Thermodynamic and Nuclear Magnetic Resonance Study of the Reactions of α- and β-Cyclodextrin with Acids, Aliphatic Amines, and Cyclic Alcohols

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Titration calorimetry was used to determine equilibrium constants and standard molar enthalpy, Gibbs energy, and entropy changes for the reactions of a series of acids, amines, and cyclic alcohols with α- and β-cyclodextrin. The results have been examined in terms of structural features in the ligands such as the number of alkyl groups, the charge number, the presence of a double bond, branching, and the presence of methyl and methoxy groups. The values of thermodynamic quantities, in particular the standard molar Gibbs energy, correlate well with the structural features in the ligands. These structural correlations can be used for the estimation of thermodynamic quantities for related reactions. Enthalpy−entropy compensation is evident when the individual classes of substances studied herein are considered, but does not hold when these various classes of ligands are considered collectively. The NMR results indicate that the mode of accommodation of the acids and amines in the α-cyclodextrin cavity is very similar, but that the 1-methyl groups in 1-methylhexylamine and in 1-methylheptylamine and the *N*-methyl group in *N*-methylhexylamine lie outside the α-cyclodextrin cavity. This latter finding is consistent with the calorimetric results. Many of the thermodynamic and NMR results can be qualitatively understood in terms of van der Waals forces and hydrophobic effects.

1. Introduction

Reactions involving cyclodextrins are of importance to the technology of drug delivery systems, separations, and foods.[1−6] These reactions also serve as excellent models for understanding the basis of inclusion chemistry and as models of (enzyme + substrate) interactions.[7] The principal factors involved in the binding are believed to be primarily van der Waals forces and hydrophobic effects. Hydrogen bonding and steric effects can also play a role. In the absence of a general model capable of separating these effects, a practical approach toward understanding these reactions is to perform thermodynamic studies in which the chemical nature of the ligand is changed in a systematic way. The trends in the results can then be examined and correlated with structural features in the ligands. Such information can provide a basis for the estimation of thermodynamic quantities and could also prove useful for the validation and calibration of computational models. Several classes of substances which react with cyclodextrins have been the subject of systematic thermodynamic studies. These include hydrocarbons,[8,9] aliphatic alcohols,[10−15] aliphatic-diols,[13,16] phenols,[17,18] cyclohexane derivatives,[19] naphthalene derivatives and other aromatic compounds,[20−23] and phenethylamine and its derivatives.[24]

In this study, we have used titration calorimetry to measure equilibrium constants and standard molar enthalpies for the reactions of a series of acids, aliphatic amines, and cyclic alcohols (Figure 1) with α- and β-cyclodextrin. The results obtained in this study together with some results from the literature have been examined to obtain information about the variation of thermodynamic quantities with structural features in the ligand such as the number of alkyl groups, the charge number, the presence of a double bond, branching, and the addition of methyl and methoxy groups. This information can be useful both for understanding the chemistry in these reactions and for estimating thermodynamic quantities.

In contrast to comprehensive NMR studies on molecular inclusion of aromatic compounds with cyclodextrins,[2,7] the complexation behavior of aliphatic ligands, such as acyclic alcohols, amines, and carboxylic acids, has not been investigated in detail by NMR. This is probably due to the fact that the chemical shift changes found for complexation reactions involving aliphatic substances are much less than those for reactions involving aromatic substances where a ring current exists. The only related NMR investigations appear to be those of Casu et al.[25] and Watanabe et al.[26] Casu et al.[25] used 300 MHz NMR to study the complexation behavior of some alkyl glycosides with α-cyclodextrin. They[25] observed appreciable downfield shifts of the guest protons, but, due to the severe interference of signals from the glycoside, they could only measure the induced shifts of the α-cyclodextrin's H1 and H2 protons. Watanabe et al.[26] studied the complexation behavior of α,ω-alkanedicarboxylates (7−12 methylene groups) with α-cyclodextrin at pD = 8 and pD = 13. Due to the ionization of two of the α-cyclodextrin's hydroxyl groups at pD = 13, the

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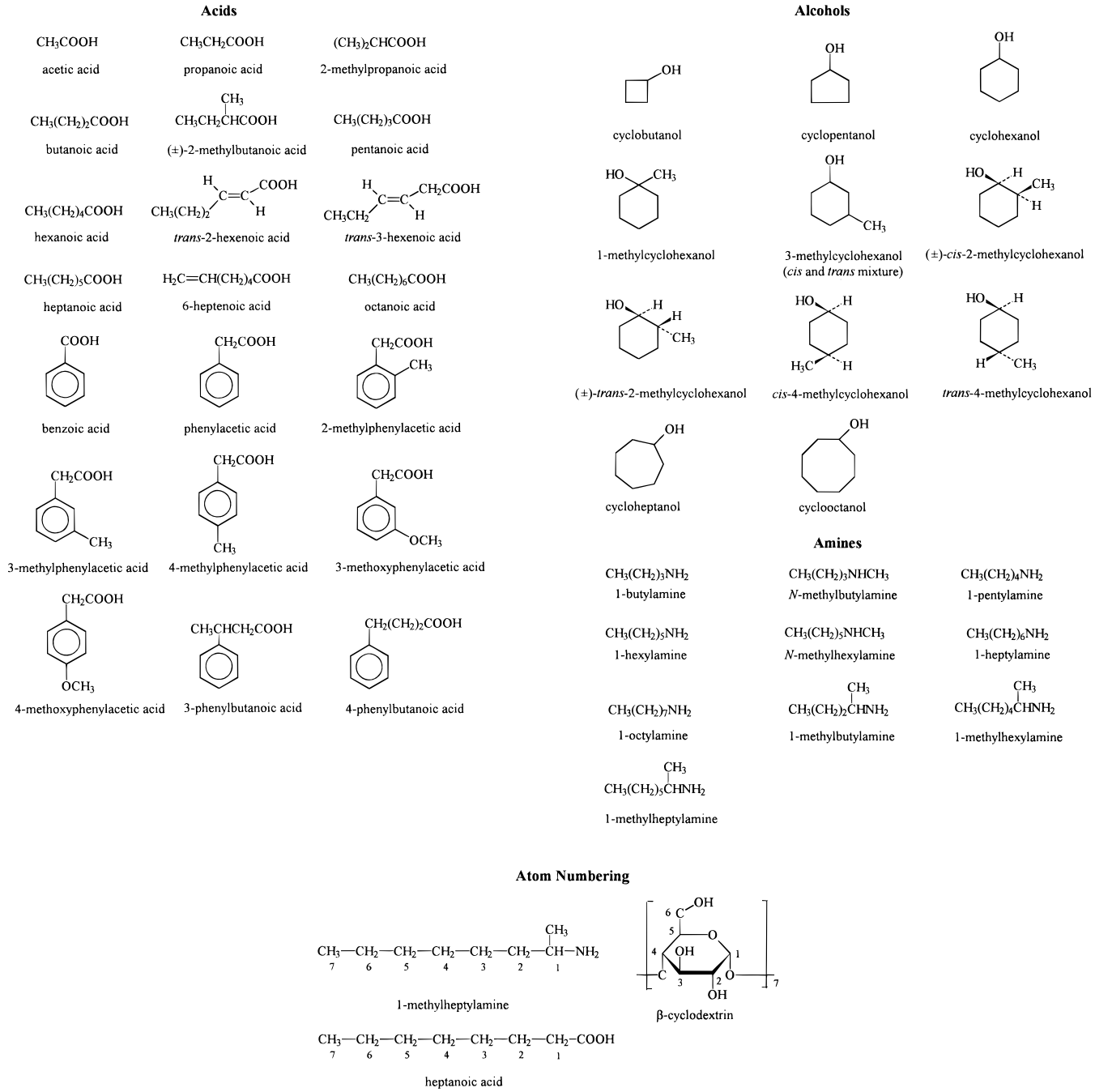

Figure 1. Structures of the ligands used in this study. Atom-numbering schemes are shown for 1-methylheptylamine and for β-cyclodextrin.

exchange rate of the α,ω-alkanedicarboxylates is significantly decreased by the electrostatic repulsion between the α-cyclodextrin's ionized hydroxyl groups and the acid's carboxylate groups. Thus, the protons of the free and complexed ligands yield independent signals at different positions. Watanabe et al.[26] also used NOESY to demonstrate through-ring inclusion of the α,ω-alkanedicarboxylates. They also found that originally equivalent methylene groups in the α,ω-alkanedicarboxylates (i.e. methylene groups located at the same distance from the terminal carboxylate groups) appear at different positions following through-ring inclusion. This is attributable to the fact that the α-cyclodextrin cavity is asymmetric. However, their study[26] did not contain any additional information on the other protons in the α-cyclodextrin upon complexation with the α,ω-dicarboxylates of varying chain length. Thus, it seemed desirable to use NMR to study the inclusion of some representative simple acids and amines, a fundamental host−guest system. The NMR results obtained in this study provide additional information on these complexation reactions and complement the calorimetric findings.

