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The Complexation Chemistry of Cyclohexaamyloses: Adducts with 1-Adamantanecarboxylic Acid and Anion

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A study is reported of complexation reactions of cyclohexaamylose (Cy) with 1-adamantanecarboxylic acid and its anion using conductometry, pH potentiometry, and ^{13}C nmr spectrometry. Binary and ternary (2 mol Cy/mol substrate) complexes are detected with both the acid and anion, and standard entropies and enthalpies of complexation are determined from the temperature dependences of the formation constants for all except the very weak ternary complex with the anion. Both the ^{13}C nmr results and the entropy of complexation confirm the earlier suggestion that the anion in binary complexation is structured with the adamantanyl group in proximity to, but not penetrating, the Cy cavity. However, a negative $\Delta S°$ for formation of this complex is reported which casts doubt on an earlier proposal that the adamantyl binary complex binding mode involves an "apolar" mechanism accompanied by loss of solvated water molecules. Values are also reported for pK_a, $\Delta H°$, and $\Delta S°$ for the aqueous dissociation of 1-adamantanecarboxylic acid.

INTRODUCTION

Cycloamyloses form stable inclusion complexes with a large variety of molecules and ions which serve as models for mechanistic, structural, and thermodynamic features of biological complexations. In particular, a great deal of attention has been focused on elucidating the bonding forces which stabilize the cycloamylose adducts. These forces have been variously described as ion–dipole (*1*), dipole–dipole (*2*), London dispersion (*3, 4*) and apolar (*5*) in nature. Also formation of cycloamylose complexes has been ascribed to a process whereby "high-energy" water trapped in the Cy cavity is released by intrusion of a substrate (*6*). Those mechanisms involving apolar bonding and "high-energy" water release imply rather large positive $\Delta S°$ values for the complex formation reaction, and an example cited by Bender *et al.* (*5*) is the complexation of 1-adamantanecarboxylate anion (to be denoted A^-) by cycloamyloses. These workers obtained a $\Delta S°$ value of $+10$ cal mol^{-1} K^{-1} for the complexation reaction with α-cyclodextrin (cyclohexaamylose, hereafter designated as Cy) and suggested "apolar" binding forces in the complex. Their $\Delta S°$ value was obtained by analysis of the temperature dependence of the formation constant derived from kinetic measurements.

Because of the complicated nature of the chemical systems employed in the experiments of Bender *et al.* and the many assumptions required to analyze the

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data, we undertook to confirm their results and to investigate the possible existence of ternary complexes of Cy with both A^- and the neutral adamantanecarboxylic acid (HA). To do this we employed a variety of experimental methods, including conductance measurements with Cy, LiA solutions; pH potentiometry (*7*) with solutions containing Cy and both HA and A^-; and ^{13}C nmr spectrometry with Cy, A^- solutions. We now report the results of these studies.

CONDUCTOMETRIC ESTIMATES OF CY-A^- FORMATION CONSTANTS

When a solution of LiA is titrated with a Cy solution, the specific conductance of the resulting mixture is decreased (*8*). The decrease is due, in part, to the effect of replacing the more mobile A^- ion with the larger and less mobile CyA^- complex resulting from the complexation reaction. Detailed model equations and procedures for data treatment for this experimental method have been discussed earlier (*9*). In the present case, each formation constant listed in Table 1 is derived from conductance measurements on about 20 solutions prepared by adding aliquots of 0.10 *F* Cy solution, up to 10 ml total, to a 50-ml portion of 0.010 *F* LiA. We are satisfied that the model equations truly represent the chemical and physical behavior of these solutions since the differences between experimental and calculated conductance data are free from trends or patterns. Furthermore, these residuals are well within our a priori precision estimate of ±0.1%. Another verification is that the value of λ°, the limiting equivalence conductance, for the CyA^- ion is substantially the same as values determined for other binary Cy complex ions. This parameter for CyA^- is given in Table 1 as 13 at 30°C, compared with 15 for the binary Cy complex with *p*-methylcinnamate (*10*).

