)	70
C ₁₀ Me ₆	72.6 (±0.2)	107
C ₁₂ Me ₆	91.8 (±0.2)	144

^a From $k = \exp(-\Delta E/RT)$.

equation.³³ On the assumption that the size of the charged N(CH₃)₃ headgroup is 100 Å³ (giving a radius of 3 Å if assumed spherical), and that the permittivity of the inside and outside are 4 (twice that of a hydrocarbon) and 80, respectively, one arrives at a value of 50 kJ/mol. This is the correct magnitude, indicating that electrostatic effects contribute considerably to the barrier. Other contributions stem from the fact that only certain configurations of the bolaform surfactant hydrocarbon chain may get through the cavity.

The rates of the “off” process depend considerably more on the length of the surfactant, also reflected in a larger variation of the activation energies. This can be understood if one considers the process as flow of charged head groups through a region of low concentrations of head groups inside the cavity. The flow rate will then depend on the concentration gradient of charged head groups outside the CD cavity. The gradient will be smaller for C₁₂Me₆ since its charged head groups have a larger effective volume to explore on either side of the CD cavity. Recall that the height of CD is 7.9 Å³⁴ while the length of a stretched C₁₂ chain is 15 Å. Or expressed in other words, the chance of a charged headgroup exploring the entry to the CD cavity is considerably larger for C₈Me₆ than for C₁₂Me₆, and therefore its “off” rate is faster.

Conclusions

Here we summarize the main conclusions of this work. Isothermal titration calorimetry can be used to obtain thermodynamic data pertaining to the formation of inclusion complexes with cyclodextrin as host. If the rate of formation is sufficiently slow, kinetic parameters can also be obtained.

The method was applied to complexes between α-, β-, and γ-cyclodextrins and alkane-bis(trimethyl ammonium dibromide) bolaform surfactants, C_nMe₆ with $n = 8, 10, 12$. For α- and β-CD mainly 1:1 complexes form, while no association was observed with γ-CD. The binding constants increase by increasing the surfactant alkyl chain length and by decreasing the cavity volume of CD. The complex formation is exothermic, with larger ΔH changes for α-CD than for β-CD. The formation of α-CD/bolaform surfactant complexes is characterized by a negative entropy change, while a positive entropy change occurs in the β-CD-containing systems. We suggest that this difference is due to the fact that the state of water inside the CD cavity depends on the cavity radius which leads to differences in the thermodynamic quantities when the water molecules are released from the cavities.

From the point of view of the kinetics, the binding of C_nMe₆ surfactants with α-CD is a slow process, with a half-life time of the complex (at 298.15 K) ranging from 180 and 38000 s⁻¹ (for C₈Me₆ and C₁₂Me₆, respectively).

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