2. Experimental Section

The principal substances used in this study, their respective Chemical Abstracts Services registry numbers, empirical formulas, molecular weights, mass fraction moisture contents, and mole fraction purities are given in Table S1 contained in the Supporting Information for this paper. In most cases, the mole fraction purities of these substances are >0.99 and in all cases are >0.95. The substances were used without further purification. The characterization of the α- and β-cyclodextrin has been described previously.[19] Moisture contents of the samples, as determined by Karl Fischer analysis, were used in the calculations of the molalities of the substances in solution. Corrections to these molalities were also made for the mole fractions of the

TABLE 1: Equilibrium Constants *K*, Standard Molar Enthalpies $\Delta_r H°$, Standard Molar Gibbs Energies $\Delta_r G°$, and Standard Molar Entropies $\Delta_r S°$ for the Reaction α-Cyclodextrin(aq) + Ligand(aq) = α-Cyclodextrin·Ligand(aq) at $T = 298.15$ K[a]

ligand	*m* (mol kg^{-1})	N	K	$\Delta_r H°$ (kJ mol^{-1})	$\Delta_r G°$ (kJ mol^{-1})	$\Delta_r S°$ (J K^{-1} mol^{-1})
acetate$^-$	0.48	2	*b*			
propanoate$^-$	0.224	2	*b*			
2-methylpropanoate$^-$	0.295	2	∼7 [c]	∼−3		
butanoate$^-$	0.148	2	12.5 ± 1.5	−10.6 ± 1.0	−6.3 ± 0.3	−14.4 ± 1.1
(±)-2-methylbutanoate$^-$	0.275	2	23.5 ± 1.0	−12.5 ± 0.4	−7.83 ± 0.11	−15.7 ± 0.4
pentanoate$^-$	0.148	2	79.9 ± 1.1	−11.51 ± 0.12	−10.86 ± 0.04	−2.2 ± 0.2
hexanoate$^-$	0.155	2	300 ± 4	−14.24 ± 0.14	−14.14 ± 0.04	−0.3 ± 0.2
trans-2-hexenoate$^-$	0.126	1	282 ± 9	−17.24 ± 0.50	−13.99 ± 0.08	−10.9 ± 1.7
trans-3-hexenoate$^-$	0.122	1	161 ± 5	−14.07 ± 0.40	−12.60 ± 0.08	−4.9 ± 1.4
heptanoate$^-$	0.090	2	843 ± 35	−17.54 ± 0.72	−16.70 ± 0.11	−2.8 ± 2.4
6-heptenoate$^-$	0.102	1	433 ± 5	−18.74 ± 0.19	−15.05 ± 0.03	−12.4 ± 0.2
octanoate$^-$	0.043	2	2449 ± 130	−20.46 ± 0.27	−19.34 ± 0.14	−3.8 ± 0.3
1-butylamine$^+$	0.313	2	14.3 ± 0.9	−9.1 ± 0.4	−6.59 ± 0.16	−8.4 ± 0.5
N-methylbutylamine$^+$	0.280	2	17.2 ± 1.0	−10.74 ± 0.53	−7.05 ± 0.15	−12.4 ± 1.8
1-methylbutylamine$^+$	0.311	2	19.6 ± 1.3	−11.2 ± 0.6	−7.38 ± 0.17	−12.8 ± 0.6
1-pentylamine$^+$	0.111	2	98.7 ± 1.0	−13.74 ± 0.14	−11.38 ± 0.03	−7.9 ± 0.2
1-hexylamine$^+$	0.084−0.190	6	389 ± 4	−17.54 ± 0.18	−14.78 ± 0.03	−9.3 ± 0.2
N-methylhexylamine$^+$	0.178	2	378 ± 14	−17.56 ± 0.66	−14.71 ± 0.10	−9.6 ± 2.2
1-heptylamine$^+$	0.095	2	1080 ± 11	−19.50 ± 0.20	−17.31 ± 0.03	−7.3 ± 0.2
1-methylhexylamine$^+$	0.200	2	439 ± 5	−17.92 ± 0.18	−15.08 ± 0.03	−9.5 ± 0.2
1-methylheptylamine$^+$	0.066	2	1130 ± 12	−19.82 ± 0.20	−17.43 ± 0.03	−8.0 ± 0.2
1-octylamine$^+$	0.050	2	2376 ± 53	−22.85 ± 0.23	−19.27 ± 0.06	−12.0 ± 0.3
cyclobutanol^0	0.227	2	30.3 ± 1.5	−11.5 ± 0.4	−8.46 ± 0.13	−10.2 ± 0.4
cyclopentanol^0	0.209	2	36.4 ± 1.0	−11.47 ± 0.19	−8.91 ± 0.13	−8.6 ± 0.3
cycloheptanol^0	0.044	2	68 ± 12	−12.5 ± 1.9	−10.5 ± 0.5	−6.7 ± 2.0
cyclooctanol^0	0.012−0.024	2	235 ± 230	−3.9 ± 2.7	−13.5 ± 9.5	32 ± 10

[a] Phosphate buffer {(NaH_2PO_4, 0.025 mol kg^{-1}) + (Na_2HPO_4, 0.025 mol kg^{-1}), pH = 6.90} was used for all reactions. The charge numbers of the ligands are those of the predominant species at pH = 6.90. The molality m of the ligand for which the measurements were performed and *N* the number of sets of titration experiments performed are given in columns 2 and 3, respectively. The molality of the α-cyclodextrin was in the range 0.0008−0.0038 mol kg^{-1}. The basis of the uncertainties is discussed in the text. [b] K and/or $\Delta_r H°$ for this reaction were too small to measure with the titration calorimeter. [c] Values designated as being approximate are uncertain by amounts that are comparable to the reported values.

impurities in the α- and β-cyclodextrin. All thermal titrations were performed with the OMEGA reaction cell of a MicroCal MC-2 calorimeter.[27,28] The calorimetric procedures have been described previously.[19,29]

Proton NMR spectra were measured at $T = 298 \pm 1$ K with a 600 MHz Bruker AM-600 instrument; D_2O solutions buffered at pD = 7.0 with {D_3PO_4 (0.10 mol dm^{-3}) + NaOD} were used for all experiments. All chemical shifts δ were relative to the DOH signal at 4.75 ppm. The concentration of α-cyclodextrin was fixed at 0.0050 mol dm^{-3} for all experiments, and an approximately equimolar amount of ligand was added to the cyclodextrin solution. The ratio of the concentration of the ligand to the concentration of the α-cyclodextrin in solution was determined from the relative intensities of the signals of the protons in the α-cyclodextrin and in the ligands.

3. Results

3.1. Calorimetry. The treatment of the data obtained with the titration calorimeter has been described previously.[19] All equilibrium constants and standard molar enthalpies of reaction reported in this paper are based on a 1:1 complexation model:

$$\text{cyclodextrin(aq)} + \text{ligand(aq)} = \text{cyclodextrin·ligand(aq)} \quad (1)$$

The equilibrium constant for this reaction is

$$K = a(\text{cyclodextrin·ligand})/\{a(\text{cyclodextrin})a(\text{ligand})\} \quad (2)$$

where *a* is the activity of the indicated substance. The standard state used for the solute is the hypothetical ideal solution of unit molality ($m° = 1$ mol kg^{-1}). Nonideality corrections are assumed to be negligible for both the measured equilibrium constants and the standard molar enthalpies of the reaction. This approximation should hold reasonably well even when dealing with a charged ligand since the reaction is charge symmetric and the activity coefficients in the numerator and denominator of eq 2 should largely cancel at low and moderate ionic strengths.

Calculations were also performed in which the cyclodextrin·(ligand)$_2$ complex was also assumed present in addition to the 1:1 complex. It was found that the additional parameters obtained from these calculations had uncertainties that were comparable to the parameters themselves and that the quality of the overall fit was not improved. Also, the fits to the titration curves with the 1:1 model showed no systematic deviations. Thus, the use of the 1:1 complexation model and a single binding site is justified and the data do not warrant more complicated models. It was also found that the values of the standard molar enthalpies of reaction $\Delta_r H°$ and equilibrium constants *K* obtained from the titration curves were not significantly affected by the random deletion of up to approximately one-third of the data points in the titration curves. This gives us additional confidence in the values of the equilibrium constants and the standard molar enthalpies of reaction.

