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Complexation reactions of β -cyclodextrin, per-(2,3,6-O-methyl) cycloheptaamylose and γ -cyclodextrin with phenolphthalein, adamantane carboxylate and adamantane acetate

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A spectrophotometric method is employed to estimate complexation constants of phenolphthalein and its mono- and divalent anions with β -cyclodextrin. Subsequent experiments employ phenolphthalein as an indicator species to determine temperature dependent complexation constants of the adamantane carboxylate and adamantane acetate anions with β -cyclodextrin, per-(2, 3, 6-O-methyl)cycloheptaamylose and γ -cyclodextrin. Analysis of the data confirms that the stoichiometries of all the complexes are 1:1 and provides values of the conditional ΔH and ΔS for the formation of complexes of phenolphthalein with the cyclodextrins. In addition, values of the thermodynamic ΔH° and ΔS° for the complexes of the adamantane derivatives with the cyclodextrins are obtained. The results indicate that no single interaction mechanism can account for all of the various reactions. Thus, the cyclodextrins cannot be regarded as passive hosts in these reactions. Moreover, the different cyclodextrins interact differently with each of substrates to which they are complexed.

INTRODUCTION

Cyclodextrins and their derivatives form complexes with a wide variety of neutral, anionic, and cationic species in aqueous solution. These complexation reactions have been subjects of numerous studies in recent years.^{1–12} Most of these studies have focused on α -cyclodextrin and β -cyclodextrin complexation reactions with various substrates and were primarily concerned with elucidating the binding mechanisms in these complexes. The proposed mechanisms most commonly involve hydrophobic interactions, van der Waals forces, and dispersion forces. In addition, the release of “high energy” wa-

ter from the cyclodextrin cavity is thought to play a central role.

Most workers have assumed that the cyclodextrin serves as an essentially inert cavity and thus, that the different cyclodextrins share a common binding mechanism. The validity of this hypothesis can be investigated by comparing the binding between various substrates and various cyclodextrins. Unfortunately, such comparisons are difficult because the results reported by different laboratories employing different methods and conditions are often not in agreement. In an attempt to resolve these inconsistencies, we have studied the complexation properties of adamantane carboxylate and adamantane acetate anions with β -cyclodextrin, per-(2, 3, 6-O-methyl)-cycloheptaamylose and γ -cyclodextrin using a modification of a spectrophotometric method employed previously⁸. The present method relies on the color-fading reaction of the cyclodextrins with phenolphthalein in basic solution. Some aspects of this reaction have previously been reported.^{9–12}

EXPERIMENTAL

β -cyclodextrin, per-(2,3,6-O-methyl)-cycloheptaamylose, and γ -cyclodextrin were obtained from the Aldrich Chemical Company as the hydrate materials. The β -cyclodextrin samples were twice recrystallized from water and vacuum dried for several days at about 100°C. The other cyclodextrins were vacuum dried and used without further purification. Samples of adamantane carboxylic

acid and adamantane acetic acid were obtained from the same source. The former material was converted to the potassium salt and then twice recrystallized from water. The vacuum dried product was used to make stock solutions. Solutions of adamantane acetate were prepared by dissolving the solid acid in NaOH, adjusting the pH to 9–10. Ethanolic phenolphthalein solutions (~0.02 F) were diluted in 200–400 volumes of water and were immediately measured into alkaline buffers. More concentrated aqueous phenolphthalein solutions formed precipitates on the vessel walls. All other materials used in the experiments were reagent grade.

Absorbance measurements at 552 nm (1 nm bandpass) employed a Beckman Acta CIII Spectrophotometer equipped with matched 1.000 cm quartz cuvetts and a thermostatted cell holder. The solutions were brought to temperature for about 10 minutes before placement in the spectrophotometer compartment where they were allowed to equilibrate for an additional 10 minutes. Selected samples that were allowed to equilibrate for a much longer time showed no apparent change in the absorbance.

A Beckman Model 71 pH meter equipped with conventional glass and reference electrodes was used to measure pH. The pH of the calibration solution, 1.00×10^{-3} F HCl in 0.25 F KCl, was set at 3.000. This procedure allowed the interpretation of pH readings in similar media as $[H^+] = 10^{-pH}$.