Attempts to fit these data with a set of model equations which included a ternary Cy complex, 2 mol of Cy per mole of A^-, in each case led to zero or very small values of the ternary formation constant with no substantial improvement in the

TABLE 1

CONDUCTANCE EXPERIMENTS ON Cy–LiA SOLUTIONS: VALUES OF K_{CyA}, THE BINARY COMPLEX FORMATION CONSTANT, AND SINGLE-ION EQUIVALENT CONDUCTANCES AT INFINITE DILUTION

Temperature (°C)	K_{CyA}	λ_A^{0}[a]	λ_{CyA}^{0}[a]	Fit[b] (mΩ^{-1})
20	182 ± 15[c]	21.58 ± 0.02[c]	11.3 ± 0.3[c]	0.3
25	140 ± 14	24.72 ± 0.03	12.6 ± 0.4	0.2
30	145 ± 15	27.65 ± 0.03	14.7 ± 0.5	0.3
45	119 ± 12	36.94 ± 0.04	19.8 ± 0.7	0.4
55	88 ± 10	44.01 ± 0.06	23. ± 1	0.4

[a] Single-ion equivalent conductances at infinite dilution, Ω^{-1} cm^2 mol^{-1}.

[b] Standard deviation of residuals at 21 conductance data points.

[c] Uncertainties are standard errors based on conductance measurement standard deviation estimates of 0.1%, approximately 0.5 to 0.9 mΩ^{-1}, depending on the temperature. Because the standard deviation of residuals found was typically 0.05%, these uncertainties are conservative.

fit. We, therefore, conclude that negligible amounts of the ternary Cy_2A^- complex were formed under the conditions of the conductance measurements. This observation was confirmed by our later potentiometric measurements, which indicated that the ternary complex represents less than 2% of the A^- concentration in the relatively dilute conductometric solutions.

POTENTIOMETRIC ESTIMATES OF THE FORMATION CONSTANTS

The addition of Cy to solutions containing both A^- and its conjugate acid HA changes the pH value of the solution. The change results from complexation of either or both buffer species by Cy which, in turn, displaces the acid–base equilibrium (*7*). The model equations and methods of data treatment are detailed in an earlier communication (*11*). In these experiments we made about 15 additions of weighed portions of Cy up to ~0.1 *F* Cy to solutions containing 1.6 to $5.0 \times 10^{-3} F$ A^- and 1.7 to $2.5 \times 10^{-4} F$ HA. We treated these data in two different ways. The first of these involved direct application of the methods described in Ref. (11). Values of pK_a, the acid dissociation constant of HA, and formation constants for the binary and ternary Cy complexes of HA (denoted by K_{CyHA} and K_{Cy_2HA}, respectively) and for the binary and ternary complexes of A^- (denoted by K_{CyA} and K_{Cy_2A}, respectively) are adjusted until the "best fit" of the experimental data is obtained. The parameter values thus obtained constitute solutions to the model equations in the least-squares sense. In analyzing the data we found it always necessary to include all four complex species in the model equations. If the weak Cy_2A^- complex was excluded, the residuals in our calculation showed systematic trends, and residual values were markedly larger than the precision or accuracy of our measurements; as a consequence, the rms fit of the data was unacceptably poor. This result led us to conclude that all four of the complex species, CyA^-, Cy_2A^-, CyHA, and Cy_2HA were present at appreciable concentration levels under the conditions of the potentiometric experiments which included Cy concentrations as high as 0.1 *F*. Although this technique could in principle be used to determine all four formation constants simultaneously, a peculiar circumstance in this system precluded solving for K_{CyA} and K_{CyHA} with satisfactory precision. The reason is the accidental near coincidence of K_{CyHA} and K_{CyA} values of adamantanecarboxylic acid and anion and the difficulty is explained as follows:

Suppose that an acid, HB, and its conjugate base, B^-, form binary complexes with Cy and that the complex formation constants are equal. Potentiometry would then indicate no change in the pH upon addition of Cy to a mixture of HB and B^-, since both species concentrations would be diminished equally by Cy complexation. Attempts to extract K_{CyHB} and K_{CyB} parameters from the data would yield spurious but equal values. For any given value of K_{CyHB}, an equal value of K_{CyB} would be found; and the quality of fit would not depend on K_{CyHB} or K_{CyB} individually. Thus in this peculiar circumstance the method determines only the ratio K_{CyHB}/K_B, but not their individual values.