Thermodynamic quantities for the reactions of the various ligands used in this study with α- and β-cyclodextrin in aqueous phosphate buffer are presented in Tables 1 and 2, respectively. The standard molar Gibbs energies of reaction and standard molar entropies of reaction given in Tables 1 and 2 were calculated from the measured equilibrium constants and standard molar enthalpies of reaction. The results and uncertainties for the equilibrium constants and standard molar enthalpies of reaction in Tables 1 and 2 were obtained as weighted averages of the results of the titration experiments done for each (ligand + cyclodextrin) pair. These uncertainties refer to two estimated standard deviations of the mean. However, in some cases (see below), these uncertainties were increased to allow either for a

TABLE 2: Equilibrium Constants K, Standard Molar Enthalpies $\Delta_r H°$, Standard Molar Gibbs Energies $\Delta_r G°$, and Standard Molar Entropies $\Delta_r S°$ for the Reaction β-Cyclodextrin(aq) + Ligand(aq) = β-Cyclodextrin·Ligand(aq) at T = 298.15 K[a]

ligand	m (mol kg^{-1})	N	K	$\Delta_r H°$ (kJ mol^{-1})	$\Delta_r G°$ (kJ mol^{-1})	$\Delta_r S°$ (J K^{-1} mol^{-1})
pentanoate$^-$	0.238	2	8.3 ± 5.5	7.9 ± 4.4	−5.3 ± 2.7	44.3 ± 5.2
hexanoate$^-$	0.156	2	46.9 ± 4.5	5.5 ± 0.3	−9.54 ± 0.25	50.4 ± 0.4
heptanoate$^-$	0.100	2	301 ± 134	1.75 ± 0.33	−14.2 ± 1.5	53.5 ± 1.5
benzoate$^-$	0.189	1	15.9 ± 1.2	−10.5 ± 0.7	−6.86 ± 0.20	−12.2 ± 0.8
phenylacetate$^-$	0.166	2	17.4 ± 2.4	−7.5 ± 0.9	−7.1 ± 0.4	−1.3 ± 1.0
3-phenylbutanoate$^-$	0.153	1	379 ± 10	−9.41 ± 0.10	−14.72 ± 0.06	17.8 ± 0.12
4-phenylbutanoate$^-$	0.144	1	435 ± 26	−11.78 ± 0.12	−15.06 ± 0.15	11.0 ± 0.19
2-methylphenylacetate$^-$	0.152	2	*b*			
3-methylphenylacetate$^-$	0.150	4	11.9 ± 1.4	−11.5 ± 1.1	−6.1 ± 0.3	−18.1 ± 1.2
4-methylphenylacetate$^-$	0.073−0.146	6	40.4 ± 1.7	−12.1 ± 0.4	−9.17 ± 0.11	−9.8 ± 0.4
3-methoxyphenylacetate$^-$	0.160	2	38.0 ± 1.1	−12.25 ± 0.23	−9.02 ± 0.08	−10.8 ± 0.3
4-methoxyphenylacetate$^-$	0.139	2	69.3 ± 1.6	−8.22 ± 0.11	−10.51 ± 0.06	7.7 ± 0.2
1-pentylamine$^+$	0.221	2	∼8[c]	∼5		
1-hexylamine$^+$	0.156	2	65 ± 16	2.5 ± 0.4	−10.4 ± 0.7	43.3 ± 0.8
1-methylhexylamine$^+$	0.163	2	76 ± 15	1.96 ± 0.22	−10.7 ± 0.55	42.5 ± 0.6
1-heptylamine$^+$	0.127	2		∼0.2		
1-octylamine$^+$	0.061	2	420 ± 137	−1.99 ± 0.26	−15.0 ± 1.0	43.6 ± 1.0
cyclobutanol^0	0.227	2	14 ± 6	3.7 ± 1.4	−6.5 ± 1.4	34.2 ± 2.0
cyclopentanol^0	0.209	2	172 ± 5	−4.56 ± 0.05	−12.76 ± 0.08	27.5 ± 0.1
1-methylcyclohexanol^0	0.145	2	1150 ± 36	−9.58 ± 0.29	−17.47 ± 0.08	26.5 ± 1.0
(±)-*cis*-2-methylcyclohexanol^0	0.110	2	981 ± 22	−9.92 ± 0.15	−17.08 ± 0.06	24.0 ± 0.6
(±)-*trans*-2-methylcyclohexanol^0	0.114	2	741 ± 10	−8.66 ± 0.09	−16.38 ± 0.04	25.9 ± 0.1
3-methylcyclohexanol^0 [d]	0.064	2	830 ± 16	−8.74 ± 0.09	−16.66 ± 0.05	26.6 ± 0.1
cis-4-methylcyclohexanol^0	0.080	2	1462 ± 26	−9.50 ± 0.10	−18.07 ± 0.05	28.7 ± 0.1
trans-4-methylcyclohexanol^0	0.072	2	2130 ± 61	−9.06 ± 0.17	−19.00 ± 0.07	33.3 ± 0.6
cycloheptanol^0	0.044	2	2197 ± 73	−12.37 ± 0.12	−19.08 ± 0.09	22.5 ± 0.2
cyclooctanol^0	0.012−0.024	2	4405 ± 484	−16.4 ± 0.5	−20.8 ± 0.3	14.8 ± 0.6

[a] Phosphate buffer {(NaH_2PO_4, 0.025 mol kg^{-1}) + (Na_2HPO_4, 0.025 mol kg^{-1}), pH = 6.90} was used for all reactions. The charge numbers of the ligands are those of the predominant species at pH = 6.90. The molality m of the ligand for which the measurements were performed and N the number of sets of titration experiments performed are given in columns 2 and 3, respectively. The molality of the α-cyclodextrin was in the range 0.0010−0.0037 mol kg^{-1}. The basis of the uncertainties is discussed in the text. [b] K and/or $\Delta_r H°$ for this reaction were too small to measure with the titration calorimeter. [c] Values designated as being approximate are uncertain by amounts that are comparable to the reported values. [d] The sample of 3-methylcyclohexanol was a mixture of the *cis* and *trans* isomers.

minimal error in the calorimetric measurements or for impurities in the samples. The standard deviations of the mean are based on the scatter of the data in a single titration experiment and were obtained from the computer program "Origin"[29] used to calculate the equilibrium constants and the standard molar enthalpies of reaction. Clearly the sensitivity of the method is reduced for reactions having small values of K (K < 10) and/or small absolute values of $\Delta_r H°$ ($|\Delta_r H°|$ < 3 kJ mol^{-1}). Also, in some instances (e.g. cyclooctanol), the solubility of the ligand is limited. These factors all place limitations on the size of the measurable signal and can lead to larger uncertainties in the thermodynamic quantities. Thus, in a few cases (see Tables 1 and 2), it was not possible to measure either K or $\Delta_r H°$ for the complexation reaction. For reasons stated previously,[24] we have adopted minimum uncertainties (0.01K and 0.01$\Delta_r H°$) for the results obtained from these experiments. Additionally, when the mole fraction purity of a ligand x was less than 0.99, the uncertainties in the equilibrium constants and standard molar enthalpies of reaction were increased (in quadrature) by the respective amounts $(1 - x)K$ or $(1 - x)\Delta_r H°$.

3.2. Assignment of Charge Numbers of Ligands. We have used two computerized databases[30,31] to locate pK's for most of the acids and approximately one third of the amines studied herein. The pK's of these acids are in the range 4.0−4.9 and the pK's of the protonated amines are in the range 10.6−10.7. On the basis of structural similarity, it is reasonable to assume that the pK's of the remaining acids and amines will fall either into or very nearly into these ranges. Clearly, the alcohols will not ionize unless placed in extremely alkaline solutions. Since the pH of 6.9 used for the experiments was well removed ($|\text{pH} - \text{p}K| \geq 2$) from the p$K$'s at which ionizations occur, the complication of having more than one species present in these solutions in any significant amount (>1%) is avoided. The charge numbers of the ligands in Tables 1 and 2 are those of the predominant species at pH = 6.90.