Complexation of phenolphthalein and its anions by β -cyclodextrin

Phenolphthalein, abbreviated here as H_2P , rapidly equilibrates with aqueous hydronium ions to form a monoanion HP^- and a dianion P^{2-} . Both H_2P and HP^- are colorless. The dianion is responsible for the familiar pink color with $\lambda_{max} = 552$ nm. Consider a mixture of H_2P and β -cyclodextrin, denoted by Cy, at some fixed ionic strength. The relevant species in solution are $[H^+]$, $[H_2P]$, $[HP^-]$, $[P^{2-}]$, $[Cy]$, $[CyH_2P]$, $[CyHP^-]$, $[CyP^{2-}]$. For a solution of known pH, the equilibrium state is characterized by 7 equations: the two acid dissociation equilibria for H_2P , the 3 complex formation equilibria, a mass balance equation for cyclodextrin, and one for phenolphthalein. The equilibrium constants are conditional constants for solutions whose ionic strength is fixed at 0.25 M.

The Beer-Lambert equation for the absorbance at 552 nm involves $[P^{2-}]$ and its molar absorptivity only, under the assumption that the only spectroactive species at 552 nm is the uncomplexed dianion. Although this assumption cannot be proved directly, evidence for its validity can be obtained by measurements of the absorbances of several replicate solutions of phenolphthalein and buffer with varying concentrations of β -cyclodextrin at wavelengths between 500 and 600 nm in increments of 5 nm.

The absorbance at each wavelength decreased with increasing concentration of cyclodextrin while the ratio of absorbances of the solutions with cyclodextrin to those without cyclodextrin remained constant within the estimated measurement uncertainty of ± 0.002 . Thus, no change in bandshape or in the position of the absorbance maximum could be detected, indicating that no new spectroactive species is formed upon complexation.

The set of 7 equations describing the equilibria together with the expression for the absorbance, contain 6 unknown parameters: the 2 phenolphthalein acidity constants, K_{a1} and K_{a2} ; the 3 complexation constants, K_o , K_1 , and K_2 of cyclodextrin with $[P^{2-}]$, $[HP^-]$, and $[H_2P]$, respectively; and the molar absorptivity of P^{2-} , ϵ . These 6 parameters can be determined simultaneously by means of a nonlinear regression analysis of the absorption vs. composition data. The absorptivity can be determined independently from the other 5 parameters by means of a separate experiment involving measurements of the phenolphthalein absorbance in a sufficiently alkaline solution without cyclodextrin where only P^{2-} is present. A comparison of this value with the value obtained in the course of determining all 6 parameters provides a check on the experimental and calculational procedures.

In order to obtain the absorbance versus composition data necessary to determine the six unknown parameters, we prepared a total of 41 solutions with seven pH values ranging from 8.90 to 10.16 and concentrations of β -cyclodextrin ranging from 0.0 to 0.17 mF. The analytical concentration of phenolphthalein in each solution was 2.8×10^{-5} F. Each solution contained 0.15% ethanol. The effect of ethanol on these mixtures was studied by preparing replicate solutions with ethanol concentrations as high as 0.5%. No effect in either the absorbance or pH was detected.

The nonlinear regression algorithm of Levenberg-Marquardt as implemented by Press et al.¹³ was used to determine the values of the 6 unknown parameters that best fit the data to the model equations. The χ^2 merit function is given by

$$\chi^2 = \sum_{i=1}^N \frac{(A_i - \hat{A}_i)^2}{\sigma_A^2 + \left(\frac{\partial \hat{A}}{\partial pH} \right)_i^2 \sigma_{pH}^2} \quad (1)$$

In this equation N is the number of data points, A_i is the i^{th} absorbance obtained at a certain pH and composition and \hat{A}_i is the best-fit value of the absorbance at the same pH and composition. σ_A and σ_{pH} are the standard deviations of the absorbance and pH with values 0.002 and 0.004, respectively. We assume that the uncertainty in the concentration measurements is negligible. The denominator is the effective variance and includes the contributions of the uncertainty from both the absorbance

and pH. If the uncertainties are small, as they are in this case, the effective variance provides an excellent approximation to the true weight.

The results of the regression analysis together with the relevant derived thermodynamic constants appear in Table 1. The value of the χ^2 merit function was 32. This value is in good agreement with the number of degrees of freedom, 35 (41 data points minus 6 parameters). Moreover, the residuals, $\hat{A}_i - A_i$, are small and appear to be randomly distributed. These results show that the data is appropriately described by the model equations, thus validating the assumptions that the complexation stoichiometries are 1:1 and that the complexation species are colorless. Parenthetically, we note that a fourth phenolphthalein species, a colorless carbinol formed in very alkaline media, which was not included in the model equations, had no noticeable effect on the analysis.