Although in the adamantanecarboxylic acid case the situation is complicated by

TABLE 2

pH POTENTIOMETRIC MEASUREMENTS ON Cy–HA–A$^-$ SOLUTIONS: 1-ADAMANTANECARBOXYLIC ACID pK_a AND COMPLEX STEPWISE FORMATION CONSTANTS K_{CyHA}, $K_{\mathrm{Cy_2HA}}$, AND $K_{\mathrm{Cy_2A}}$

Temperature (°C)	pK_a	K_{CyHA}	$K_{\mathrm{Cy_2HA}}$	$K_{\mathrm{Cy_2A}}$	Fit[d]
25[a]	5.06 ± 0.01	136 ± 18[e]	572 ± 75[e]	4 ± 1	0.003
25[b]	5.02 ± 0.01	149 ± 10	567 ± 35	9 ± 1	0.003
30[a]	5.13 ± 0.01	103 ± 9	528 ± 44	3 ± 0.1	0.002
35[a]	5.12 ± 0.01	111 ± 14	341 ± 45	4 ± 1	0.003
35[b]	5.08 ± 0.01	122 ± 25	315 ± 97	13 ± 5	0.005
45[a]	5.13 ± 0.01	74 ± 6	225 ± 18	3 ± 0.1	0.002
45[b]	5.09 ± 0.01	84 ± 17	201 ± 62	10 ± 4	0.003
55[c]	5.10 ± 0.01	44 ± 9	147 ± 31	—[f]	0.005

[a] Measurement solution contains 2.5×10^{-4} F HA, 1.6×10^{-3} F A$^-$.

[b] Measurement solution contains 1.67×10^{-4} F HA, 5.04×10^{-3} F A$^-$.

[c] Measurement solution contains 5.0×10^{-4} F HA, 3.21×10^{-3} F A$^-$.

[d] Standard deviation of residuals of about 15 measurements, in pH units.

[e] Uncertainties are joint parametric uncertainty limits (*15*) based on residual standard deviations listed in column 6. This means that the true values for pK_a, K_{CyHA}, and $K_{\mathrm{Cy_2A}}$ are estimated to fall simultaneously in their respective intervals with a confidence of 95%.

[f] Not detected.

the ternary complexes which are formed as well, we have noted this type of behavior. Thus, if at 25°C K_{CyA} is set to any value between 100 and 300, the "best fit" value of the parameter K_{CyHA} is essentially equal to the preset value of K_{CyA}. Yet $K_{\mathrm{Cy_2A}}$ and $K_{\mathrm{Cy_2HA}}$ are affected only slightly by this setting. In the setting range $100 < K_{\mathrm{CyA}} < 300$ the fit is acceptable, and the pattern of residuals did not have strong trends. K_{CyA} values beyond this range, however, showed strong trends in the residuals and markedly poorer fits.

Because of this peculiarity, we decided to treat the data in the following alternative way: at each temperature the value of K_{CyA} was preset and not allowed to vary in the model equations, i.e., K_{CyA} was withdrawn as an adjustable parameter. The data was then fit by the usual methods to obtain optimal values of pK_a, K_{CyHA}, and stepwise $K_{\mathrm{Cy_2A}}$ and $K_{\mathrm{Cy_2HA}}$. These appear in Table 2. The preset K_{CyA} values employed in these calculations were obtained from the conductance data after smoothing a plot of log K_{CyA} vs 1/T by a weighted least-squares procedure. This smoothing was done in order to minimize the effect of spurious scatter in the conductance K_{CyA} values.

ANALYSIS OF PARAMETER UNCERTAINTIES

Although the least-squares fitting routine automatically supplies statistical uncertainties, we wished also to set maximum error bounds on our K values which might result from systematic errors in our measurements. In order to do this, we first made estimates of the maximum likely errors inherent in the various experimental quantities employed in the conductance experiments. Then each such quantity was perturbed independently by an appropriate amount, the fitting calculation was repeated, and the new K values compared with the former values. For example, after the value of the LiA reagent concentration in the conductance calculation was changed by 0.5%, new K_{CyA} and $\lambda°$ values were obtained and compared with the earlier "best" values.

In this procedure, the quality of the fit remained excellent as reflected by the constant 0.025% rms deviation obtained with each perturbation. The results of these calculations appear in Table 3 along with an estimate of the maximum likely excursion represented as $\Sigma_i |(1/P)(dP/dx_i)\Delta x_i|$, where P designates a parameter and the x_i signify the various experimental quantities subject to systematic perturbation Δx_i.

