Binding Mechanisms in Cyclohexaamylose Complexes

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Abstract: Formation constants for binary complexes of cyclohexaamylose (Cy) with alkanoic/alkanoate, meta,para-substituted phenol/phenolate, and benzoic/benzoate acid/base substrates are determined by means of pH potentiometry and visible spectrophotometry. Thermodynamic parameters $\Delta H°$ and $\Delta S°$ are extracted from the temperature dependences of these constants and together with ^{13}C NMR measurements are utilized to estimate intrinsic ^{13}C chemical shifts for adduct species. Interpretation of these NMR shifts indicates that meta and para cyano, nitro, and carboxylic acid substituents are preferentially bound in the C5–C6 zone of the Cy cavity. Observed linear correlations of $\Delta H°$ vs. $\Delta S°$ and displacements of anomeric C1 resonance vs. $\Delta H°$ data sets are discussed in terms of dipolar interactions which appear to be the main binding force in these reactions.

Cyclohexaamylose, to be denoted here as Cy, and its derivatives form complexes with a large number of organic and inorganic molecules and anions in aqueous solution.[1,2] In recent years the structural,[3,4] thermodynamic,[5,6] and dynamic[7,8] properties of these complexes have been the subjects of numerous investigations. The importance of these complexes and their properties is related to their mimicry of biological enzyme systems. Thus, the rates and mechanisms of numerous Cy-catalyzed reactions, for example, ester hydrolyses,[9,10] have been studied.

The purpose of our research is to obtain an understanding of the binding forces which operate in these systems and their relationship to steric and electronic structural factors. An interesting illustration of this phenomenology is the differing behavior of *m*- and *p*-phenylene substrates in Cy complexation reactions. Both 3- and 4-nitrophenyl acetates appear to have comparable complexation constants with Cy, but only hydrolysis of the meta-substituted ester is appreciably catalyzed by Cy.[9a] Apparently the catalytic activity results from the proximity of the meta ester carbonyl with nucleophilic secondary hydroxylate groups of Cy in the complex, while para ester carbonyl groups are too far removed from the catalytic sites.[9b] It seemed that a comparative study of the structural and thermodynamic properties of a variety of such substrates would be a useful starting point in investigating the nature of steric effects in Cy complexations.

In this work we report a study of the Cy complexes of *m*- and *p*-hydroxybenzoic acids (MHBA and PHBA), *m*- and *p*-nitrobenzoic acids (MNBA and PNBA), *m*- and *p*-nitrophenols (MNP and PNP), *m*- and *p*-cyanophenols (MCP and PCP), propionic acid (PA), cyclohexanecarboxylic acid (CHCA), trimethylacetic acid (TMA), and the corresponding conjugate bases $MBHA^-$, $PHBA^-$, etc. (Our abbreviation system for substrates is to use an acronym derived from the common chemical name and to distinguish anions by appending a charge symbol. For example, BA is benzoic acid and BA^- is benzoate anion.) We have measured the formation constants of Cy complexes of these substrates at various temperatures and from their temperature dependences have calculated values for the thermodynamic parameters $\Delta H°$ and $\Delta S°$. Then we utilize these thermodynamic results together with ^{13}C NMR chemical shift measurements to estimate intrinsic chemical shifts for the complex species from which we deduce structural information. Also we have observed correlations between the thermodynamic data and ^{13}C NMR chemical shift displacements and will attempt to interpret these correlations in terms of bonding and steric factors.

Estimation of Formation Constants and Thermodynamic Parameters

Cy formation constant values with the various substrate species studied here were obtained with either of two methodologies. The first of these is a pH potentiometric technique described in detail elsewhere.[11-13] Briefly, this involves measurement of the pH of a solution composed of an acidic substrate species AH and its conjugate base A^-. Portions of Cy are added to the solution, and the pH value varies depending on the relative affinities of the acid and conjugate base for Cy. Model equations describing the acid/base and complexation equilibria are fitted to the data with the aid of a computer program which also provides estimates of the statistical uncertainties of the derived equilibrium constants. We monitor the validities of the model equations and complexation stoichiometries by observing the "quality of fit" and absence of trend in the residuals, the differences between calculated and experimental data.

The second method involves spectrophotometric measurements with acidic substrates and their conjugate bases in solutions which are buffered at a pH value near pK_a of the chromophoric acid/base pair and in the presence of differing Cy concentrations. The measurement relies on both the different absorptivities of the acid and conjugate base at a given wavelength of incident radiation and on the relative affinities of the conjugate acid/base species for Cy. Experimental details and computational strategies have been described previously.[14]

Estimates of complex formation constants and their uncertainties appear in Table I. In these calculations we obtained activity coefficient estimates from the Debye-Hückel equation $\log \gamma_i = -Az_i^2 I^{1/2}/(1 + BaI^{1/2})$ where the temperature-dependent parameters A and B were obtained from the Robinson and Stokes tabulation.[15] The "ion-size" parameter a was uniformly taken as 0.9 nm for H_3O^+ and 1.2 nm for anionic Cy complexes. Values of a for uncomplexed substrate ions were taken as 0.7 nm except for PA^- and TMA^- which were 0.4 and 0.6, respectively. The

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Table I. Formation Constants of CyAH and CyA^- Complexes at Various Temperatures Measured by pH Potentiometry

substrate	T, °C	K_{CyAH}[a]	SE[b]	K_{CyA^-}[c]	SE[b]
p-hydroxybenzoic acid (PHBA)	15	3710	115	17.2	0.5
	25	1032	7	11.5	0.1
	30	752	3	9.7	0.1
	40	416	1	7.0	0.1
	49.5	262	5	6.5	0.3
p-cyanophenol (PCP)	15	204	1	838	4
	25	140	1	632	5
	35	94	1	399	1
	45	77	1	275	2
p-nitrobenzoic acid (PNBA)	5	576	7.5	21	2.4
	15	490	50	75	18
	30	172	2	27.4	0.4
	40	114	18	25	13
m-hydroxybenzoic acid (MHBA)	20	678	2	6.8	1.2
	30	353	3	3.4	0.3
	50	108	3	0.4	0.6
m-cyanophenol (MCP)	25	95	1	479	1
	35	71	1	307	2
	45	50	1	190	1
m-nitrobenzoic acid (MNBA)	20	152	15	50	9
	30	105	2	42.4	0.6
	40	66	6	29	4
	50	37	8	16	6
m-nitrophenol (MNP)	20	152	5	328	9
	30	79	4	171	7
	45	43	2	90	4
	55	29	5	60	8
propionic acid (PA)	15	47.3	0.4		
	30	31.1	0.3		
	45	20.3	0.2		
cyclohexanecarboxylic acid (CHCA)	15	87.1	0.5		
	25	50.2	0.3		
	30	38.8	0.3		
	40	23.9	0.2		
	50	13.9	0.2		
trimethylacetic acid (TMA)	15	18.7	0.5	25.6[d]	1.3
	25	15.3	0.4	15.8[d]	0.9
	30	13.7	0.5	13.7[d]	1.2
	40	9.3	0.4	10.6[d]	1.2

[a] CyAH binary complex formation constants. [b] Standard error estimate in K. [c] CyA^- binary complex formation constants. [d] Cy_2TMA stepwise ternary formation constant.

ionic strength was always less than 0.01 M in the pH potentiometric experiments and was 0.15 M in the spectrophotometric experiments.