3.3. Comparisons with Earlier Literature. The thermodynamic results from the literature on the reactions of these ligands with α- and β-cyclodextrin are summarized in Table 3. Siimer et al.[32] reported $K = 10 \pm 1$ for the reaction of benzoate$^-$ with β-cyclodextrin at the temperature T = 303.15 K. We adjust this result to T = 298.15 K with the value of $\Delta_r H°$ for this reaction determined in this study and obtain $K = 9 \pm 1$. This value is not in agreement with the result $K = 15.9 \pm 1.2$ reported herein. Matsui and Mochida[10] used a spectrophotometric method to study the reaction of cyclobutanol, cyclopentanol, cycloheptanol, and cyclooctanol with α- and β-cyclodextrin. They[10] reported that the standard error in their measured values of log K was ±0.04, but did not give estimates of total uncertainties. We shall assume that a reasonable assignment of random error in their results for log K is approximately two standard errors (±0.08). On the basis of this assumption, their results for the equilibrium constants for the reactions of all of the cyclic alcohols with α-cyclodextrin and for the reaction of cyclobutanol with β-cyclodextrin are in agreement with the results of the present study. Their[10] result for the equilibrium constant for the reaction of cyclooctanol with α-cyclodextrin is more precise than our result. This is due to the reduced sensitivity of the calorimetric method when studying a reaction that has a small absolute value of $\Delta_r H°$. However, their results for the equilibrium constants for the reactions of cyclopentanol, cycloheptanol, and cyclooctanol are systematically lower than the results obtained in this study. Matsui and Mochida[10] used a (H_2SO_4 + Na_2SO_4) buffer in their studies involving α-cyclodextrin and a (citrate + phosphate) buffer in their studies involving β-cyclodextrin. Citrate, however, is known to bind to β-cyclodextrin.[33] Therefore, one expects systematic differ-

TABLE 3: Literature Values of the Equilibrium Constants *K* and Standard Molar Enthalpies $\Delta_r H°$ for the Reactions of α- and *β*-Cyclodextrin with Organic Ligands

ligand	*K*	$\Delta_r H°$ (kJ mol^{-1})	*T* (K)	buffer	pH	method	ref
			α-cyclodextrin(aq) + Ligand(aq) = α-Cyclodextrin·Ligand(aq)				
cyclobutanol^0	39 ± 7		298.15	$H_2SO_4 + Na_2SO_4$	1.2	spectrophtometry	10
cyclopentanol^0	46 ± 8		298.15	$H_2SO_4 + Na_2SO_4$	1.2	spectrophotometry	10
cycloheptanol^0	79 ± 13		298.15	$H_2SO_4 + Na_2SO_4$	1.2	spectrophotometry	10
cyclooctanol^0	178 ± 30		298.15	$H_2SO_4 + Na_2SO_4$	1.2	spectrophotometry	10
			β-Cyclodextrin(aq) + Ligand(aq) = β-Cyclodextrin·Ligand(aq)				
benzoate$^-$	10 ± 1	−19.0 ± 1.4[a]	303.15	none	?	calorimetry	32
cyclobutanol^0	15 ± 3		298.15	citrate + phosphate	6.4	spectrophotometry	10
cyclopentanol^0	120 ± 11		298.15	citrate + phosphate	6.4	spectrophotometry	10
cycloheptanol^0	1700 ± 290		298.15	citrate + phosphate	6.4	spectrophotometry	10
cyclooctanol^0	2000 ± 340		298.15	citrate + phosphate	6.4	spectrophotometry	10

[a] Siimer et al.[32] reported a negative value of $\Delta_r H°$ for the dissociation reaction of the complex β-cyclodextrin·benzoate$^-$(aq). This corresponds to a positive value for $\Delta_r H°$ for the complexation reaction as written above. We have assumed that the sign of their[32] reported enthalpy is in error and have reversed it in this table.

ences between results obtained with the interacting citrate buffer and with a noninteracting[24] phosphate buffer. This was also found to be the case when acetate was used instead of phosphate buffer[24] in the study of cyclodextrin complexation reactions. Specifically, the equilibrium constants obtained with acetate buffer were, in nearly all cases, 10−50% lower than those obtained with phosphate buffer.[24]

Ross and Rekharsky[34] have recently carried out a thermodynamic investigation using model compounds to obtain a set of thermodynamic parameters that are characteristic of hydrogen bonding and hydrophobic effects. In their investigation, they studied the reactions of four *n*-amines, *N*-methylhexylamine$^+$, 1-methylhexylamine$^+$, 1-hexanoate$^-$, and 1-heptanoate$^-$ with α-cyclodextrin and the reactions of 3-phenylbutanoate$^-$ and *cis*-4-methylcyclohexanol with β-cyclodextrin. The thermodynamic quantity of principal interest in their study was the standard molar heat-capacity change $\Delta_r C°_p$, which was obtained from the dependence of $\Delta_r H°$ on temperature. The measurements done by Ross and Rekharsky[34] were done independently of the results of the present study and are based on the results of a single titration experiment performed at each temperature. The results of the current study for the aforementioned reactions are either in complete agreement or near agreement with the results obtained by Ross and Rekharsky.[34]

3.4. NMR. The results of the NMR measurements are given in Tables 4 and 5. As is the case with the calorimetric results, the predominant species in solution are the alkylammonium$^+$ and alkanoate$^-$ ions. The ligand (guest) protons G*n* are numbered sequentially from the methylene adjacent to the ammonium or carboxylate group. The cyclodextrin (host) protons H*n* are numbered as usual (see Figure 1). Due to the presence of chiral centers in 1-methylhexylamine$^+$ and 1-methylheptylamine$^+$, the values of the chemical shifts for the G2 protons are different and are distinguished as G2a and G2b. Similarly, it is necessary to distinguish the H6 protons of α-cyclodextrin. As exemplified in Figure 2 for the complexation of octylamine$^+$ with α-cyclodextrin, all of the ligand protons (G1 to G8) show significant downfield shifts upon complexation, while the complexation-induced chemical shift changes $\Delta\delta$ of the cyclodextrin protons (H1 to H6) are much smaller in scale and more scattered in direction. Except for relatively small deviations ($\delta < 0.02$), the chemical shifts of the G1, G2, G3, and G*n* protons of the amines appear at 2.91, 1.58, 1.29, and 0.80, respectively, while the chemical shifts of the G1, G2, G3, and G*n* protons of the acids appear, respectively, at 2.10, 1.47, 1.22, and 0.80. This constancy in these chemical shifts is consistent with the absence of any micelle formation.

4. Discussion

4.1. General Ideas and Approach. The most likely mode of complexation of ligands to cyclodextrins consists of insertion of the hydrophobic portion of the ligand into the cyclodextrin cavity with the polar group of the ligand remaining solvent exposed at the wide top end of the cavity.[2] In general, the complexation is noncovalent. A combination of hydrophobic effects and van der Waals forces and, in some cases, hydrogen bonding between the ligand and the cyclodextrin is involved. The resultant of all these interactions is described by the thermodynamic quantities. Although, at present, it does not appear possible to obtain a rigorous, quantitative breakdown of the relative contributions of these various interactions for any specific (ligand + cyclodextrin) reaction, we believe that the following *qualitative* picture is useful for understanding these complexation reactions. Namely, hydrophobic effects should be typified by negative values of the standard molar heat-capacity change $\Delta_r C°_p$ and, at or near $T = 298.15$ K, small positive values of $\Delta_r H°$ ($<\sim$10 kJ mol^{-1}) and positive values of $\Delta_r S°$.[35−38] Also, when the ligand is in the cyclodextrin cavity, there is the possibility of attractive van der Waals interactions as well as hydrogen bonding.[24,34] These attractive interactions are characterized by negative $\Delta_r H°$'s. Using the simple qualitative argument that a ligand that is strongly bound within the cyclodextrin cavity has lost some freedom of motion, one expects it to have a lower entropy than if it were weakly bound within the cavity. Thus, one should expect some "enthalpy−entropy compensation" for these complexation reactions. Also, since the α-cyclodextrin cavity (approximate internal dimensions 4.9 Å × 7.9 Å) is smaller than the β-cyclodextrin cavity (approximate internal dimensions 6.2 Å × 7.9 Å)[1] and since van der Waals forces are critically dependent on distance of separation, one expects that these forces will be larger ($\Delta_r H°$ more negative) for the complexation of a given ligand to α-cyclodextrin than to β-cyclodextrin. This assumes the same mode of inclusion of that ligand into both α- and β-cyclodextrin. Accordingly, the van der Waals interactions will be highly dependent on the size and possibly the shape of the ligand. Clearly, if a ligand cannot be accommodated within the cyclodextrin cavity, steric effects play a dominant role. While these concepts are not new,[18,35,39−43] it will be seen in the following discussion that these rather straightforward ideas provide a useful qualitative framework with which to account for much of the thermodynamic data.