Similarly, error bounds for conductance K_{CyA} along with estimates of other systematic errors inherent in the potentiometric experiments were used to set error limits for K_{CyHA}, $K_{\mathrm{Cy_2A}}$, and $K_{\mathrm{Cy_2HA}}$ as indicated in Table 4. Estimation of $\Delta H°$ and $\Delta S°$ for the complexation reactions were determined from our K vs T data using the well-known thermodynamic equations $d \ln K/d(1/T) = -\Delta H°/R$ and $d(T \ln K)/dT = \Delta S°/R$. The slopes of plots appropriate to these equations were calculated by a weighted least-squares procedure, and standard error estimates were derived as described in an earlier communication (*12*). The results of these calculations are summarized in Table 5 along with estimates of the maximum probable error in the values obtained from the extreme slopes of $\ln K$ vs $1/T$ or $T \ln K$ vs T plots, where maximum excursions of $\ln K$ or $T \ln K$ are readily

TABLE 3

EFFECT OF SYSTEMATIC ERRORS ON CONDUCTOMETRIC PARAMETER VALUES AT 30°

	Propagated |error| (%)		
Error source	K_{CyA}	λ_{A}^0	λ_{CyA}^0
Cell constant, ±0.3%	1.0	0.7	0.7
λ_{Li}^0, ±0.2%	1.0	0.4	0.8
LiA concentration, ±0.4%	0.6	0.8	1.5
Cy concentration, ±0.5%	1.5	0.9	0.3
Solvent blank conductance, ±0.2 μΩ	0.2	0.1	0.2
Viscosity correction, ±10%[a]	7.2	0.0	3.7
Activity coefficient of A^-, ±0.2 nm[b]	0.8	0.3	0.0
Activity coefficient of CyA^-, ±0.2 nm[b]	0.4	0.0	0.4
Total	12.7	3.2	7.6

[a] The value of η/η_0 is calculated from the equation $\eta/\eta_0 = 1 + 0.00385v$ instead of $\eta/\eta_0 = 1 + 0.0035v$ in Ref. (8).

[b] Debye–Hückel ion size parameters adjusted by 0.2 nm in the activity coefficient correlation.

TABLE 4

EFFECT OF SYSTEMATIC ERRORS ON pH POTENTIOMETRIC PARAMETER VALUES AT 30°

Error source	Propagated |error|				
	pK_a	K_{CyHA} (%)	K_{Cy_2HA} (%)	K_{Cy_2A} (%)	Fit[a]
HA concentration, 0.5%	0.002	0.4	0.6	3.2	0.0016
A^- concentration, 0.5%	0.002	0.4	0.6	2.0	0.0015
pH correction[b]	0.000	0.1	1.0	6.5	0.0015
Volume correction[c]	0.000	0.1	0.2	0.4	0.0015
Meter standardization, 0.020 pH	0.020	0.0	0.0	0.0	0.0015
K_{CyA} value, 142 ± 12.7%[d]	0.001	10.8	1.8	15.5	0.0021
Cy purity, 0.5%	0.001	0.9	1.8	0.4	0.0015
Activity coefficient of A^-, 0.2 nm[e]	0.002	2.0	2.4	4.0	0.0015
Activity coefficient of CyA^-, 0.2 nm[e]	0.000	0.3	0.1	0.4	0.0015
Activity coefficient of Cy_2A^-, 0.2 nm[e]	0.000	0.2	0.1	0.4	0.0015
Total	0.028 pK	15.2%	8.6%	32.8%	

[a] Standard deviation of residuals of approximately 15 measurements, in pH units.

[b] The corrected pH is calculated from $\mathrm{pH} = \mathrm{pH_{obs}} + 0.50g_{Cy}/V$ instead of $\mathrm{pH} = \mathrm{pH_{obs}} + 0.55g_{Cy}/V$ in Ref. (10).

[c] The total volume is calculated from $V = V_{in} + 0.6g_{Cy}$ instead of $V = V_{in} + 0.7g_{Cy}$ in Ref. (9).

[d] The maximum error bound from Table 3.

[e] Change in activity coefficients as reflected by changing the Debye–Hückel ion size parameter by 0.2 nm.

found from the data in Tables 3 and 4. Because of the relative weakness of the Cy_2A^- complex, the values of K_{Cy_2A} could not be determined with sufficient precision to warrant treatment in this manner, and so thermodynamic parameters for this complexation are not included.