With the assumption of exclusively binary (1:1 stoichiometry) Cy substrate complexes, our model equations were able to fit the experimental data in all cases (except TMA) to within our a priori estimates of ±0.002 pH and ±0.4 mg of Cy in the pH potentiometric experiments and ±0.005 absorbance unit in the spectrophotometric measurements. In addition, the patterns of residuals appeared to be randomly scattered and free from systematic trends. However, in the case of TMA the data could not be fit until the existence of a ternary Cy_2TMA complex was also assumed by the model equations. In the cases of MHBA, PNBA, and MNBA, it was possible to obtain proper fits by assuming both CyAH and CyA^- binary complexes but each CyA^- adduct turned out to be extremely weak relative to the corresponding CyAH complex. In situations such as this the formation constant of the weaker complex is not accurately determined by the fit of the model equations to the data. Therefore, we have entered the K_{CyA^-} values in Table I, but no further quantitative conclusions will be drawn from them. The weak CyA^- binary complexes are simply reported to exist.

Values of $\Delta H°$ and $\Delta S°$ for these complexation reactions were obtained from the temperature-dependent equilibrium constant data in Table I with the aid of the thermodynamic relations $(\partial RT \ln K/\partial T)_P = \Delta S°$ and $(\partial R \ln K/\partial T^{-1})_P = -\Delta H°$. Van't Hoff plots of $RT \ln K$ vs. T and $R \ln K$ vs. T^{-1} were always linear, and so we conclude that $\Delta H°$ and $\Delta S°$ are each essentially constant in the temperature range of our experiments. Uncertainties in these values are derived from the root-mean-square scatter of $RT \ln K$ or $R \ln K$ points about the least-squares lines and are included with $\Delta H°$ and $\Delta S°$ values in Table II. Values of the thermodynamic functions for a number of related Cy complexation reactions are listed there for the sake of comparison.

It is fairly evident that a correlation exists between the $\Delta H°$ and $\Delta S°$ values listed in Table II; the plot in Figure 1 confirms the correlation and shows that it is linear. We believe that ternary complexes should be excluded from this correlation since these presumably involve Cy·Cy interactions as well as the cyclohexaamylose·substrate interactions present in binary complexes. For reasons which will be explained later we exclude the binary complexes of 1-adamantanecarboxylate and cyclohexanecarboxylic acid as well. But 20 complexes remain to be included, and this

Table II. Standard Formation Enthalpies and Entropies of CyAH and CyA^- Complexes

substrate	abbreviation	$-\Delta H°_{CyAH}$[a]	SE[b]	$-\Delta S°_{CyAH}$[c]	SE[b]	$-\Delta H°_{CyA^-}$[a]	SE[b]	$-\Delta S°_{CyA^-}$[c]	SE[b]	ref
formic acid	FA	0.74	0.11	−0.3	0.4					11
acetic acid	AA	2.68	0.03	4.5	1					11
		1.2	0.1	−13						5
propionic acid	PA	5.14	0.07	10.0	0.2					
cyclohexanecarboxylic acid	CHCA	9.44	0.06	23.9	0.2					
trimethylacetic acid	TMA	4.7	0.4	10.3	1.2					
		(6.2	0.74	17.2	2.5)[d]					
adamantanecarboxylic acid	ACA	5.6	0.7	9.	2	3.4	0.6	1.3	1.9	16
		(9.5	0.6	19.	2.)[e]					16
						1.2	0.4	−10	2	17
benzoic acid	BA	10.15	0.15	20.9	0.5	3.9	0.3	8.4	1.1	11
		9.6	0.1	18						5
p-hydroxybenzoic acid	PHBA	11.6	0.06	25.1	0.2	6.1	0.16	15.5	0.5	
p-nitrophenol	PNP	(7.3	0.3	14	1	11.2	0.4	22	1)[f]	14
		7.3	1.5	15						5
		7.2	0.2	13.4	0.7					6
		4.2		1.3		7.2		8.9		18
p-cyanophenol	PCP	6.1	0.5	10.4	1.6	6.9	0.5	10.6	1.7	
p-nitrobenzoic acid	PNBA	8.1	0.1	16.5	0.4					
m-hydroxybenzoic acid	MHBA	11.5	0.1	26.4	0.4					
m-nitrophenol	MNP	9.0	0.6	20.7	1.7	9.2	0.4	20.0	1.4	
		7.9	0.2	16.7	1					6
m-cyanophenol	MCP	6.1	0.4	11.5	1.3	8.7	0.4	17.0	1.2	
m-nitrobenzoic	MNBA	8.4	1.0	18.5	3.4					

[a] kcal mol^{-1}. [b] Standard error estimates. [c] cal K^{-1} mol^{-1}. [d] For stepwise formation of Cy_2TMA ternary complex. [e] For stepwise formation of Cy_2ACA ternary complex. [f] By spectrophotometry. All other data are by pH potentiometry.

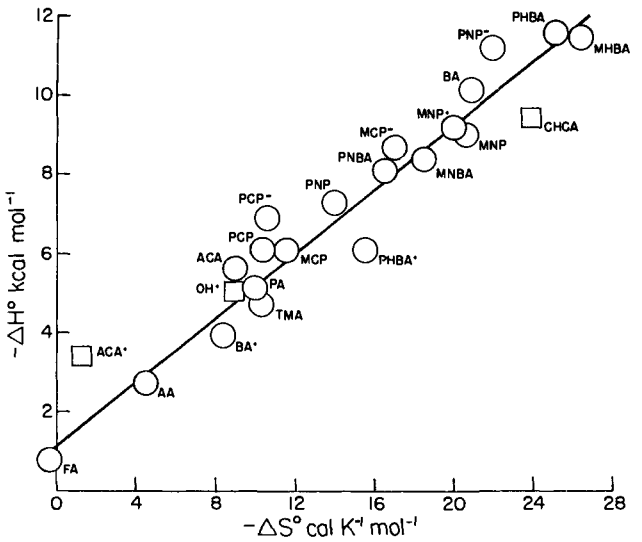

Figure 1. Correlation of $\Delta H°$ vs. $\Delta S°$ parameters for cyclohexaamylose complexations. The line drawn represents a least-squares fit, $\Delta H° = (403 \pm 24\ \text{K})\Delta S° - (1.2 \pm 0.4)10^3$ cal mol^{-1}, to 20 substrate systems denoted by circles. Points denoted by squares were not included in this correlation.

is a sufficiently large set of data to yield conclusions that are statistically meaningful.