The ligands used in this study were selected so as to allow for the examination of how several structural features affect the thermodynamics of complexation reactions of cyclodextrins. The features examined are (1) the number of alkyl groups in the

TABLE 4: Chemical Shifts δ of Ligand Protons and Chemical Shift Changes $\Delta\delta$ upon Complexation of Ligands with α-Cyclodextrin in Aqueous Phosphate Buffer at pD = 7.0 and $T = 298 \pm 1$ K[a,b]

		δ or $\Delta\delta$									
ligand	[H]/[G][c]	G1	G2a	G2b	G3	G4	G5	G6	G7	G8	1-Me	*N*-Me
1-pentylamine$^+$	0	2.91	1.58		1.27	1.27	0.82					
	1.04	2.94	1.63		1.33	1.33	0.86					
	$\Delta\delta$:	−0.03	−0.05		−0.06	−0.06	−0.04					
1-hexylamine$^+$	0	2.92	1.59		1.30	1.25	1.24	0.80				
	1.04	2.96	1.65		1.39	1.36	1.35	0.87				
	$\Delta\delta$:	−0.04	−0.06		−0.09	−0.11	−0.11	−0.07				
1-methylhexylamine$^+$	0	3.28	1.57,	1.50	1.30	1.25	1.24	0.81			1.22	
	0.93	3.31	1.64,	1.54	1.38	1.34	1.34	0.85			1.25	
	$\Delta\delta$:	−0.03	−0.07,	−0.04	−0.08	−0.09	−0.10	−0.04			−0.03	
N-methylhexylamine$^+$	0	2.94	1.60		1.30	1.25	1.24	0.80				2.63
	0.96	2.99	1.66		1.38	1.35	1.35	0.86				2.65
	$\Delta\delta$:	−0.05	−0.06		−0.08	−0.10	−0.11	−0.06				−0.02
1-heptylamine$^+$	0	2.92	1.59		1.30	1.28	1.22	1.22	0.80			
	1.00	2.96	1.65		1.38	1.38	1.35	1.35	0.85			
	$\Delta\delta$:	−0.04	−0.06		−0.08	−0.10	−0.13	−0.13	−0.05			
1-methylheptylamine$^+$	0	3.28	1.57,	1.50	1.28	1.28	1.22	1.22	0.80			
	1.08	3.32	1.66,	1.54	1.37	1.37	1.34	1.34	0.85			
	$\Delta\delta$:	−0.04	−0.09,	−0.04	−0.09	−0.09	−0.12	−0.12	−0.05			
1-octylamine$^+$	0	2.90	1.57		1.29	1.24	1.22	1.20	1.20	0.78		
	1.00	2.95	1.64		1.36	1.36	1.36	1.31	1.31	0.83		
	$\Delta\delta$:	−0.05	−0.07		−0.07	−0.12	−0.14	−0.11	−0.11	−0.05		
pentanoate$^-$	0	2.11	1.45		1.23	0.81						
	0.92	2.13	1.50		1.27	0.84						
	$\Delta\delta$:	−0.02	−0.05		−0.04	−0.03						
hexanoate$^-$	0	2.10	1.47		1.23	1.19	0.80					
	1.02	2.14	1.55		1.32	1.30	0.85					
	$\Delta\delta$:	−0.04	−0.08		−0.09	−0.11	−0.05					
heptanoate$^-$	0	2.10	1.47		1.21	1.21	1.21	0.79				
	0.92	2.14	1.55		1.33	1.33	1.33	0.86				
	$\Delta\delta$:	−0.04	−0.08		−0.12	−0.12	−0.12	−0.07				
octanoate$^-$	0	2.10	1.47		1.21	1.21	1.21	1.21	0.79			
	1.02	2.13	1.53		1.31	1.31	1.31	1.31	0.84			
	$\Delta\delta$:	−0.03	−0.06		−0.10	−0.10	−0.10	−0.10	−0.05			

[a] The atom-numbering scheme is discussed in the text and in Figure 1. [b] The pooled standard deviation of the δ values is 0.011. [c] The quantity [H]/[G] is the ratio of the concentration of the α-cyclodextrin (the host) to the concentration of the ligand (the guest). The concentration of α-cyclodextrin was 0.0050 mol dm^{-3}. Under these conditions, the complexation of ligand and α-cyclodextrin is not complete; the values of the fractions α of ligand and α-cyclodextrin that are complexed are given in the Discussion section.

ligand, (2) branching (i.e. comparison of results for primary and secondary ligands), (3) the charge number on the ligand, (4) the presence of a double bond, and (5) the addition of methyl groups and methoxy groups to a central moiety. The matter of enthalpy−entropy compensation is also discussed.

4.2. General Trends. The values of $\Delta_rS°$ for all but one of the reactions (α-cyclodextrin + cyclooctanol) involving α-cyclodextrin are negative (see Table 1); these reactions are "enthalpy driven" at $T = 298.15$ K. In contrast, the values of $\Delta_rS°$ are positive for most of the reactions of β-cyclodextrin with the various ligands reported in Table 2. Thus, for the reactions with β-cyclodextrin, there is a substantial entropic contribution to $\Delta_rG°$. Additionally, the values of $\Delta_rH°$ for nearly all of the reactions involving α-cyclodextrin are more exothermic than the values of $\Delta_rH°$ for the corresponding reactions involving β-cyclodextrin. Cycloheptanol and, again, cyclooctanol are the exceptions.

4.3. The CH_2 Increment. Plots of the standard molar Gibbs energies, enthalpies, and entropies for the reactions of various classes of ligands with both α- and β-cyclodextrin as a function of N_C, the number of hydrocarbon carbon atoms (i.e. CH, CH_2, and CH_3 groups) in the chemical formula of the ligands, are shown in Figures 3−8. According to this convention, the carbon in the carboxylate group is not counted in the calculation of N_C. The most striking features in these plots (see Figures 3, 4, 6, and 7) is the regular dependence of $\Delta_rG°$ and $\Delta_rH°$ on N_C. It is also seen that there are characteristic differences between the various classes of ligands.

The $\Delta_rG°$ results for the aliphatic *sec*-amines, alkane-1,2-diols, and neutral aliphatic *n*-acids can be adequately represented by straight lines in Figure 3. The data for the remaining classes of ligands in Figure 3 and all of the results in Figure 6 can be represented by quadratic equations of the form $\Delta_rG° = a_1 + a_2N_C + a_3(N_C)^2$, where a_1, a_2, and a_3 are adjustable parameters. A quantity of particular interest in Figures 3 and 6 is the increment in $\Delta_rG°$ per alkyl group. We have calculated $d\Delta_rG°/dN_C$, the slope of the linear fits of $\Delta_rG°$ against N_C, for each class of ligand. The values of $d\Delta_rG°/dN_C$ range from −2.6 kJ mol^{-1} (the reactions of the *sec*-alkanols with α-cyclodextrin) to −3.8 kJ mol^{-1} (reactions of the alkane-1,2-diols with α-cyclodextrin) and −4.5 kJ mol^{-1} (reactions of the ionized aliphatic *n*-acids with β-cyclodextrin). The values of $d\Delta_rG°/dN_C$ for the remaining classes of ligands are in a remarkably narrow range of −3.5 to −2.5 kJ mol^{-1}. The average values of $d\Delta_rG°/dN_C$ (all classes of ligands included) are −3.1 and −3.3 kJ mol^{-1} for the reactions of these ligands with α- and β-cyclodextrin, respectively. The standard deviations in these quantities are small: 0.12 and 0.25 kJ mol^{-1}, respectively.

Some regularity is also seen in the standard molar enthalpies of the reactions involving α-cyclodextrin. Here, the range of values of $d\Delta_rH°/dN_C$ obtained from linear fits of $\Delta_rH°$ against N_C is −4.8 to −1.9 kJ mol^{-1}. The average value of $d\Delta_rH°/dN_C$ is −3.4 kJ mol^{-1} (standard deviation $s = 0.3$ kJ mol^{-1}). Somewhat less regularity is seen (Figure 7) for the standard molar enthalpies of reaction with β-cyclodextrin. Here, the range of values of $d\Delta_rH°/dN_C$ is −4.8 to −0.6 kJ mol^{-1}. The

TABLE 5: Chemical Shifts δ of α-Cyclodextrin Protons and Chemical Shift Changes $\Delta\delta$ upon Complexation with Aliphatic Acids and Amines in Aqueous Phosphate Buffer at pD = 7.0 and $T = 298 \pm 1$ K[a,b]