The estimates of the uncertainties in the values of the parameter given in Table 1 were obtained using Monte Carlo methods.¹⁴ Although these uncertainties could be obtained by a propagation of variance procedure, it has been found that these estimates may be in error in non-linear problems especially if there are uncertainties in both dependent and independent variables.¹⁴ In this problem, the Monte Carlo estimates are approximately 20–50% higher than those given by the propagation of variance method.

The acidity constants for phenolphthalein listed in Table 1 are in good agreement with those of Gaizer et al.¹⁵ They found $K_{a1} = 1.3(\pm 0.4) \times 10^{-9}$ and $K_{a2} = 2.9(\pm 0.3) \times 10^{-10}$ at ionic strength 0.1 M and 25°C. Using the appropriate activity coefficients, our estimates of the acidity constants at the same ionic strength are $K_{a1} = 1.06(\pm 0.07) \times 10^{-9}$ and $K_{a2} = 4.3(\pm 0.1) \times 10^{-10}$. The minor difference in the values of K_{a2} is probably due to the uncertainties in the values of the activity coefficients.

Our value of ϵ ($3.4 \times 10^4 \text{ M}^{-1}\text{cm}^{-1}$) can be compared to the values of Okubo and Kuroda¹², $\epsilon = 2.62 \times 10^4 \text{ M}^{-1}\text{cm}^{-1}$, and Taguchi¹⁰, $\epsilon = 3.06 \times 10^4 \text{ M}^{-1}\text{cm}^{-1}$. It is important to note that these values are dependent on the specific experimental circumstances. Okubo and Kuroda used a pH 10.4 glycine buffer mixture; Taguchi used a 0.1 F NaCl solution made up to pH 10.5 with NaOH.

Table 1 Conditional and Thermodynamic Acidity Constants and β -Cyclodextrin Complexation Constants of Phenolphthalein at 25°C

	ionic strength 0.25M	thermodynamic value ^(a)
K_{a1}	$1.16(\pm 0.07) \times 10^{-9}$	$0.72(\pm 0.04) \times 10^{-9}$
K_{a2}	$5.10(\pm 0.14) \times 10^{-10}$	$1.98(\pm 0.05) \times 10^{-10}$
K_2	$7.8(\pm 1.2) \times 10^4$	$7.8(\pm 1.2) \times 10^4$
K_1	$8.4(\pm 0.5) \times 10^4$	$8.9(\pm 0.6) \times 10^4$
K_0	$3.07(\pm 0.08) \times 10^4$	$3.89(\pm 0.10) \times 10^4$
ϵ	$3.40(\pm 0.02) \times 10^4 \text{ M}^{-1}\text{cm}^{-1}$	

^a Based on ionic activity coefficients from the extended Debye-Huckel equation with $a^\circ = 0.9\text{nm}$ for H^+ , HP^- and P^{2-} and $a^\circ = 1.4\text{nm}$ for β -cyclodextrin complexes.

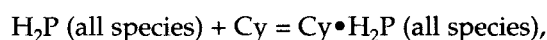
After adjusting Taguchi's absorptivity by means of the acidity constants listed in Table 1, we find his value to be in good agreement with ours.

We verified our calculated value of ϵ by means of a series of experiments, not involving complexation, in which 0.1–0.3 mL of 0.25 F NaOH were pipetted into a thermostatted 2.00 mL solution (20°–50°C) of H_2P in 0.15 F or 0.25 F KCl. Under these conditions the color-fading reaction of P^{2-} with hydroxide ions to form the carbinol proceeds at a noticeable rate so the absorbance was extrapolated to $t = 0$, the mixing time. After correcting for dilution, we obtained values between $3.38 \times 10^4 \text{ M}^{-1}\text{cm}^{-1}$ at 50°C and $3.44 \times 10^4 \text{ M}^{-1}\text{cm}^{-1}$ at 20°C. In these solutions, at least 99% of the phenolphthalein is present as the dianion before carbinol formation. The slight decrease in ϵ with increasing temperature is attributable to the thermal expansion of the solutions. These results confirm the value ϵ obtained from the model of the cyclodextrin-phenolphthalein system.

Having established that the model equations adequately describe the acid-base and complexation properties of β -cyclodextrin with phenolphthalein we are now in a position to employ the dye as a photometric indicator to investigate other complexation reactions involving γ - and other cyclodextrins.