Other correlations of the type $\Delta H°$ vs. $\Delta S°$ are well-known in other applications of thermodynamics and chemical kinetics,[19,20] and an extensive literature exists warning that experimental error rather than chemical effects may be at the root of such correlations. The article of Krug et al.[21] gives a detailed analysis of the problem and offers a statistical test by which a given linear $\Delta H°$ vs. $\Delta S°$ regression can be judged to be due to experimental error or to valid chemical effects. In our case a linear regression of $\Delta H°$ (in cal mol^{-1}) vs. $\Delta S°$ based on 20 binary complexes yields a slope of 403 K and an intercept on the $\Delta H°$ axis of -1.2×10^3 cal mol^{-1}. This slope is called the "compensation temperature" and is denoted by T_c. The standard error estimates are 24 K and 0.4×10^3 cal mol^{-1} for the slope and intercept, respectively. Krug et al.[21] show that if the correlation were due to statistical experimental error alone, a straight line with slope T_{hm} would result, where T_{hm} is the harmonic mean of the temperatures of the K vs. T data used to construct the Van't Hoff plots leading to the $\Delta H°$ and $\Delta S°$ values. Our temperatures typically varied from 288 to 328 K, and so an average $T_{hm} = 305 \pm 5$ K is appropriate to these experiments. Although our slope of 403 K seems far removed from T_{hm}, it is conceivable that this difference might be attributed to random fluctuations, and to test this hypothesis, we calculate 95% confidence limits for the observed slope. Following Krug et al.[21] we find $t_{18,0.025} = 2.10$ and 95% confidence limits for the slope = $403 \pm (2.10)(24) = 455$ and 352 K. Thus we can assert with 95% confidence that observed slopes between 455 and 352 K can be due to statistical error. Our $T_{hm} = 305$ K is well below this interval, and so we are well justified in asserting that our observed $\Delta H°$ vs. $\Delta S°$ correlation is due to chemical effects inherent in these complexes.

The value of T_c obtained here is to be compared with two other values reported earlier, 265[5] and 427 K.[22] There is reason to doubt both these values since some of the $\Delta H°$ and $\Delta S°$ values used in the correlations have since been shown to be grossly inaccurate.[11,23] The second value is remarkably close to ours, but the coincidence may be fortuitous since complex formation constants used in the earlier work were determined by assuming binary complex formation between Cy and the para-substituted cinnamate anions. This has been shown to be incorrect for *p*-methylcinnamate anion[23] and with other cinnamic acids.[24,25]

We interpret the correlation observed here as implying a single interaction mechanism between Cy and the various substrates. Such an interaction mechanism must of necessity be divorced from the wide range of structurally varied substrate species and so must be associated with some common attribute of these systems, the solvent H_2O or the host Cy. However, since our observed T_c is well outside the 250–320 K range characteristic of processes dominated by aquation phenomena,[20] we associate this $\Delta H°$ vs. $\Delta S°$ with some feature of the Cy molecule. In other words, we hypothesize that all 20 substrates with their various functional groups and their differing electrical charges all form complexes with Cy by the same fundamental mechanism and that this common mechanism leads to substrate–host bonds all of the same type but differing only in relative strength as reflected by the $\Delta H°$ values. Furthermore, that mechanism does not involve changes in aquation, the interaction is not accompanied by net stripping of water molecules from the substrate nor the exclusion of water from the Cy cavity as previously suggested.[26-28]

The following observation casts an interesting sidelight on this correlation and the common interaction mechanism suggested by it. If we wished to detect the formation of a complex between Cy and hydroxide ion, we would combine aqueous solutions of Cy and NaOH and then determine the extent of OH^- inclusion according to eq 1, by measuring the pH of the equilibrium mixture.

$$\text{Cy(aq)} + \text{OH}^-\text{(aq)} = \text{CyOH}^-\text{(aq)} \quad (1)$$

This pH in conjunction with known analytical concentrations determines K_{CyOH^-}, and the temperature dependence of K_{CyOH^-} determines $\Delta H°$ and $\Delta S°$ for this reaction. In fact, we have already carried out and reported the results of these experiments,[29] but in that communication we envisaged the reaction occurring to be eq 2 instead, i.e., the ionization of Cy as an acid. We found

$$\text{Cy(aq)} = \text{Cy}^-\text{(aq)} + \text{H}^+\text{(aq)} \quad (2)$$

$\Delta H° = 8.4 \pm 0.4$ kcal mol^{-1} and $\Delta S° = -28 \pm 1$ cal mol^{-1} K^{-1} for this ionization. Clearly, no further experimentation is necessary to find K_{CyOH^-} and its thermodynamic parameters. If the reaction $H^+(aq) + OH^-(aq) = H_2O$ for which $\Delta H° = -13.36$ kcal mol^{-1} and $\Delta S° = 19.3$ cal mol^{-1} K^{-1} [30] is added to reaction 2, the result is

$$\text{Cy(aq)} + \text{OH}^-\text{(aq)} = \text{Cy}^-\text{(aq)} + \text{H}_2\text{O} \quad (3)$$

for which $\Delta H° = -5.0 \pm 0.4$ kcal mol^{-1} and $\Delta S° = -9 \pm 1$ cal mol^{-1} K^{-1}. Reaction 3 is indistinguishable from reaction 1 by pH potentiometry alone because neither the structure of the anion $CyOH^-$ with an hydroxide ion substrate in its cavity nor the structure of the anion Cy^-, whose formula implies no guest within the cavity, has an effect on solution pH. Yet the thermodynamic parameters for reaction 3 fall on our correlation line to within the statistical uncertainty of that line. We interpret this observation to mean that the interaction of aqueous hydroxide ion with Cy is the same as the other 20 substrates used for the correlation. Furthermore, since it is unlikely that the strongly aquated hydroxide ion is stripped of its water molecules in forming this complex, the existence of a $CyOH^-$ complex in the group of 21 binary complexes falling on the correlation line lends further

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weight to our hypothesis that deaquation is not an important mechanism in forming these complexes.

If the interaction mechanism that gives rise to the $\Delta H°$ vs. $\Delta S°$ correlation is not deaquation, then it must be associated with changes in the conformation and motion of the glucosyl residues and perhaps with changes in interglucosyl hydrogen bonding in the Cy molecule alone. In an effort to probe further into these structural changes, we obtained ^{13}C NMR spectra of a large number of the complexation systems discussed here.