		δ or $\Delta\delta$						
ligand	[H]/[G][c]	H1	H2	H3	H4	H5	H6a	H6b
none		4.99	3.57	3.92	3.53	3.78	3.80	3.85
1-pentylamine$^+$	1.04	4.99	3.58	3.89	3.53	3.76	3.78	3.83
	$\Delta\delta$:	0.00	−0.01	0.03	0.00	0.02	0.02	0.02
1-hexylamine$^+$	1.04	5.01	3.60	3.90	3.54	3.77	3.80	3.85
	$\Delta\delta$:	−0.02	−0.03	0.02	−0.01	0.01	0.00	0.00
1-methylhexylamine$^+$	0.93	5.00	3.60	3.89	3.54	3.76	3.79	3.84
	$\Delta\delta$:	−0.01	−0.03	0.03	−0.01	0.02	0.01	0.01
N-methylhexylamine$^+$	0.96	5.01	3.60	3.89	3.54	3.76	3.79	3.84
	$\Delta\delta$:	−0.02	−0.03	0.03	−0.01	0.02	0.01	0.01
1-heptylamine$^+$	1.00	5.01	3.60	3.89	3.55	3.77	3.79	3.84
	$\Delta\delta$:	−0.02	−0.03	0.03	−0.02	0.01	0.01	0.01
1-methylheptylamine$^+$	1.08	5.01	3.60	3.89	3.55	3.77	3.79	3.84
	$\Delta\delta$:	−0.02	−0.03	0.03	−0.02	0.01	0.01	0.01
1-octylamine$^+$	0.83	4.99	3.60	3.89	3.57	3.78	3.80	3.84
	$\Delta\delta$:	0.00	−0.03	0.03	−0.04	0.00	0.00	0.01
pentanoate$^-$	0.92	5.00	3.56	3.91	3.52	3.76	3.79	3.84
	$\Delta\delta$:	−0.01	0.01	0.01	0.01	0.02	0.01	0.01
hexanoate$^-$	1.02	5.00	3.56	3.91	3.53	3.77	3.79	3.85
	$\Delta\delta$:	−0.01	−0.01	0.01	0.00	0.01	0.01	0.00
heptanoate$^-$	0.92	5.00	3.56	3.91	3.54	3.78	3.79	3.85
	$\Delta\delta$:	−0.01	0.01	0.01	−0.01	0.00	0.01	0.00
octanoate$^-$	1.02	5.01	3.56	3.90	3.57	3.78	3.79	3.84
	$\Delta\delta$:	−0.02	0.01	0.02	−0.04	0.00	0.01	0.01

[a] The atom-numbering scheme for α-cyclodextrin is described in Figure 1. [b] The pooled standard deviation of the δ values is 0.011. [c] The quantity [H]/[G] is the ratio of the concentration of the α-cyclodextrin (the host) to the concentration of the ligand (the guest). The concentration of α-cyclodextrin was 0.0050 mol dm^{-3}. Under these conditions, the complexation of ligand and α-cyclodextrin is not complete; the values of the fractions α of ligand and α-cyclodextrin that are complexed are given in the Discussion section.

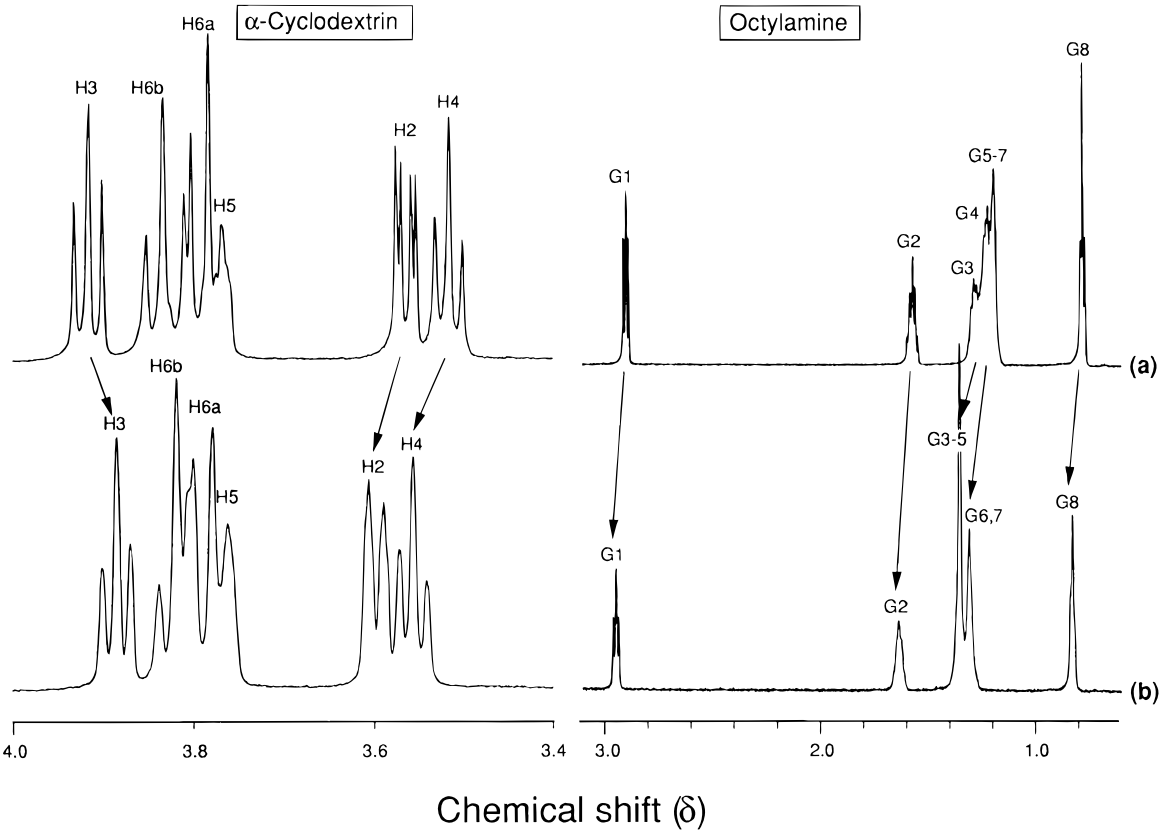

Figure 2. Proton NMR spectra of (a) free octylamine and α-cyclodextrin measured separately and (b) their equimolar mixture. The conditions of measurement are described in the Experimental Section.

average value of $d\Delta_r H°/dN_C$ is −2.5 kJ mol^{-1} (s = 0.6 kJ mol^{-1}). The standard molar entropies of reaction (Figures 5 and 8) are even less regular: the average values of $d\Delta_r S°/dN_C$ are 0.46 J K^{-1} mol^{-1} (s = 0.9 J K^{-1} mol^{-1}) and 2.6 J K^{-1} mol^{-1} (s = 1.9 J K^{-1} mol^{-1}) for the reactions involving α- and β-cyclodextrin, respectively.

It has been noted[14−16,46] that a value of $d\Delta_r G°/dN_C$ (i.e. a CH_2 increment) of ∼ −3 kJ mol^{-1} at T = 298.15 K is typical for the transfer of an alkyl group in a hydrocarbon chain from water to the interior of a micelle and not too far from the CH_2 increment for the transfer of an alkane from water to a liquid hydrocarbon phase. Thus, the pooled value of $d\Delta_r G°/dN_C$ =

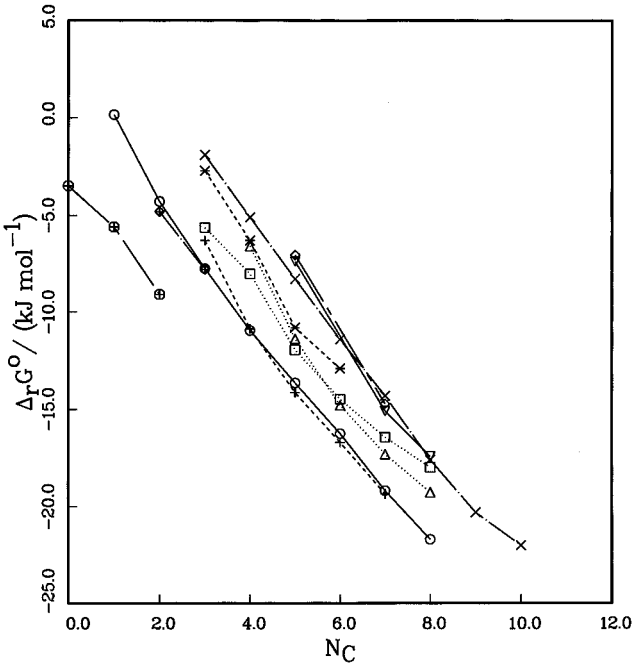

Figure 3. Standard molar Gibbs energies $\Delta_r G°$ for the reactions of various classes of ligands with α-cyclodextrin as a function of N_C, the number of hydrocarbon carbon atoms in the chemical formula of the ligand; that is, the carbon in the carboxylate group is not counted. The symbols and their significance are as follows: (○ connected with —) *n*-alkanols; (△ connected with ···) aliphatic *n*-amines; (+ connected with ---) ionized aliphatic *n*-acids; (× connected with — · —), alkane-1,ω-diols; (◇ connected with — - —) *N*-methylbutylamine$^+$ and *N*-methylhexylamine$^+$; (▽ connected with —) aliphatic *sec*-amines; (□ connected with ...) *sec*-alkanols; (* connected with ---) alkane-1,2-diols; (◆ connected with — · —) ionized aliphatic *sec*-acids; (⊗ connected with — — —) neutral aliphatic *n*-acids. The sources of the data are as follows: *n*-alkanols, Matsui and Mochida[10] (N_C = 1, 2, 7, and 8) and Hallén et al.[14] (N_C = 3−6); alkane-1,ω-diols, Bastos et al.;[16] *sec*-alkanols, Matsui and Mochida[10] (N_C = 8) with the remaining data from Rekharsky et al.;[15] alkane-1,2-diols, Andini et al.;[13] neutral aliphatic *n*-acids, Gelb et al.;[44,45] aliphatic *n*-amines, aliphatic *sec*-amines, ionized aliphatic *n*-acids, *N*-methylbutylamine$^+$, and *N*-methylhexylamine$^+$, this study.