^{13}C NMR SPECTROMETRIC STUDIES

Because of the very slight solubility of adamantanecarboxylic acid, we could not measure ^{13}C nmr spectra of this system, and so only Cy–A^- systems are discussed. The ^{13}C nmr spectra of 5% D_2O (v : v aqueous) solutions containing Cy (0–0.1 *F*) and A^- (0.04–0.09 *F*) consist of six resonance lines expected from nonequivalent carbons of Cy and five lines corresponding to the anion. Assignments of substrate resonances are consistent with symmetry factors, additivity correlations and relative relaxation rates of methylene vs methine nuclei (*13*). Conductometric and pH potentiometric estimates of $\log K_{CyA} = 2.5$ and $\log K_{Cy_2A} = 0.5$ (at 30° C) were treated as known parameters to obtain $\delta_0^{(Cy)}$, $\delta_1^{(Cy)}$, $\delta_2^{(Cy)}$, $\delta_0^{(A^-)}$, $\delta_1^{(A^-)}$, and $\delta_2^{(A^-)}$ intrinsic chemical shifts by previously reported computational methods (*11*), and the results of these calculations are listed in Table 6. The

TABLE 5

STANDARD THERMODYNAMIC PARAMETERS CALCULATED FROM TEMPERATURE DEPENDENCES OF THE EQUILIBRIUM CONSTANTS

	$\Delta H°$ (kcal mol^{-1})	± Uncertainties		$\Delta S°$ (cal mol^{-1} K^{-1})	± Uncertainties	
		Statistical[c]	Maximum[d]		Statistical[c]	Maximum[d]
Acid dissociation[a]	−0.8	0.6	0.6	−26	2	3
CyA$^-$ formation[b]	−3.4	0.6	1.2	−1.3	1.9	1.8
CyHA formation[a]	−5.6	0.7	1.6	−9	2	4
Cy$_2$HA stepwise[a] formation	−9.5	0.6	1.2	−19	2	4

[a] Calculated from data given in Table 2.
[b] Calculated from data given in Table 1.
[c] Standard error estimates of least-squares line parameters.
[d] Propagated maximum probable errors due to sources listed in Tables 3 and 4.

following discussion of resonance displacements in binary and ternary complexes deals firstly with A$^-$ and then with Cy carbons.

A$^-$ Resonance Displacements

Formation of the binary complex does not perturb the C1, C2 resonances ($\Delta\delta_1^{(A-1)} = -0.03$ and $\Delta\delta_1^{(A-2)} = 0.01$ ppm), but these are appreciably displaced in

TABLE 6

^{13}C nmr DISPLACEMENTS[a] OF Cy AND A$^-$ CARBONS IN BINARY[b] AND TERNARY[c] COMPLEXES

Cy				A$^-$			
C No.	$\delta_0^{(Cy)}$	$\Delta\delta_1^{(Cy)}$	$\Delta\delta_2^{(Cy)}$	C No.	$\delta_0^{(A-)}$	$\Delta\delta_1^{(A-)}$	$\Delta\delta_2^{(A-)}$
1	102.41	0.25	0.03	α[d]	189.15	−0.77	−1.57
2	72.88	0.11	0.19	1	43.26	−0.03	−0.31
3	74.47	0.08	0.01	2	40.64	0.01	0.39
4	82.26	0.12	0.22	3	37.38	0.43	0.80
5	73.07	0.16	0.08	4	29.22	−0.02	−0.06
6	61.59	−0.10	0.47				
SE	0.020	0.036	0.17		0.017	0.045	0.22
rms fit		0.007				0.009	

log $K_{CyA} = 2.15$; log $K_{Cy_2A} = 0.50$ fixed at values obtained from conductometric and potentiometric methods

[a] $\Delta\delta_n = \delta_n - \delta_0$, ppm. Negative numbers correspond to upfield displacements.
[b] Designated by $n = 1$ subscript.
[c] Designated by $n = 2$ subscript.
[d] Carboxylate carbon.

the ternary complex (−0.31 and 0.39 ppm, respectively). Similarly, perturbation of the carboxylate carbon increases from −0.77 ppm in the binary complex to −1.57 ppm in the ternary. This pattern suggests that the carboxylate terminal of A^- interacts more strongly with Cy in the ternary than in the binary adduct. Earlier ^{13}C nmr studies with carboxylic acids and their anions seem to indicate that insertion of a carboxylate terminal into the Cy cavity results in a displacement of about −3 ppm, but much smaller perturbations result when the carboxylate group is external to the Cy cavity. For example the ternary Cy complexes of 4-biphenylcarboxylate (*9*) and *p*-methylcinnamate (*10*) feature carboxylate $\Delta\delta$ values of about −3 ppm; but the Cy, benzoate complex (*11*), in which the phenyl ring is preferentially bound, displaces the carboxylate resonance by only −0.76 ppm. Consequently, we interpret the observed $\Delta\delta^{(A^-\alpha)}$ values as a binary complex in which the hydrocarbon terminus is proximal to Cy and a ternary complex where the A^- substrate is occluded between two Cy molecules. The $\Delta\delta_2^{(A^-\alpha)}$ value of only −1.57 ppm obtained in this case compared with the −3 ppm values cited above is probably due to the bulky adamantyl group preventing deep carboxylate insertion into the Cy cavity.