Complexation of phenolphthalein with β -cyclodextrin, per-(2,3,6-O-methyl)cycloheptaamylose, and γ -cyclodextrin in carbonate buffer mixtures

We now describe a series of experiments designed to study the complexation reactions of H_2P with β -cyclodextrin (7-Cy), per-(2,3,6-O-methyl)cycloheptaamylose (7-MCy), and γ -cyclodextrin (8-Cy). Our purpose was to determine the stoichiometries of the complexes with 7-MCy and 8-Cy and to obtain values for the conditional equilibrium constants for the reactions:



where Cy now represents any of the cyclodextrins.

A 1:1 mixture of Na_2CO_3 and NaHCO_3 (0.0125 F in each) with an ionic strength of 0.15 M set by KCl served as a buffer. The pH, standardized against a commercial phosphate buffer of $\text{pH} = 7.00 \pm 0.02$ at 25°C, was 9.94. The H_2P concentration was 4.8×10^{-5} F in solutions containing 7-Cy or 7-MCy and 4.4×10^{-5} F in solutions containing 8-Cy. The concentrations of 7-Cy and 7-MCy varied from 0 to about 3×10^{-4} F; those of 8-Cy varied from 0 to 2×10^{-3} F. At the lower temperatures, the absorbances varied from 1.1 for the uncomplexed mixtures to approximately 0.2; at the higher temperatures they varied from 1.1 to about 0.6. By making replicate mixtures we estimated the uncertainty in absorbance as ± 0.004 .

We begin the analysis of the experiments by noting that the same set of model equations applies to these reactions. Since the experiments are carried out at constant ionic strength and the solutions are buffered by a relatively concentrated carbonate mixture we can express the equilibrium and mass balance equations in the convenient form

$$\frac{\epsilon b F_p}{A} = \frac{1}{\alpha} + \frac{\epsilon b \beta F_{cy}}{\epsilon b + \beta A} \quad (2)$$

where

$$\frac{1}{\alpha} = \frac{[H^+]^2}{K_{a1} K_{a2}} + \frac{[H^+]}{K_{a2}} + 1 \quad (3a)$$

and

$$\beta = \frac{K_2 [H^+]^2}{K_{a1} K_{a2}} + \frac{K_1 [H^+]}{K_{a2}} + K_o \quad (3b)$$

In these equations, b is the path length of the radiation through the absorbing medium, α is the fraction of uncomplexed phenolphthalein present in the form $[P^{2-}]$, and β is an overall or conditional complexation constant. Both α and β depend on the pH, ionic strength, and temperature. F_p and F_{cy} are the formal (analytical) concentrations of phenolphthalein and cyclodextrin, respectively. Using the simplex method as implemented by Press, et al.¹³, we obtained optimized values of α and β as a function of temperature from absorbance versus composition (F_p and F_{cy}) data and the previously determined values of ϵ . The calculation minimizes χ^2 , the goodness-of-fit parameter. The uncertainty in absorbance was set at ± 0.004 . In each calculation, the value of χ^2 per degree of freedom was nearly always in the range from 0.5 to 1.5, close to the expected value of 1. We conclude that complexation of H_2P by all three cyclodextrins is indeed 1:1 as was assumed in the model equations.

Table 2 lists the values of α and β . We note first that each series of measurements that employed a different cyclodextrin complexing agent provides an independent value of α . Since this parameter depends on the H_2P acidity constants, the buffer composition, and the ionic strength which are common to all three series of experiments the values of α should be essentially identical. This is observed to be the case.

The value of α is related to the conditional equilibrium constant for the reaction $H_2P + 2 CO_3^{2-} (0.0125F) = P^{2-} + 2 HCO_3^- (0.0125F)$ by the simple relationship $K = \alpha/(1-\alpha)$. Using the data in Table 2 we obtain values of K at each temperature. These values of K are monotonic with temperature. The van't Hoff plot results in a straight line with $\Delta H = 1.19 \pm 0.05$ kcal mol⁻¹ and $\Delta S = +5.6 \pm 0.2$ cal mol⁻¹K⁻¹. The rms scatter of points about the regression line was about 0.01 lnK units, corresponding to an approximate 1% uncertainty in K , a result consistent with the estimated uncertainty in α .