^{13}C NMR Spectrometric Results

The ^{13}C NMR spectra of 5% D_2O (v/v aqueous) solutions containing substrate species and Cy consist of resonance lines corresponding to six nonequivalent Cy carbons and the expected number of lines due to substrate species. No additional lines beyond these could be detected above the noise level. Assignments of substrate resonances given in Table III are consistent with symmetry factors, relative relaxation rates of protonated vs. unprotonated carbons, and approximate additivity of substituent displacements.[31] Earlier communications[11,32] should be consulted for details of the methods by which we determine ^{13}C NMR resonance displacements due to complexation reactions in these systems. Our notation is as follows. The experimentally observed chemical shifts are denoted by the symbols $\delta_{obsd}{}^{Cyn}$, $\delta_{obsd}{}^{AHn}$, or $\delta_{obsd}{}^{A^-n}$ where the integer n (or other symbol α, β, etc.) refers to a particular carbon in the species indicated. However, we are interested rather in the unknown intrinsic resonances symbolized by $\delta_0{}^{Cyn}$, $\delta_0{}^{AHn}$, or $\delta_0{}^{A^-n}$ in the uncomplexed species and by $\delta_1{}^{Cyn}$, $\delta_1{}^{AHn}$, or $\delta_1{}^{A^-n}$ in the bound species. The subscript 1 denotes a binary complex. These intrinsic resonances are extracted from δ_{obsd} measurements made with solutions having known analytical concentrations F_{Cy}, F_{AH}, and F_{A^-} by sets of model equations expressing the equilibrium and conservation relationships involved. Values of the intrinsic chemical shift parameters and their uncertainties result from a multiple linear regression analysis. In these experiments, F_{Cy} typically ranged from 0.02 to 0.1 M, and F_{AH} or F_{A^-} was between 0.02 and 0.15 M where the lesser A^- or AH concentrations were due to limited solubilities. Complexation constants required in these calculations were obtained either directly from independent potentiometric or spectrophotometric measurements at the appropriate temperature or from a calculation based on previously known $\Delta H°$ and $\Delta S°$ values. It was assumed throughout that aqueous complexation constants could be adequately applied to the 5% D_2O/H_2O mixtures used here.

The results of our experiments appear in Tables III and IV. Also, for the sake of completeness we show in these tables the earlier reported values for 1-adamantanecarboxylate and benzoate anions and formic, acetic, and benzoic acids. We report here chemical shift displacements due to complexation; i.e., $\Delta\delta_1 \equiv \delta_1 - \delta_0$ for each resonance.

However, before proceeding to draw conclusions from these data, we wish to interject here a brief discussion concerning possible isomeric forms of Cy complexes, a possibility noted in earlier work.[23] While we cannot preclude the existence of such complexes on direct experimental grounds, we interpret our data to indicate that isomeric forms are remote possibilities. First, ^1H NOE experiments[4,33] clearly demonstrate that single structures featuring CO_2H and NO_2 entries from the secondary hydroxyl end exist for both BA and PNP^- binary complexes with Cy. The resonance displacements $\Delta\delta_1{}^{Cy6}$ for these complexes are −0.44 and −0.52 ppm, respectively. Our results in Table IV show that all $\Delta\delta_1{}^{Cy6}$ displacements for complexes involving CO_2H and NO_2 (as well as CN) insertions have very similar values. If these values represent the weighted average of intrinsic displacements of two isomeric forms, then (i) the isomeric ratios in each case are essentially the same and (ii) the intrinsic displacements of the two isomers are the same. As seen from Tables I and II, the various substrates have quite different affinities for Cy. Thus, the possibility that they have the same isomeric ratios is very unlikely. Also, these substrates feature widely variant electronic structures. It is equally unlikely that interactions of each member of a given isomeric pair with Cy would yield equal resonance displacements. Similar arguments can be advanced for our substrate resonance results; therefore the following discussion of chemical shift displacements is based on the supposition of a single dominant complex species. This discussion is divided into two principal parts, the first of which deals with substrates and the second with Cy.

Displacements of Substrate Resonances

Cy·RCO_2H and Cy·RCO_2^- Complexes. Because of the low solubility of PA, CHCA, TMA, and ACA complexes, we were unable to detect ^{13}C NMR signals for substrate carbons in these systems. The C1 displacements of −2.10 and −2.45 ppm of FA and AA reflect inclusion of these molecules into the Cy cavity.[11] In contrast to these neutral carboxylic acids the anions ACA^- and BA^- seem to bind Cy with the solvated group directed away from the Cy cavity.[11,16] No complexes were detected with PA^-, TMA^-, or CHA^- anions.

Cyclohexaamylose-*p*-Phenylene Complexes. Earlier ^1H and ^{13}C NMR studies[4,33] have shown that BA, PNP, and PNP^- complexes of Cy involve insertion of the carboxylic acid or nitro group into the cavity. This orientation is reflected by the shielding of included ipso carbons ($\Delta\delta_1{}^{BA1}$ −1.18, $\Delta\delta_1{}^{PNP4}$ −1.21, and $\Delta\delta_1{}^{PNP^-4}$ −1.13) compared with deshielding of corresponding para carbons ($\Delta\delta_1{}^{BA4}$ 0.93, $\Delta\delta_1{}^{PNP1}$ 1.88, and $\Delta\delta_1{}^{PNP^-1}$ 1.17). These opposed displacements imply the magnitudes and directions of electric fields induced in these aromatic substrates by the Cy cavity. We note similar patterns of displacements with PHBA ($\Delta\delta_1{}^{PHBA1}$ −0.78 and $\Delta\delta_1{}^{PHBA4}$ 0.72) and further that $\Delta\delta_1{}^{PHBA\alpha}$ −1.65 is similar to the value of $\Delta\delta_1{}^{BA\alpha}$ −1.70 and conclude that the carboxylic acid group of PHBA is directed into the Cy cavity in this complex. In a similar fashion the displacements of C4 and C1 of $PNBA^-$ of −1.18 and 2.13 ppm, respectively, which are markedly close to the corresponding displacements of −1.21 and 1.88 ppm in PNP, suggest insertion of the nitro group in the Cy·$PNBA^-$ complex as has been suggested for the Cy·PNP complex.[33] The displacement of the $PNBA^-$ carboxylate carbon (−1.40 ppm) is considerably smaller than the −3-ppm displacement of carboxylate anions occluded in the Cy cavity in the ternary 4-biphenylcarboxylate[36] and *p*-methylcinnamate[23] and is consistent with an orientation where the CO_2^- terminal of $PNBA^-$ is directed away from Cy. In view of the foregoing trends in substrate orientation, i.e., insertion of carboxylic acid and nitro groups into the Cy cavity, we sought information on the structure of the PNBA complex. However, the low solubility of PNBA and the relatively long relaxation times of unprotonated PNBA carbons did not allow satisfactory measurement of the ^{13}C NMR spectra required. Work is in progress to resolve the structure of this interesting complex.

Values of C4 and C1 displacements in PCP and PCP^- ($\Delta\delta^{PCP4}$ −1.66, $\Delta\delta_1{}^{PCP1}$ 1.40, $\Delta\delta_1{}^{PCP^-4}$ −0.59, and $\Delta\delta_1{}^{PCP^-1}$ 0.87) along with shielding of the cyano carbons ($\Delta\delta_1{}^{PCP\alpha}$ −0.69 and $\Delta\delta_1{}^{PCP^-\alpha}$ −0.70) indicate that the cyano group of these substrates is directed toward Cy in these complexes.