These conclusions seem to be supported by the substantial $\Delta\delta_1^{(A^-3)}$ value which indicates binding at the hydrocarbon terminal in the binary complex. The increased perturbation at C3 in the ternary complex presumably results from tighter binding. The lack of C4 displacements in both the binary and ternary complexes is difficult to interpret and may result from counterbalancing interactions.

Cy Resonance Displacements

The $\Delta\delta_1^{(Cy)}$ values listed in Table 6 do not seem to indicate a preferential Cy binding site in the binary complex. Values of $\Delta\delta_1^{(Cy2)}$ and $\Delta\delta_1^{(Cy3)}$ corresponding to perturbations at the wide Cy cavity are comparable to $\Delta\delta_1^{(Cy5)}$ and $\Delta\delta_1^{(Cy6)}$, which imply proximity to Cy5, Cy6 carbons at the narrow Cy cavity. Instead, it seems likely that the CyA^- complex is a mixture of head (wide rim, 2°-hydroxyl) and tail (narrow rim, 1°-hydroxyl) structures each bound to the adamantyl terminal of A^-.

Interpretation of $\Delta\delta_2^{(Cy)}$ values is made difficult by the rather large uncertainty in these parameters which result from the small formation constant. It does seem likely, however, that at least one Cy tail is involved in binding the ternary complex, because the C6 carbon resonance is substantially displaced in Cy_2A^- ($\Delta\delta_2^{(Cy6)} = 0.47$ ppm). As a result, head-to-tail and tail-to-tail structures are possible, and we must leave open the question whether one of these isomers is dominant.

INTERPRETATIONS OF ΔH° AND ΔS° VALUES

We shall attempt to utilize information gained in this study together with patterns observed with other Cy complexes in our earlier work (*11*) to speculate on the binding mechanism of these complexes. But first, being unaware of previous determinations, we report as a by-product of this study, values of $\Delta H^\circ = -0.8 \pm 0.6$ kcal mol^{-1} and $\Delta S^\circ = -26 \pm 2$ cal mol^{-1} K^{-1} for the aqueous dissociation of 1-adamantanecarboxylic acid and note that these values are typical of other weak carboxylic acids (*14*) such as acetic, propionic, butyric, and isobutyric acids with ΔH° values of -0.1, -0.2, -0.7, and -0.8 kcal mol^{-1} and ΔS° values of -22, -23, -24, and -25 cal mol^{-1} K^{-1}, respectively. This observation will be useful in the ensuing discussion.