The interpretation of the thermodynamic parameters is complicated by the fact that uncomplexed H_2P is present as a mixture of H_2P , HP^- and P^{2-} species. However, examination of the equilibrium constants in Table 1 suggests that the relative amount of H_2P is essentially negligible (2–3%). Consequently, the equilibrium constant above describes the reaction $HP^- + CO_3^{2-} = P^{2-} + HCO_3^-$. ΔH and ΔS for the second phenolphthalein dissociation can then be obtained from the present results and the protonation enthalpy and entropy of the CO_3^{2-} ion. From the temperature dependence of the pH of the carbonate buffer solutions, we find $\Delta H = 3.4 \pm 0.2$ kcal mol⁻¹ and $\Delta S = 34. \pm 1.$ cal mol⁻¹K⁻¹ for the protonation reaction. Finally we obtain $\Delta H = 4.6 \pm 0.2$ kcal mol⁻¹ and $\Delta S = -28. \pm 1.$ cal mol⁻¹K⁻¹ as estimates for the enthalpy and entropy for the dissociation reaction $HP^- = H^+ + P^{2-}$ at ionic strength 0.15. These results appear to be new.

The comparison of the values of β obtained here with those from previous studies is not straightforward because the ionic strength and, more importantly, the pH used here are different from those used in the previous work. Nevertheless, some comparisons are possible. Taguchi¹⁰ obtained a value of 3.7×10^4 for the conditional complexation constant of 7-Cy with H_2P in unbuffered solutions at pH=10.5 at 20°C. Analysis of the complexation constants at 10, 15, 20, and 30°C led to $\Delta H = 5.8$ kcal mol⁻¹ and $\Delta S = +1$ cal mol⁻¹K⁻¹. Okubo and Kuroda¹² report a conditional complexation constant with 7-Cy of 3.1×10^4 at 25°C. They obtained $\Delta H = 8.2$ kcal mol⁻¹ and $\Delta S = -6.9$ cal mol⁻¹K⁻¹ based on data at

Table 2 Values of α and β for the Complexation of Phenolphthalein with 7-Cy, 7-MCy, and 8-Cy at Various Temperatures

$t, ^\circ C$	α <u>β-Cyclodextrin</u>	$10^3 \beta$
14.3	0.685 \pm 0.003 ^a	88.7 \pm 1.2
20.4	0.695	60.7 \pm 0.6
25.3	0.696	47.5 \pm 0.6
34.4	0.709	27.5 \pm 0.2
45.2	0.726	14.8 \pm 0.1
50.1	0.733	10.9 \pm 0.1
<u>Per-(2,3,6-O-methyl)-Cycloheptaamylose</u>		
14.3	0.685	36.6 \pm 0.3
20.4	0.695	21.6 \pm 0.2
25.3	0.697	14.8 \pm 0.2
34.4	0.707	7.3 \pm 0.2
45.2	0.728	3.3 \pm 0.1
50.1	0.733	2.2 \pm 0.1
<u>γ-Cyclodextrin</u>		
18.1	0.692	3.86 \pm 0.03
24.7	0.698	3.14 \pm 0.02
33.0	0.707	2.28 \pm 0.02
41.8	0.713	1.69 \pm 0.01
50.3	0.731	1.17 \pm 0.01

a. Uncertainties in α are all 0.002–0.003.

25, 30 and 35°C. Buvari and Barcza¹¹ report a complexation constant of 2.2×10^4 at 25°C in 4×10^{-3} F Na_2CO_3 at ionic strength of 0.1 M. The present result, $\beta = 4.75 \times 10^4$ for 7-Cy at 25.3°C appears to be in approximate agreement with the values above.

We can also compare the present result with one calculated from the equilibrium constants given in the last section. This estimate is based on independent experiments involving different chemical samples and stock solutions. Using Table 1 together with estimates of the ionic activity coefficients in accord with the description given in the footnotes of that Table, we find a value of $\beta = 4.7 \times 10^4$ at 25°C, a result in remarkable agreement with the present result.

We obtained values of ΔH and ΔS values for the overall complexation reactions of the cyclodextrins with H_2P species by means of van't Hoff analysis of the temperature dependence of β given in Table 2. The plots are linear and the rms scatter about the line was about ± 0.03 lnK units. These results are listed in Table 3. The uncertainties represent standard error estimates derived by propagation of variance.

Of the results in Table 3, only those for 7-Cy can be compared with previous work. The present results are significantly different from earlier ones for 7-Cy even given the somewhat different set of experimental conditions employed here. While the earlier results pertain to conditions of higher pH where α , the fraction of uncomplexed H_2P present as P^{2-} , is nearly 0.9 compared to our value of 0.7, it is difficult to reconcile the differences in the values of ΔH and ΔS on this basis. The detailed interpretation of the results in Table 3 is made difficult by a variety of factors including the presence of Cy-P^{2-} , Cy-HP^- , and, to a lesser extent, $\text{Cy-H}_2\text{P}$. However, it is useful to note that the three cyclodextrins studied here show significantly different complexation enthalpies and entropies with H_2P .