The BA^- complex features shielding of the para carbon ($\Delta\delta_1{}^{BA^-4}$ −0.65), deshielding of the ipso carbon ($\Delta\delta_1{}^{BA^-1}$ 0.49), and relatively weak shielding of the carboxylate (α) carbon ($\Delta\delta_1{}^{BA^-\alpha}$ −0.76), and we have interpreted this pattern in terms of inclusion of the phenyl ring rather than the carboxylate terminal.[11] The $PHBA^-$ complex seems likely to have the same orientation, and this is consistent with the small upfield displacement of the carboxylate carbon ($\Delta\delta_1{}^{PHBA^-\alpha}$ −0.77). However, the phenylene displacements at C1 and C4 ($\Delta\delta_1{}^{PHBA^-1}$ −1.08 and $\Delta\delta_1{}^{PHBA^-4}$ 1.21) do not have the expected polarity, and this may be due to perturbation of the

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(33) Bergeron, R. J.; Channing, M. A.; Gibeily, G. J.; Pillor, D. M. *J. Am. Chem. Soc.* **1977**, *99*, 5146–5151 and references cited therein.
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(35) Harata, K.; Vedaira, H.; Tanaka, J. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1627–1634.
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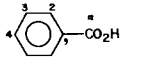
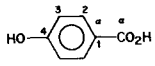
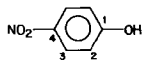
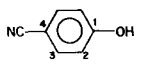
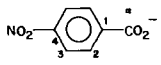
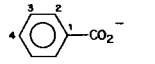
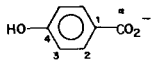
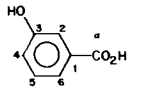
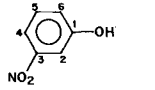
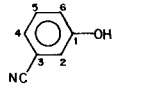
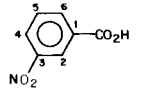
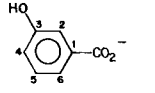
Table III. Intrinsic Displacements[a] of Unbound Substrate ^{13}C Resonances[b] in the CyAH or CyA^- Complexes

substrate		δ_0S^1	$\Delta\delta_1S^1$	δ_0S^2	$\Delta\delta_1S^2$	δ_0S^3	$\Delta\delta_1S^3$	δ_0S^4	$\Delta\delta_1S^4$	δ_0S^5	$\Delta\delta_1S^5$	δ_0S^6	$\Delta\delta_1S^6$	δ_0S^α	$\Delta\delta_1S^\alpha$	SE[c]	ref
FA	HCO_2H	166.88	−2.1														11
AA	CH_3CO_2H	177.78	−2.45	21.52	0.48												11
ACA^-		43.26	−0.03	40.64	0.01	37.83	0.43	29.22	−0.02					189.15	−0.77	0.04	16
BA		130.91	−1.18	130.64	1.59	120.74	−0.76	134.72	0.93					171.97	−1.70	0.05	11
PHBA		122.54	−0.78	133.21	1.70	116.48	−0.85	161.81	0.72					171.55	−1.65	0.03	
PNP		163.75	1.88	116.77	0.23	127.50	0.87	141.47	−1.21							0.03	
PNP^-		178.57	1.17	120.07	−0.39	128.97	1.43	134.91	−1.33							0.03	
PCP		161.44	1.40	117.39	0.30	135.76	−0.16	102.89	−1.66					121.59	−0.69	0.04	
PCP^-		173.18	0.87	120.71	−0.23	135.68	0.17	94.54	−0.59					124.00	−0.70	0.04	
$PNBA^-$		143.85	2.13	130.61	0.66	124.54	0.28	149.87	−1.18					174.45	−1.40	0.04	
BA^-		137.33	0.49	129.84[d]	0.52	129.34[d]	−0.52	132.24	−0.65					176.62	−0.76	0.07	11
$PHBA^-$		129.28	−1.08	132.28	0.34	116.05	0.22	159.69	1.21					176.24	−0.77	0.07	
MHBA		132.52	−1.19	117.22	2.00	156.81	0.64	121.78	0.73	131.15	−1.19	122.72	1.45	171.53	−1.26	0.03	
MNP		157.57	1.14	111.29	0.80	149.72	−0.71	116.37	0.18	131.49	−0.05	123.59	1.26			0.04	
MNP^-		168.23	0.21	110.35	0.97	150.33	−0.86	113.50	0.11	130.82	−0.35	127.44	1.50			0.03	
MCP		157.07	1.22	119.88[d]	0.21	112.87	−1.33	125.54	−0.33	131.81	0.19	122.13[d]	1.20	120.61	−0.27	0.04	
MCP^-		167.49	0.23	119.26	0.63	112.43	−1.59	122.83	−0.75	131.64	−0.29	125.85	1.21	122.07	−0.23	0.04	
MNBA		125.45	−0.49	130.43[d]	3.06	149.14	−0.34	131.79[d]	−0.85	128.67[d]	−0.97	136.74	1.40	169.32	−1.12	0.03	
$MNBA^-$		139.21	1.14	124.64	0.00	148.81	−0.77	126.64	−0.11	130.57	0.41	136.19	1.41	173.87	−0.78	0.04	
$MHBA^-$		130.35	0.10	116.76	1.03	156.64	0.73	119.29	−0.30	130.73	−0.79	121.99	−0.05	176.17	−0.39	0.14	

[a] $\Delta\delta_1S^n \equiv \delta_1S^n - \delta_0S^n$ in ppm. Sn superscripts refer to nonequivalent carbon index (n) of substrate S = AH or A^-. Negative signs indicate upfield displacements. [b] δ_0S^n in ppm downfield from external Me_4Si. [c] Standard errors of $\Delta\delta_1S^n$ values. [d] Tentative assignments.