In recent work (Gelb, Schwartz, and Laufer, unpublished results) we have shown that precisely determined ΔH°, ΔS°, and $\Delta\delta^{(\mathrm{CY}\ 1)}$ values for binary Cy–substrate complexations are linearly correlated and that based on 20 complexes the $\Delta H^\circ/\Delta S^\circ$ ratio is 430 K determined with a 95% confidence interval of ± 24 K. The ΔH°, ΔS° correlation reflects the simultaneous effect of substrate binding on the energetics of the complexing pair and on the internal motion of the Cy macrostructure. A stronger Cy–substrate complex implies a stronger bond, leading to a more negative ΔH°, and also implies deeper penetration of substrate into the Cy cavity with consequent constraint of Cy motion and a more negative ΔS°. The ΔH°, $\Delta\delta^{(\mathrm{Cy}\ 1)}$ correlation reflects the energetics of complexation and the simultaneous effect of complexation on the relative orientations of the glucosyl residues which affects the magnetic environment of the conformationally sensitive C1. A stronger complex leads to a greater perturbation of the orientation of neighboring groups near the C1 atom, and hence, to a greater perturbation of the local field at that nucleus. With these interpretations in mind, we note that the binary CyA$^-$ complex deviates markedly from the ΔH°, ΔS° correlation but not from the ΔH°, $\Delta\delta^{(\mathrm{Cy}\ 1)}$ correlation. A complex having ΔH° of -3.4 kcal mol^{-1} would be expected to have ΔS° of about -7.5 but only -1.3 cal K^{-1} mol^{-1} is observed. This means that the internal motion of the Cy torus is not constrained as much as would be expected for a complex of this strength; and so we further interpret this to mean that the A$^-$ ion does not penetrate into the Cy cavity, as appears to happen with the other substrates we have studied. This interpretation is in agreement with Bender's (*5*) similar observation. Other corroborating evidence is (1) that space-filling models clearly show that the adamantyl group is much too bulky to enter the cavity and (2) the relatively small displacement $\Delta\delta_1^{(\alpha)}$ of the carboxylate carbon on A$^-$ indicates that the carboxylate group, which is small enough to enter the cavity, is oriented away from the Cy in the complex. We note that the ΔH°, $\Delta\delta^{(\mathrm{Cy}\ 1)}$ values for A$^-$ fit the correlation observed previously. A comparison with the binary complex Cy–benzoate ion is useful (*11*). ΔH°, ΔS°, and $\Delta\delta^{(\mathrm{CY}\ 1)}$ values of -3.9 ± 0.3, -8.4 ± 1.1, and 0.22 ± 0.06 compare with -3.4 ± 0.6, -1.3 ± 1.9, and 0.25 ± 0.04 of the CyA$^-$ complex, respectively. The near identity of ΔH°, $\Delta\delta^{(\mathrm{Cy}\ 1)}$ values implies that the reorientation of glucosyl residues about C1 is not associated with the depth of substrate penetration, but simply on the strength of substrate–Cy binding. The more negative ΔS° for the benzoate–Cy complex reflects a structure involving deeper insertion of the phenyl group into the Cy cavity with concurrent restraint of Cy internal motion.

While precise ΔH° and ΔS° values could not be determined for the ternary complex Cy$_2$A$^-$, the information that is available fits nicely with these ideas. The very small magnitude of $K_{\mathrm{Cy_2A^-}}$ indicates that the complex is quite weak and thus

$\Delta G°$ of formation is near zero. Also $K_{\mathrm{Cy_2A}}$ values do not seem to correlate with temperature, and so $\Delta S°$ and $\Delta H°$ must each be near zero also. The observed $\Delta\delta_2^{(\mathrm{Cy}\ 1)}$ is virtually zero; and so this very weak complex either leaves the Cl environment unperturbed, which seems the more likely case, or perturbs Cl on the two Cy molecules in opposite directions of similar magnitude—but such fortuitous cancellation is unlikely. In this ternary complex, the A^- carboxylate must be capped by one Cy but, as mentioned in the previous section, the observed $\Delta\delta_2^{(\alpha)} = -1.57$ ppm for this weak complex is much less than similar observations for carboxylates of other smaller complexed anions.

We note that for the CyHA complex, the $\Delta H°/\Delta S°$ ratio is about 620 K, which is somewhat above the 430 K observed with 20 other substrates. It would appear that the bulky adamantyl group prevents deep insertion of the carboxylic acid group; as $\Delta S° = -9$ eu mol^{-1} is not as negative, as would be expected on the basis of the correlation of the small substrates.

It is noteworthy that the $\Delta H°/\Delta S°$ for the ternary $\mathrm{Cy_2HA}$ complex is about 500 K, which is somewhat above the statistical uncertainty of 430 K. We hesitate to place much significance on this fact, because the correlation is based on binary complexes and so does not reflect any effects of Cy–Cy interactions on the entropics of the constituents as, indeed, must exist in this case. However, we might venture to suggest that $\Delta S° = -19$ eu mol^{-1} is as negative as it is for such a bulky substrate because of the additional constrictions on Cy internal motion by these Cy–Cy interactions.