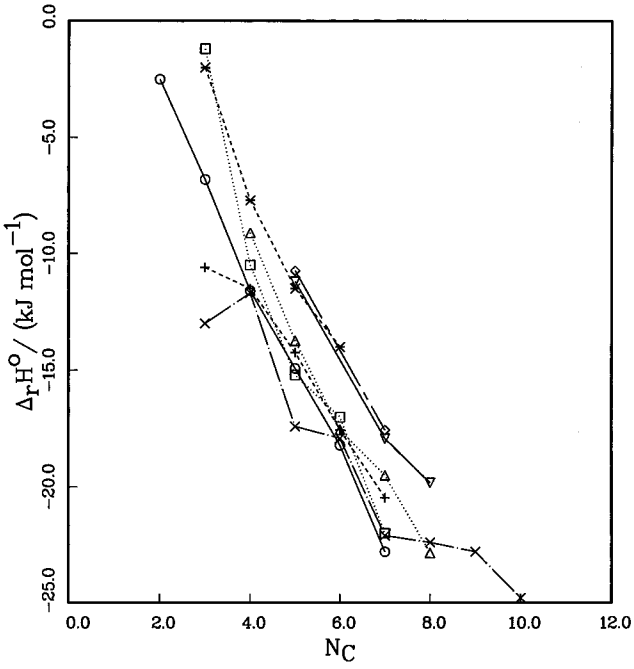

Figure 4. Standard molar enthalpies $\Delta_r H°$ for the reactions of various classes of ligands with α-cyclodextrin as a function of N_C, the number of hydrocarbon carbon atoms in the chemical formula of the ligand; that is, the carbon in the carboxylate group is not counted. The symbols and their significance are as follows: (○ connected with —), *n*-alkanols; △ connected with ···), aliphatic *n*-amines; (+ connected with ---) ionized aliphatic *n*-acids; (× connected with — · —) alkane-1,ω-diols; (◇ connected with —-—) *N*-methylbutylamine$^+$ and *N*-methylhexylamine$^+$; (▽ connected with —) aliphatic *sec*-amines; (□ connected with ···) *sec*-alkanols; (* connected with ----) alkane-1,2-diols. The sources of the data are as follows: *n*-alkanols, Andini et al.[13] (N_C = 2), Rekharsky et al.[15] (N_C = 4), and Hallén et al.[14] (N_C = 3, 5, 6, and 7); alkane-1,ω-diols, Bastos et al.;[16] *sec*-alkanols, Rekharsky et al.;[15] alkane-1,2-diols, Andini et al.;[13] aliphatic *n*-amines, aliphatic *sec*-amines, ionized aliphatic *n*-acids, *N*-methylbutylamine$^+$, and *N*-methylhexylamine$^+$, this study.

−3.2 kJ mol^{-1} found herein is both indicative of and consistent with the presence of hydrophobic effects. Also, the somewhat more negative value of $d\Delta_r H°/dN_C$ for the reactions of the ligands with α-cyclodextrin than with β-cyclodextrin is consistent with the presence of increased van der Waals interactions for the alkyl groups in the α-cyclodextrin cavity in comparison to that in the β-cyclodextrin cavity.

4.4. Enthalpy−Entropy Compensation. To examine enthalpy−entropy compensation in these complexation reactions, we have constructed plots of the standard molar enthalpies as a function of the standard molar entropies. A slope of 236 ± 93 K was obtained from a plot that used *all* of the results for the reactions with β-cyclodextrin discussed herein. This value is in agreement with a typical compensation temperature of ∼300 K, which is obtained if the enthalpy−entropy compensation is essentially complete. However, for the reactions with α-cyclodextrin, the $\Delta_r H°$'s were found to be poorly correlated with the $\Delta_r S°$'s and a meaningful slope could not be obtained using all of the results. Following Bertrand et al.[18] and our earlier practice,[15,19,24] we also examined the differences in thermodynamic quantities for the exchange reaction

$$\text{α-cyclodextrin·ligand(aq)} + \text{β-cyclodextrin(aq)} = \quad (3)$$

$$\text{α-cyclodextrin(aq)} + \text{β-cyclodextrin·ligand(aq)}$$

These quantities were obtained by combination of the appropriate thermodynamic quantities for the reactions of the various ligands with α- and β-cyclodextrin. Thus, a slope of 485 ± 136 K was obtained from a plot of $\Delta_r H°$ vs $\Delta_r S°$ for these exchange reactions. This latter, somewhat uncertain, slope is greater than the slopes (range of 239−360 K) obtained in previous studies.[15,18,19,24]

However, some enthalpy−entropy compensation is evident when individual classes of substances are considered. This is demonstrated in plots of $\Delta_r H°$ vs $\Delta_r S°$ (Figures 9 and 10) for the reactions of the various classes of ligands considered herein. Note, however, that two points (one for the reaction of butanoate$^-$ with α-cyclodextrin and the other for the reaction of 2-propanol with β-cyclodextrin) were not included in the least-squares fits used to obtain the straight lines in Figures 9 and 10. It is also seen in these figures that the slopes of the linear fits for the various classes of ligands vary by substantial amounts. Thus, no meaningful slope or compensation temperature can be obtained.

The alkane-1,ω-diols[16] present a particularly interesting case. They display a zigzag pattern in the plots of $\Delta_r H°$ and $\Delta_r S°$ against N_C (Figures 4 and 5). Also, their slopes in Figure 5 and in the enthalpy−entropy plot (Figure 9) are opposite in sign to those seen for the other classes of substances. Interestingly, even though they cannot be represented properly by a straight line in Figure 9, they are well represented by a smooth curve in the plot of $\Delta_r G°$ against N_C (Figure 3). Thus, as pointed out by Bastos et al.,[16] there is a strong "enthalpy−entropy compensation" for this class of ligand.

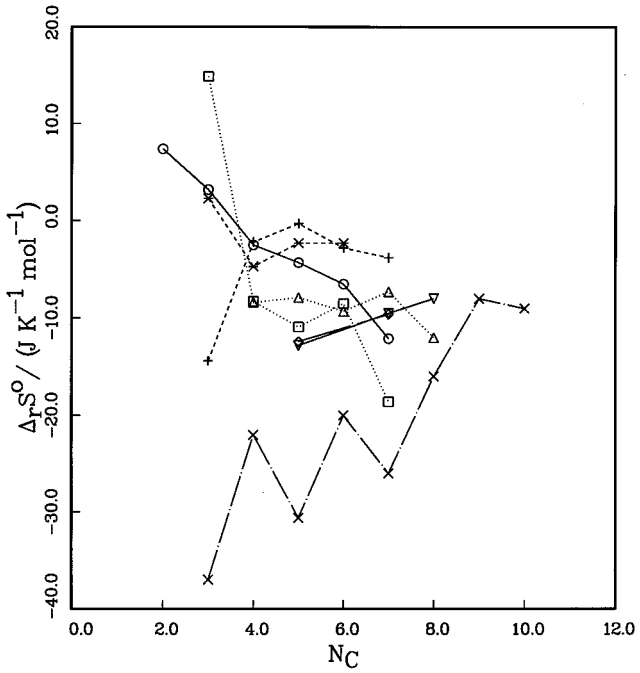

Figure 5. Standard molar entropies $\Delta_r S°$ for the reactions of various classes of ligands with α-cyclodextrin as a function of N_C, the number of hydrocarbon carbon atoms in the chemical formula of the ligand; that is, the carbon in the carboxylate group is not counted. The symbols and their significance are as follows: (○ connected with —), *n*-alkanols; (△ connected with ···) aliphatic *n*-amines; (+ connected with ---) ionized aliphatic *n*-acids; (× connected with — · —) alkane-1,ω-diols; (◇ connected with — - —) *N*-methylbutylamine$^+$ and *N*-methylhexylamine$^+$; (▽ connected with —) aliphatic *sec*-amines; (□ connected with ···) *sec*-alkanols; (* connected with (---) alkane-1,2-diols. The values of $\Delta_r S°$ were calculated from the values of $\Delta_r G°$ and $\Delta_r H°$ used, respectively, in Figures 3 and 4.