Table IV. Intrinsic Displacements[a] of Unbound Cy ^{13}C Resonances[b] in the CyAH or CyA^- Complexes

substrate	$\Delta\delta_1^{Cy1}$	$\Delta\delta_1^{Cy2}$	$\Delta\delta_1^{Cy3}$	$\Delta\delta_1^{Cy4}$	$\Delta\delta_1^{Cy5}$	$\Delta\delta_1^{Cy6}$	SE	log $K_{30\,°C}$	ref
FA	0.05	0.10	0.10	−0.08	−0.36	−0.24	0.04	0.609	11
AA	0.16	0.01	0.15	−0.07	−0.26	−0.31	0.04	0.949	11
PA	0.30	0.14	0.23	0.05	−0.37	−0.42	0.07	1.493	
CHCA	0.58	0.16	0.44	0.30	−0.23	−0.40	0.06	1.589	
TMA	0.24	0.00	0.00	0.23	−0.03	−0.15	0.05	1.136	
ACA^-	0.25	0.11	0.08	0.12	0.16	−0.10	0.04	2.15	16
BA	0.46	0.11	0.24	0.04	−0.39	−0.44	0.03	2.766	11
PHBA	0.49	0.14	0.31	0.06	−0.51	−0.47	0.03	2.881	
PNP	0.42	−0.05	0.37	0.10	−0.20	−0.46	0.03	2.251	
PNP^-	0.49	0.26	0.27	−0.03	−0.29	−0.52	0.03	3.209	
PCP	0.37	−0.11	0.34	0.01	−0.02	−0.41	0.04	2.105	
PCP^-	0.39	0.19	0.21	−0.15	−0.04	−0.44	0.04	2.701	
$PNBA^-$	0.50	0.11	0.39	0.03	−0.12	−0.43	0.03	1.437	
BA^-	0.22	0.18	−0.02	0.12	0.13	0.05	0.06	0.986	11
$PHBA^-$	0.32	0.36	0.10	0.28	−0.01	0.05	0.06	0.987	
MHBA	0.47	0.21	0.11	0.14	−0.50	−0.43	0.03	2.548	
MNP	0.42	0.02	0.25	0.14	−0.15	−0.42	0.03	2.11	
MNP^-	0.38	0.16	−0.02	0.21	−0.13	−0.25	0.03	2.40	
MCP	0.38	−0.06	0.25	0.06	0.01	−0.41	0.04	1.901	
MCP^-	0.41	−0.13	0.09	0.10	−0.06	−0.38	0.04	2.624	
MNBA	0.41	−0.04	0.40	0.23	−0.31	−0.27	0.04	2.021	
$MNBA^-$	0.25	0.13	0.24	0.11	−0.14	−0.17	0.04	1.626	
$MHBA^-$	0.21	0.34	0.06	0.32	0.12	0.18	0.13	0.53	

[a] $\Delta\delta_1^{Cyn} \equiv \delta_1^{Cyn} - \delta_0^{Cyn}$ in ppm. *Cyn* superscripts refer to nonequivalent carbon index (*n*) of Cy. Negative signs indicate upfield displacements. [b] δ_0^{Cyn} values are 102.41, 72.88, 74.47, 82.26, 73.07, and 61.59 ± 0.02 for C1, C2, C3, C4, C5, and C6, respectively.

phenolic OH substituent which presumably is hydrogen bonded in water and may undergo solvation changes in complex. Decreased solvation of the phenol accompanying complexation might result in an increased resonance interaction with the aromatic system and give rise to the observed ^{13}C NMR displacements. This seems a likely possibility because increased solvation by polar solvents is known to inhibit substituent, ring interaction by resonance.[37]

Cyclohexaamylose-*m*-Phenylene Complexes. In the *p*-phenylene series we noted that nitro, cyano, and carboxylic acid terminals are included in the Cy cavity in the binary complexes but *p*-phenylenecarboxylates and -phenolates are not. This trend persists in the *m*-phenylene series MNP, MNP^-, $MNBA^-$, MCP, and MCP^- where we observe consistent shielding of appropriate ipso carbons ($\Delta\delta_1^{MHBA1}$ −1.19, $\Delta\delta_1^{MNP3}$ −0.70, $\Delta\delta_1^{MNP^-3}$ −0.86, $\Delta\delta_1^{MNBA^-3}$ −0.77, $\Delta\delta_1^{MCP3}$ −1.33, and $\Delta\delta_1^{MCP^-3}$ −1.59) along with deshielding of the corresponding para carbons. The −0.78-ppm perturbation of the Cα resonance in the $MNBA^-$ complex closely matches the corresponding displacements of Cα resonances in BA^- and $PHBA^-$, confirming that the nitro group of this substrate is included in the Cy cavity.

The upfield displacement ($\Delta\delta_1^{MHBA\alpha}$ −1.26) of the carboxylic acid resonance in MHBA is somewhat smaller than that observed with BA or PHBA (−1.70 and −1.65 ppm) as are the cyano carbons in MCP and MCP^- compared to the corresponding *p*-phenylene resonances (−0.27 and −0.23 ppm compared with −0.69 and −0.70 ppm). A number of factors may be responsible for this trend and these include the following: a more shallow penetration of the *m*-phenylene substrates into the Cy cavity; off-axis alignment of the meta substrate in the Cy cavity; or a lower polarizability of the meta substrates compared with the para. We note here that MHBA, MCP, and MCP^- cause similar perturbations of C6 in Cy, as discussed in a later section, and that these result in resonance displacements similar to those found in the para substrate systems. Consequently, the second and third factors appear more likely as causes of the smaller displacements observed with these meta substrates.

The MNBA substrate contains both carboxylic acid and nitro groups which have been shown to enter the Cy cavity in other binary complexes. In this case both ipso carbons are shielded ($\Delta\delta_1^{MNBA1}$ −0.49 and $\Delta\delta^{MNBA3}$ −0.34), and the upfield −1.12-ppm carboxylic acid displacement seems somewhat smaller than might be expected. Resolution of the question as to which of the substituent groups enters the Cy cavity is complicated by a number of factors. First, we were unable to make unambiguous assignments for the very closely spaced C2, C4, and C5 resonances. Second, steric factors may play a role here. In order to visualize the steric constraints on this system, we made space-filling models and concluded that nitro or carboxylic acid groups would not penetrate the cavity as deeply as in BA, PHBA, and MHBA complexes, and this observation was confirmed by the small C6 displacement of Cy. As a result, the $\Delta\delta^{MNBA\alpha}$ value of −1.12 could be rationalized on the basis of shallow carboxylic acid insertion in the Cy cavity. However, other explanations are feasible, including possible isomeric complexes. We are continuing to study this system.

Displacements of ^{13}C NMR resonances of $MHBA^-$ on complexation with Cy are similar to those of BA^- resonances. Slight shielding of the carboxylate carbon ($\Delta\delta_1^{MHBA^-\alpha}$ −0.39) indicates that this substituent does not interact appreciably with the Cy cavity. However, it is unclear as to whether or not the phenolic substituent enters the Cy cavity. Substantial shielding occurs at C5 (−0.79 ppm) and is accompanied by deshielding at opposing C2 (1.33 ppm). This might indicate an orientation by which C5 is directed toward the Cy cavity with both the carboxylate and phenolic substituents directed away from Cy. The observed displacements are equally well accounted for by a model featuring insertion of the phenolic group into the cavity. This structure seems the preferable one in that C3, ipso to the phenol OH group of $MHBA^-$, is deshielded as is C4 of $PHBA^-$ ($\Delta\delta_1^{MHBA^-3}$ 0.73 and $\Delta\delta_1^{PHBA^-4}$ 1.21). Transfer from bulk solution to the Cy cavity would be expected to have similar effects on phenolic resonance interaction with the ring in both ions.