Complexation of cyclodextrins with adamantane carboxylate and adamantane acetate ions

In this section we describe the use of phenolphthalein-cyclodextrin complexation reactions as photometric indicator systems to estimate Cy complexation constants with other substrate species.

Consider a series of buffered mixtures containing H_2P , various concentrations of cyclodextrin, and a second complexing agent X which complexes with cyclodextrin

only. The solutions now contain 2 additional species: X and CyX . The mass balance equation for cyclodextrin now includes $[\text{CyX}]$. The 2 additional equations are the complex formation equilibrium constant for $[\text{CyX}]$ and a mass balance equation for F_X , the formal concentration of X. We assume that neither X nor CyX have appreciable absorbance at 552 nm.

After some algebra, we obtain

$$\frac{\epsilon F_p}{A} = \frac{1}{\alpha} + \beta[\text{Cy}] \quad (4)$$

$[\text{Cy}]$ is determined by the implicit equation

$$F_{\text{Cy}} = [\text{Cy}] \left(1 + \frac{\beta A}{\epsilon} + \frac{K_x F_x}{1 + K_x [\text{Cy}]} \right) \quad (5)$$

In Eqs. 4 and 5, α and β have the same significance as before and we have set the path length, b , equal to 1.

Although we could use the values of α and β determined previously to calculate K_x , we choose to regard α and β as well as K_x as the unknown parameters. Two sets of α and β values are obtained. The first set is derived from solutions not containing X; the second from solutions containing X. We find the two sets are in agreement, providing evidence that the model is correct. For example, the values of α and β obtained from an analysis of 5 solutions containing $0-2.5 \times 10^{-4}$ F 7-MCy at 25.3°C were 0.697 and 1.479×10^4 , respectively. When the same data were combined with absorbance versus composition data for 4 additional solutions containing either 3.1×10^{-4} F or 1.7×10^{-4} F 7-MCy and adamantane carboxylate (AC) in concentrations between 4.0×10^{-4} F and 1.0×10^{-3} F, the values of α and β were 0.696 and 1.474×10^4 , respectively.

This analysis depends on the further assumption that there is no direct interaction between any of the H_2P species and X. This assumption was confirmed by preparing buffered phenolphthalein mixtures containing various concentrations of adamantane acetate (AA) and AC. These solutions had absorbances essentially identical to those prepared with KCl only. Consequently, neither AA nor AC has any significant interaction with phenolphthalein species.

Complexation formation constants of AA and AC with the various cyclodextrins at various temperatures are listed in Table 4. In each regression, χ^2 , based on an uncertainty of ± 0.004 in the absorbance, was approximately equal to the number of degrees of freedom. The uncertainties given in Table 4 are 68% confidence intervals derived by the Monte Carlo procedure.

It is interesting to note that for each temperature, the complexes of AA with the three cyclodextrins are 2–3 times stronger than the corresponding complexes of AC. It seems extraordinary that all three cyclodextrins can distinguish in such a uniform manner two such nearly identical substrates. A previous study¹⁶ showed that 7-

Table 3 Conditional Enthalpies and Entropies of Complexation of Phenolphthalein by 7-Cy, 7-MCy and 8-Cy

	$\Delta H, \text{kcal mol}^{-1}$	$\Delta S, \text{cal mol}^{-1} \text{K}^{-1}$
7-Cy	-10.8 \pm 0.2	-14.8 \pm 0.7
7-MCy	-14.4 \pm 0.2	-29.2 \pm 0.6
8-Cy	-7.0 \pm 0.3	-7.4 \pm 1.0

Table 4 Conditional Complexation Constants of AA and AC with 7-Cy, 7-MCy and 8-Cy at ionic strength = 0.15 M

t, °C	7-Cy	
	K for AC complexation	K for AA complexation
20.4	40.8(±0.7) × 10 ³	122.(±3.) × 10 ³
25.3	36.0(±0.6) × 10 ³	107.(±2.) × 10 ³
34.4	26.4(±0.4) × 10 ³	71.9(±1.5) × 10 ³
45.2	18.8(±0.3) × 10 ³	45.5(±0.1) × 10 ³
50.1	15.7(±0.3) × 10 ³	35.8(±0.5) × 10 ³
t, °C	7-MCy	
	K for AC complexation	K for AA complexation
20.4	12.2(±0.2) × 10 ³	35.0(±0.9) × 10 ³
25.3	10.6(±0.2) × 10 ³	27.8(±0.8) × 10 ³
34.4	8.8(±0.2) × 10 ³	19.2(±0.4) × 10 ³
45.2	6.0(±0.3) × 10 ³	11.5(±0.5) × 10 ³
50.1	5.5(±0.2) × 10 ³	8.5(±0.7) × 10 ³
t, °C	8-Cy	
	K for AC complexation	K for AA complexation
18.1	239.±9.	0.92(±0.02) × 10 ³
24.7	268.±9.	1.03(±0.02) × 10 ³
33.0	306.±9.	1.16(±0.02) × 10 ³
41.8	332.±9.	1.20(±0.03) × 10 ³
50.3	337.±9.	1.27(±0.03) × 10 ³