A most significant result of this study is the determination of $\Delta S° = -1.3$ cal mol^{-1} K^{-1} for the complexation of 1-adamantanecarboxylate with α-cyclodextrin, which is at variance with the value $\pm 10 \pm 2$ cal mol^{-1} K^{-1} reported recently by Komiyama and Bender (*5*), who used different methodology. These authors interpret the large positive entropy change as confirming the "apolar" nature of the complex binding mechanism. Our determination casts some doubt on that interpretation; and considering the importance of the ramifications of this disagreement, we have taken pains to ensure the reliability of our value. Our conductance technique used solutions containing only the salt $\mathrm{Li^+A^-}$ and Cy and at concentrations sufficiently low that ternary complexes did not form. Furthermore, by excluding extraneous chemical species in solution we need not worry about other possible interactions of these with the principals, which interactions would inflict undetected systematic errors on the K_{CyA} values. Our detailed error analysis indicates that the statistical uncertainty, a standard error estimate of ±1.9 cal mol^{-1} K^{-1}, and the maximum probable propagated systematic error of ±1.8 cal mol^{-1} K^{-1}, fail to account for the observed discrepancy of more than 11 entropy units; and so the two discordant values cannot be attributed to predictable measurement errors in our two methods.

In addition to our negative $\Delta S°$ of complexation, other evidence exists casting doubt on the "apolar" binding mechanism, which involves the release of solvation water molecules from A^- or Cy or both. As mentioned earlier in this section, the standard entropy change for the dissociation of HA is typical of other weak carboxylic acids. Consequently, we must conclude that whatever the extent of hydration of HA and A^- solutes, these are similar to other carboxylic acids, say acetic acid and acetate ion. We prefer to think of the methyl group of acetic acid as relatively unhydrated, but admit the contrary possibility. Nevertheless, acetic acid dissociates with $\Delta S^\circ = -22$ cal mol^{-1} K^{-1}, and so it is unlikely that much hydration water is released from the methyl with this dissociation. Similarly, we are led to the conclusion that whatever the solvation structure of HA, it is not changed on dissociation either; and so HA and A^- must have virtually the same solvation. Yet, we observe $\Delta S^\circ = -9$ eu mol^{-1} for the formation of the CyHA and $\Delta S^\circ = -19$ eu mol^{-1} for the stepwise formation of Cy_2HA and note that at least one of these complexations must be between a Cy and the adamantyl group of HA. Clearly, the binding of Cy with adamantyl here cannot be substantially "apolar" in the sense of releasing solvation waters, because the entropy changes are too negative. Therefore, it is unlikely also that the binding of Cy with the adamantyl group of the anion A^- is apolar either. These results do not in themselves confirm any particular binding mechanism in formation of CyA^- or CyHA complexes. They do, however, tend to cast doubt on any mechanism requiring a large positive ΔS° in these reactions, such as those connected with extensive reorganization of solvent molecules.

EXPERIMENTAL

Samples of α-cyclodextrin were obtained from the Aldrich Chemical Company and were allowed to stand open to the atmosphere until attaining constant weight. Samples prepared in this way were used without further purification, gave no spurious ^{13}C nmr peaks under high S/N conditions (~200/1), and had satisfactory C,H analyses. 1-Adamantanecarboxylic acid samples, obtained from the same source, were first purified by neutralizing nearly boiling aqueous mixtures of the acid with NaOH to pH 10, followed by acidification of the boiling mixture to recover the acid, which was isolated by filtration. The white crystals of acid were converted to the lithium salt by addition of LiOH to a hot aqueous mixture of the acid to pH 10. The lithium salt was collected and recrystallized from water and dried *in vacuo*. Analyses by pH potentiometric titration with standard HCl indicated purities of 99.7–99.9%. Stock solutions of LiA for conductance experiments were prepared directly from the purified salt and their concentrations rechecked by titration. HA, A^- solutions for pH potentiometry were prepared by partial acidification of LiA solutions with HCl and the concentrations of both HA and A^- were confirmed by titrations with NaOH and with HCl.

An Orion 801 pH meter equipped with conventional glass and reference electrodes was employed for pH measurements after standardization with 0.05 *m* potassium hydrogen phthalate at the appropriate temperature. Solutions were continuously purged with nitrogen to exclude atmospheric CO_2.

Conductance measurements were made with the aid of a General Radio Bridge equipped with a dip-type conductance cell. Special care was taken to ensure thermal equilibration after each addition of 0.1 *F* Cy solution. We followed the same practices as employed in our earlier conductometric experiments (*1*, *9*).

Measurements with a number of LiA solutions between 5 and 50 m*F* gave consistent values of $\lambda^{\circ}_{A^-}$ confirming that the salt is completely ionized in water and that the identity of the cation does not play a role in our conclusions. Additionally, no ion association involving Cy,A^- complexes could be detected.

^{13}C nmr spectra in 5% D_2O (v/v) solution were obtained with a Varian CFT-20 nuclear magnetic resonance spectrometer under conditions similar to those described previously (*2, 11*).

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