Displacements of Cy Resonances

In Figure 2 we plot displacements $\Delta\delta_1^{Cy1}$ of C1 resonances due to complexation for 21 binary complexes against $\Delta H°$ for the corresponding complex-forming reactions. A linear regression calculation of $\Delta\delta_1^{Cy1}$ on $\Delta H°$ yields slope and intercept values of −0.038 (±0.004) ppm mol $kcal^{-1}$ and 0.09 (±0.03) ppm, respectively, where the uncertainties are standard error estimates. The root-mean-square scatter from the least-squares line is 0.05 ppm as compared with our average uncertainty of ±0.06 ppm for individual $\Delta\delta_1^{Cy1}$ values. We conclude, therefore, that this correlation represents a direct correspondence between $\Delta\delta_1^{Cy1}$ and the energetics of the complexation reactions. To understand this correspondence, we call upon the same argument used to un-

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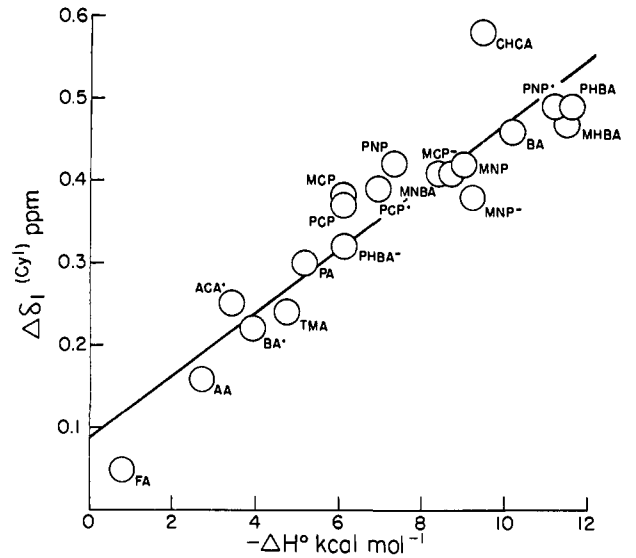

Figure 2. Correlation of anomeric Cy C1 displacement $\Delta\delta_1^{Cy1}$ vs. $\Delta H°$ parameters for cyclohexaamylose complexation reactions. The line drawn represents a least-squares fit, $\Delta\delta_1^{Cy1}$ = (−0.038 ± 0.004 ppm mol kcal^{-1})$\Delta H°$ + (0.09 ± 0.03) ppm, to 20 substrate systems.

derstand the $\Delta H°$ vs. $\Delta S°$ correlation: even though the substrates included here span a wide range of structural, electrical, magnetic, and dipolar diversities, they all come together into the same $\Delta\delta_1^{Cy1}$ vs. $\Delta H°$ correlation. Therefore, the mechanism of interaction which is reflected by the correlation must be dominated by a common attribute, viz., the host molecule rather than some particular diverse property of the substrates. Furthermore, in support of this assertion we note that the anomeric carbon atoms of Cy are substantially screened from direct interaction with the substrate species by neighboring Cy oxygen and carbon atoms. Thus the C1 atoms are not influenced by direct interaction with the substrates. Instead, we associate the observed displacements $\Delta\delta_1^{Cy1}$ with conformational changes of glucosyl residues. These come about by interaction of permanent or induced dipoles in the substrate species with Cy glucosyl residues and result in their rotations about C1–O–C4 linkages. These in turn perturb the magnetic environment of conformationally sensitive C1.[38] Increased bonding interaction and corresponding increased glucosyl rotation yield larger $\Delta\delta_1^{Cy1}$ values. This picture is supported by our observation that local dipole fields and total Cy dipole moments are highly sensitive to orientation of the glucosyl residues. We made approximate dipole moment calculations based on solid phase atomic coordinates[39] and estimates of charge distributions based on atomic electronegativities,[40,41] for a number of possible torsional orientations of the six glucosyl residues. While dipole moments derived from these calculations have no absolute significance, they seem to confirm that rotations about interglucosyl linkages substantially alter electric fields in or near the Cy cavity.

Displacements of other Cy carbon resonances do not seem well correlated with $\Delta H°$, $\Delta S°$, or $\Delta G°$ values. These carbons are not effectively screened from the Cy cavity, and their ^{13}C NMR resonances reflect dipolar, anisotropic ring current and steric compression interactions with the various substrate species.[42] We note, however, that the substrates seem to subdivide into two groups on the basis of the displacements $\Delta\delta_1^{Cy6}$. The first of these two groups includes substrates which strongly shield the C6 atoms and consists of species in which electronegative cyano, nitro, or carboxylic acid substituents may closely approach C6. Thus, PNP, PNP⁻, BA, PHBA, and AA as well as MHBA, MNP, MCP, and MCP⁻ and substrates have $\Delta\delta_1^{Cy6}$ values near −0.4 to −0.5. The second group is characterized by small displacements of C6 and consists of substrates which are too bulky to penetrate the Cy cavity such as ACA⁻ and TMA or which lack groups which might interact with C6 such as BA⁻. PHBA⁻ and MHBA⁻ are included in this group as well. From these observations we conclude that displacement of the C6 resonance is the result of electronic shielding due to the proximity with an electron-rich group and, furthermore, that these substituents are similarly placed in complexes of both meta and para substituents. However, it is important to realize that these displacements are not related to the cyclohexaamylose-substrate bonding mechanism since the $\Delta\delta_1^{Cy6}$ values are essentially uncorrelated with $\Delta H°$. This interpretation of C6 resonance displacement seems to be confirmed by the intermediate $\Delta\delta_1^{Cy6}$ values found for MNBA⁻, MNBA, and MNP⁻ complexes (−0.17, −0.27, and −0.25 ppm, respectively). The observed substrate resonance displacements apparently indicate that the nitro terminals of MNBA⁻ and MNP⁻ enter the cavity in the complexes. But while some ambiguity remains that the MNBA complex may exist as isomeric forms, it seems clear that the carboxylic acid group strongly interacts with the Cy cavity. In all three cases space-filling models have indicated that the bulk of the meta-substituted solvated carboxylate, solvated phenolate, and relatively unsolvated carboxylic acid groups prevents insertion of electron-rich substrates beyond the ring of C5 carbons of Cy. Therefore, relatively small C6 resonance displacements compared with the corresponding para substrates would be expected.

Discussion

The correlations of $\Delta H°$ vs. $\Delta S°$ and $\Delta\delta_1^{Cy1}$ vs. $\Delta H°$ which are reported here are symptomatic of the nature of the bonding mechanism between Cy and various substrates in binary complexes. The mechanism is predominantly due to dipolar or induced dipolar forces and is characterized by a compensation temperature of 403 ± 24 K. The apolar or hydrophobic bonding mechanisms often suggested by others[26,28] do not seem to play a major role in these reactions. These mechanisms are generally ascribed to entropy-driven reactions, those in which the enthalpic contribution to the free energy change is relatively minor.[43] The formation of binary Cy complexes with those substrates studied here follows an opposite pattern. In each case a favorable enthalpy term dominates an unfavorable entropy term, and so we conclude that hydrophobic contributions to binding cannot play a major role. Similar conclusions were drawn by Otagiri et al.[44] for complexes of barbiturates and β-cyclodextrin.