a. Uncertainties are 68% Monte Carlo confidence intervals.

Cy and 7-MCy distinguish between the adamantane ammonium (ANH₃⁺) and adamantane methyl ammonium (ACH₂NH₃⁺) ions. Complexes of ACH₂NH₃⁺ are about 3–5 times stronger than those of ANH₃⁺ for both cyclodextrins. However, as we shall see from the analysis of ΔH° and ΔS° for the complexation reactions, the selectivity in these systems is not manifested in a simple manner.

Enthalpies and entropies for these reactions are obtained from a van't Hoff analysis of the equilibrium constants and are listed in Table 5. The scatter about the van't Hoff lines, which varied from ±0.03 to ±0.05 lnK units, correspond to uncertainties of 3–5% in the equilibrium constants and are in approximate agreement with the regression estimates of 2–3% uncertainty in the individual K values. The slight discrepancy results from neglecting the uncertainty in temperature.

Because we wish to compare our values of ΔH and ΔS , obtained from solutions with an appreciable ionic strength, to those for similar reactions reported as ΔH° and ΔS° (ionic strength equal to zero), we use the results of Table 4 to estimate the thermodynamic complexation constants at each temperature. The required activity coefficients were obtained from the Debye-Huckel equation. The values of A and B are given by Robinson and Stokes¹⁷. The sizes of the various ions, AC, AA, and their 7-Cy, 7-MCy, and 8-Cy complexes, were set at 0.7, 0.8, 1.4, 1.5, and 1.6 nm, respectively. The resulting values of ΔH° and ΔS° for the various complexation reactions resulting from the van't Hoff analyses are listed in Table 5. In addition to these values, we include the corresponding values for the complexation reactions of 6-Cy

with AC¹⁸ and 7-Cy and 7-MCy with the adamantane ammonium ANH₃⁺ and adamantane methyl ammonium ACH₂NH₃⁺ ions¹⁶.

Finally, we calculate ΔH° and ΔS° values for the substitution reactions of the carboxylate substrates with the various cyclodextrins along with corresponding values for substitution of the ammonium substrates with 7-Cy and 7-MCy. Substitution equilibrium constants are obtained from a comparison of the complexation constants at each temperature. Van't Hoff analyses of these substitution constants provide values of ΔH° and ΔS° .

DISCUSSION

The data of Table 5 show a marked difference between the binding properties of the cyclodextrins with the substrate adamantane derivatives. The complexations involving 8-Cy have small unfavorable reaction enthalpies and are entirely entropy driven. These reactions appear to fit the classic model of hydrophobic bonding. That is, solvent water molecules "trapped" at the hydrocarbon surface and within the 8-Cy cavity are released into the bulk solution upon insertion of the hydrocarbon moiety into the Cy cavity.

In contrast to the 8-Cy complexations, 6-Cy, 7-Cy, and 7-MCy complexations with both AA and AC substrates are enthalpy driven. The AA complexations have markedly unfavorable reaction entropies indicating a net increase in bonding and subsequent ordering of the com-

Table 5 Complexation Enthalpies and Entropies of 6-Cy, 7-Cy, 7-MCy and 8-Cy with Various Substrates

substrate	conditional values		thermodynamic values	
	ΔH , kcal mol ⁻¹	ΔS , cal mol ⁻¹ K ⁻¹	ΔH° , kcal mol ⁻¹	ΔS° , cal mol ⁻¹ K ⁻¹
8-Cy				
AC	2.0±0.3	17.9±1.0	2.1±.3	18.2±1.0
AA	1.8±0.2	20.0±0.8	1.8±0.2	20.0±0.8
7-Cy				
AC	-6.1±0.2	0.3±0.6	-6.1±0.2	0.5±0.6
AA	-8.0±0.4	-3.6±1.2	-7.9±0.4	-3.5±1.2
ANH ₃ ⁺			-5.9±0.5	-1.8±1.5
ACH ₂ NH ₃ ⁺			-4.1±0.7	6.9±2.2
7-MCy				
AC	-5.1±0.3	1.2±1.0	-5.1±0.3	1.5±1.0
AA	-8.8±0.4	-9.3±1.3	-8.8±0.4	-9.0±1.4
ANH ₃ ⁺			-2.0±0.5	1.4±1.5
ACH ₂ NH ₃ ⁺			-2.4±0.5	3.4±1.6
6-Cy				
AC			-3.4±0.6	-1.3±1.9