We mentioned earlier that two of the binary complexes studied were excluded from the $\Delta H°$ vs. $\Delta S°$ correlation, and these were with the substrates 1-adamantanecarboxylate anion, ACA⁻, and cyclohexanecarboxylic acid, CHCA. These were excluded because of severe deviations from the correlation line, and while it is certainly possible that the deviations are statistical artifacts, we believe that they are in reality due to certain features in the bonding mechanism peculiar to these two substrates and not common to the other 20 substrates. Consequently, we make the following speculations on the Cy·ACA⁻ and Cy·CHCA but with some reservation. For Cy·CHCA $\Delta S°$ for the formation reaction is −23.9 ± 0.2 cal mol^{-1} K^{-1} which is about 4 cal mol^{-1} K^{-1} more negative than predicted by the correlation line on the basis of the observed $\Delta H°$ value of −9.44 kcal mol^{-1}. This more negative $\Delta S°$ value may be the result of restricted motion of the normally flexible cyclohexane ring in the complex. We constructed space-filling models of Cy and CHCA which revealed that the cyclohexane ring is effectively immobilized when inserted into the Cy cavity. This restriction of substrate's conformational motion in the complex would not be a feature in common with the other substrates studied here and so would lead to an additional ordering which would displace the Cy·CHCA complex from the $\Delta H°$ vs. $\Delta S°$

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correlation in the observed negative $\Delta S°$ direction.

In contrast we note that in the case of Cy·ACA$^-$, $\Delta S° = -1.3 \pm 1.9$ cal mol^{-1} K^{-1} which is about 4 cal mol^{-1} K^{-1} more positive than the value of −5.5 cal mol^{-1} K^{-1} corresponding to the observed $\Delta H° = -3.4$ kcal mol^{-1} on the correlation line. Again we speculate with reservation that this deviation is due to a mechanistic peculiarity involving a partial contribution of hydrophobic bonding to the formation of this complex. The positive entropic deviation may be due to release of solvent water molecules ordered around the exceptionally large hydrocarbon upon complexation with Cy. If this is true, it is important to note that this hydrophobic contribution ($-T\Delta S° \approx -1.2$ kcal mol^{-1}) represents only about one-third of the favorable free energy change ($\Delta G° \approx -3.0$ kcal mol^{-1}) for complexation. The complexation is dominated by the enthalpic contribution of −3.4 kcal mol^{-1}.[16] This behavior turns our attention to the ^{13}C NMR behavior of the 1-adamantanecarboxylate anion system. We note that C1 displacement of Cy in the Cy·ACA$^-$ complex conforms to the $\Delta\delta_1^{Cy1}$ vs. $\Delta H°$ correlation so that the unusual behavior of Cy·ACA$^-$ cannot be ascribed to some difference in macrocycle conformation resulting from interaction with the large hydrocarbon substrate. It is interesting that the binary complex of Cy with the parent acid ACA does seem to conform to the $\Delta H°$ vs. $\Delta S°$ correlation. This is readily explained by a structure involving inclusion of the carboxylic acid terminal of ACA in the Cy cavity. In that case no appreciable change in the substrate solvation would occur, and a "normal" $\Delta H°$ and $\Delta S°$ relationship would be observed. While the postulated Cy·ACA structure seems likely by analogy to other carboxylic acids, we attempted to confirm this hypothesis by NMR spectral measurements but were unable to do so because of the very low solubility of ACA.

We wish to emphasize that our speculations on internal constraint in Cy·CHCA and on hydrophobic effects in Cy·ACA$^-$ are made with reservation. The bonding in these complexes and in the others studied here is predominantly dipolar. This conclusion is based on a variety of thermodynamic and structural evidences, as discussed in earlier sections. Furthermore, the correlations found here strongly support a binding picture in which dipolar interactions between the macrocycle and substrate result in conformational changes in Cy. These directly determine the entropy change on complexation.

Experimental Section

Cyclohexaamylose (α-cyclodextrin) obtained from the Aldrich Chemical Co. was exposed to the atmosphere for several days to ensure complete conversion to the hexahydrate as determined by vacuum drying at 100 °C. ^{13}C NMR spectra obtained under high S/N (>200) conditions indicated negligible impurity concentrations. Finally, pH measurements with 0.1 M Cy solution gave no indication of acidic or basic impurities. All other materials were reagent grade, and most solids were recrystallized from water before use.

Spectrophotometric measurements employed a Beckman Acta III spectrophotometer equipped with a thermostated sample compartment and 1.00-cm quartz cells. pH potentiometric experiments were made with the aid of an Orion 801 pH meter equipped with conventional glass and reference electrodes. The electrodes were recalibrated frequently, and no appreciable meter drift was detected.

Single-temperature (30 ± 2 °C) ^{13}C NMR data were obtained with a Varian CFT-20 nuclear magnetic resonance spectrometer operating in the Fourier transform mode (30° tip angle, 2-s acquisition time, spectral width 4 KHz, 1–2-s pulse delay, and 1–10 K acquisitions). Variable-temperature measurements of Cy ^{13}C resonances were carried out on a Bruker HX-270 spectrometer with instrument settings of 90° tip angle, 7-kHz spectral width, 0.6-s acquisition time, and 200 acquisitions. In all of these experiments proton-decoupled spectra were recorded from a single 10-mm sample tube for each series of measurements.

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The Mechanism of Catalysis of the Thio-Claisen Rearrangement

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Abstract: The cyclization-induced rearrangement mechanism proposed by Overman[10] to account for nucleophilic catalysis of the thio-Claisen rearrangement has been tested by application of two criteria, viz., the secondary kinetic deuterium isotope effect at the β (side chain) carbon in phenyl allyl sulfide and the substituent rate effect. The results ($k_H/k_D = 1.05$ and log $k_{X_p}/k_H = 0.25\sigma^+$) do not support the mechanism. Instead, they can be construed to support the previously validated mechanism of nucleophilic triggering of sigmatropic rearrangement.[9]

The thio-Claisen rearrangement has been recognized to be of general preparative interest and widely applied for such purposes.[1-3] Since the first recorded example[4] of this reaction in 1962, the mechanistic relationship to the oxy-Claisen has been elucidated in a series of articles[5-8] culminating in the formulation of a mechanism of nucleophilic triggering of concerted (3,3) sigmatropic rearrangement of phenyl allyl sulfides (**1**) to account for the role of a wide variety of both neutral and anionic nucleophiles.[9] The proposed reaction course and details of the TS‡

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