plex compared with the reactant substances. Complexation reactions of ANH_3^+ with both 7-Cy and 7-MCy are enthalpy driven with ΔS° approximately equal to 0. The corresponding complexations of $\text{ACH}_2\text{NH}_3^+$ are both enthalpy and entropy driven. It is worth noting that while the 7-MCy complexes with AA and AC are only approximately 3–4 times weaker than the corresponding complexes with 7-Cy, the 7-MCy complexes with ANH_3^+ and $\text{ACH}_2\text{NH}_3^+$ are approximately 100 times weaker than the corresponding 7-Cy complexes.

These results suggest that there is no single property of the substrate that can account for the differences in ΔH° and ΔS° of these reactions. Furthermore, the differing interactions of the various substrates, which themselves have nearly identical steric properties, with a given cyclodextrin suggest that simple mechanisms such as water expulsion from the cyclodextrin cavity or van der Waals interactions cannot alone account for the observed behavior. We conclude that any explanation of the bonding and ordering interactions of these reactions must take into account alterations in the structure and solvation of the cyclodextrins themselves.

To further demonstrate this point, we note that 7-Cy, 7-MCy and 8-Cy are capable of distinguishing between AA and AC substrates in spite of their apparent similarity. Likewise, 7-Cy and 7-MCy distinguish between ANH_3^+ and $\text{ACH}_2\text{NH}_3^+$ substrates. Conversely, the results in Table 6 indicate that each substrate has different interactions with the different cyclodextrins. Each of the substitution reactions listed in the Table represents, in a formal sense, the addition of a methylene group to the substrate. Yet there appears to be no simple correspondence of ΔH° and ΔS° for this process with either the different cyclodextrins or with the ammonium and carboxylate substrates. Thus, although the cyclodextrins seem to be a series of nearly identical chemical homologs, their complexations do not appear to be charac-

terizable in terms of a single interaction mechanism. This conclusion implies that changes within the cyclodextrin molecule and changes in cyclodextrin solvation consequent to the complexation reactions may play at least as great a role in determining the complexation properties as hydrophobic effects, van der Waals interactions and other effects that are usually cited.

In closing, we note an apparent compensation effect present in 6-Cy complexations with approximately 40 neutral, anionic and cationic substrate species.¹⁸ Complexation enthalpies and entropies in these systems are related by a simple correlation equation $\Delta H^\circ = (410 \pm 15)\Delta S^\circ - 1.2(\pm 0.2) \times 10^3$ with ΔH° in cal mol⁻¹ and ΔS° in cal mol⁻¹K⁻¹. Clearly the values of ΔH and ΔS for the AA and AC complexations by 7-Cy, 7-MCy, and 8-Cy do not conform to this correlation. In spite of the apparent chemical similarity of the larger cyclodextrins to 6-Cy their binding properties appear to be markedly different. This observation is contrary to the common perception that the cyclodextrin host plays a passive role in the complexations. The results of this study indicate that theoretical descriptions of these reactions must take account of the role played by the cyclodextrin host as well as that of the substrate species.

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Table 6 Enthalpy and Entropy Changes for the Substitution
Reactions: AA + CyAC = AC + CyAA and $\text{ACH}_2\text{NH}_3^+ + \text{CyANH}_3^+ = \text{ANH}_3^+ + \text{CyACH}_2\text{NH}_3^+$

	ΔH° , kcal mol ⁻¹	ΔS° , cal mol ⁻¹ K ⁻¹
AA+CyAC=AC+CyAA		
7-Cy	-1.8±0.2	-3.8±0.6
7-MCy	-2.8±0.5	-7.4±1.6
8-Cy	-0.3±0.1	1.8±0.4
$\text{ACH}_2\text{NH}_3^+ + \text{CyANH}_3^+ = \text{ANH}_3^+ + \text{CyACH}_2\text{NH}_3^+$		
7-Cy	1.8±1.0	8.6±3.4
7-MCy	-0.5±0.2	2.1±0.5