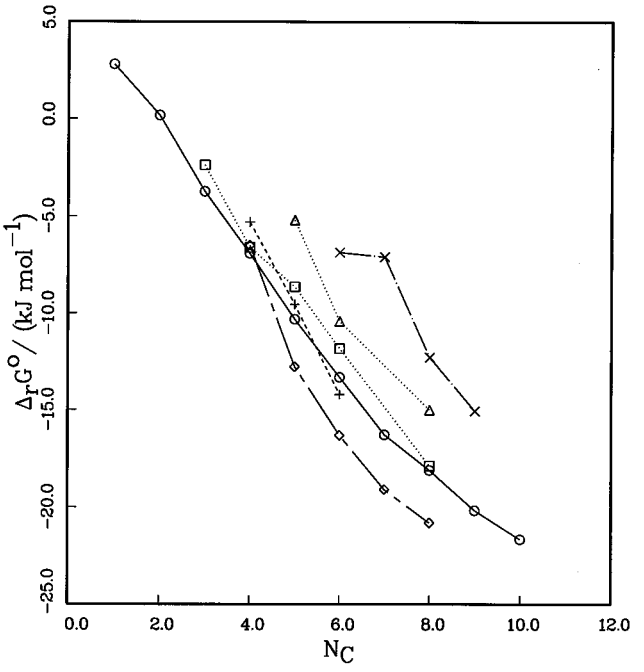

Figure 6. Standard molar Gibbs energies $\Delta_r G°$ for the reactions of various classes of ligands with β-cyclodextrin as a function of N_C, the number of hydrocarbon carbon atoms in the chemical formula of the ligand; that is, the carbon in the carboxylate group is not counted. The symbols and their significance are as follows: (○ connected with —) *n*-alkanols; (△ connected with ···) aliphatic *n*-amines; (+ connected with ---) ionized aliphatic *n*-acids; (× connected with — · —) benzoate$^-$, phenylacetate$^-$, 3-phenylpropanoate$^-$, and 4-phenylbutanoate$^-$; (□ connected with ···) *sec*-alkanols; (◇ connected with — - —) cyclic alcohols. The sources of the data are as follows: cyclic alcohols, Rekharsky et al.[19] (N_C = 6) with the remaining data from this study; *n*-alkanols, Rekharsky et al.[15] (N_C = 3 and 4) with the remaining data from Matsui and Mochida;[10] *sec*-alkanols, Matsui and Mochida[10] (N_C = 8) with the remaining data from Rekharsky et al.;[15] aliphatic *n*-amines, ionized aliphatic *n*-acids, benzoate$^-$, phenylacetate$^-$, and 4-phenylbutanoate$^-$, this study; 3-phenylpropanoate$^-$, Rekharsky et al.[24]

4.5. Branching. The differences in the $\Delta_r G°$, $\Delta_r H°$, and $\Delta_r S°$ for the reactions of *n*- and *sec*-aliphatic alcohols, acids, and amines with α- and β-cyclodextrin are conveniently represented in terms of the exchange reaction

$$\textit{sec}\text{-ligand(aq)} + \text{cyclodextrin}\cdot\textit{n}\text{-ligand(aq)} = \quad (4)$$

$$\textit{n}\text{-ligand(aq)} + \text{cyclodextrin}\cdot\textit{sec}\text{-ligand(aq)}$$

Thermodynamic quantities for reaction 4 are obtained by combination of the appropriate thermodynamic quantities for the reactions of the primary and secondary ligands with the pertinent cyclodextrin. These quantities are summarized in Table 6. The averages and respective standard deviations of these quantities for the reactions involving α-cyclodextrin are $\langle\Delta_r G°\rangle$ = 2.6 kJ mol^{-1}, s = 0.26 kJ mol^{-1}; $\langle\Delta_r H°\rangle$ = 1.6 kJ mol^{-1}, s = 0.65 kJ mol^{-1}; and $\langle\Delta_r S°\rangle$ = −2.9 J K^{-1} mol^{-1}, s = 2.4 J K^{-1} mol^{-1}. The averages and respective standard deviations of these quantities for the reactions involving β-cyclodextrin are $\langle\Delta_r G°\rangle$ = 1.0 kJ mol^{-1}, s = 0.31 kJ mol^{-1}; $\langle\Delta_r H°\rangle$ = 1.3 kJ mol^{-1}, s = 1.4 kJ mol^{-1}; and $\langle\Delta_r S°\rangle$ = 1.0 J K^{-1} mol^{-1}, s = 4.0 J K^{-1} mol^{-1}. Thus, it is seen that the differences in thermodynamic quantities associated with chain branching are reasonably constant, particularly for the $\Delta_r G°$'s.

It is interesting to examine the thermodynamic effects of substitution of a methyl group near the charged amino group. This was done by comparing the thermodynamic results for the following sets of reactions: {1-butylamine$^+$, 1-methylbutylamine$^+$, and *N*-methylbutylamine$^+$} with α-cyclodextrin; {1-hexylamine$^+$, 1-methylhexylamine$^+$, and *N*-methylhexylamine$^+$} with α-cyclodextrin; {1-heptylamine$^+$ and 1-methylheptylamine$^+$} with α-cyclodextrin; and {1-hexylamine$^+$ and 1-methylhexylamine$^+$} with β-cyclodextrin. Within each set of reactions, the values of the respective thermodynamic quantities K, $\Delta_r G°$, $\Delta_r H°$, and $\Delta_r S°$ are nearly the same. From this result and on the basis of the concepts and results previously presented, it is likely that the methyl groups attached either to the C1 carbon (e.g. in 1-methylbutylamine$^+$, 1-methylhexylamine$^+$, and 1-methylheptylamine$^+$) or to the nitrogen in *N*-methylbutylamine$^+$ and in *N*-methylhexylamine$^+$ are located outside the cyclodextrin cavity.

4.6. Charge on the Ligand. The equilibrium constants for the complexation reactions of the ionized aliphatic acids are significantly smaller than the equilibrium constants for the corresponding reactions of the aliphatic neutral acids.[44,45] Examination of results[21,47] for the respective complexation reactions of benzoate$^-$ and the neutral benzoic acid species with α- and β-cyclodextrin shows that this same situation holds for these reactions. These observations are consistent with the general rule seen in the literature (see Inoue et al's[20] Table 2) that the presence of a charge on a ligand correlates with a smaller equilibrium constant for the reaction of that ligand with α- and β-cyclodextrin than for the corresponding reaction of the uncharged ligand. A likely rationale for this phenomenon is that the polar, charged portion of the ligand is solvent exposed at the wide top end of the cyclodextrin cavity.[2] Thus, in this situation, there will be an attractive interaction between the polar charged portion of the ligand and the (polar) bulk water molecules existing just outside the cyclodextrin cavity. This attractive interaction should lead to a lower value of the

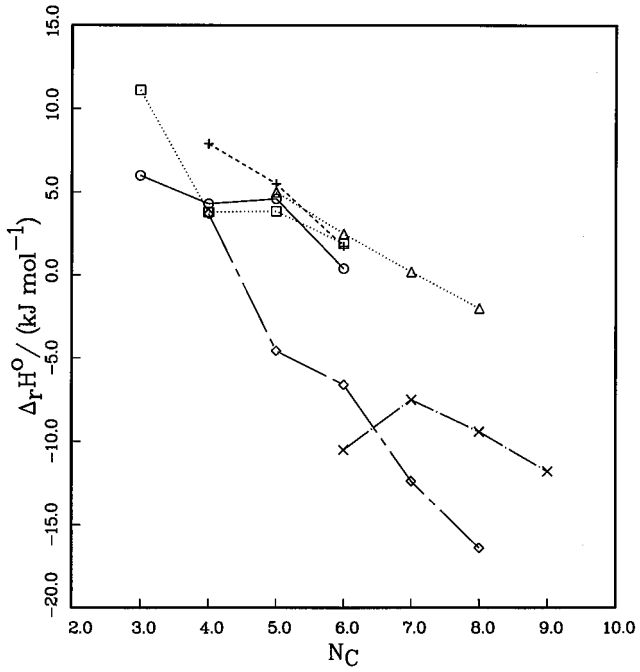

Figure 7. Standard molar enthalpies $\Delta_r H°$ for the reactions of various classes of ligands with β-cyclodextrin as a function of N_C, the number of hydrocarbon carbon atoms in the chemical formula of the ligand; that is, the carbon in the carboxylate group is not counted. The symbols and their significance are as follows: (○ connected with —) *n*-alkanols; (△ connected with ···), aliphatic *n*-amines; (+ connected with ---) ionized aliphatic *n*-acids; (× connected with — · —) benzoate$^-$, phenylacetate$^-$, 3-phenylpropanoate$^-$, and 4-phenylbutanoate$^-$; (□ connected with ···) *sec*-alkanols; (◇ connected with — - —) cyclic alcohols. The sources of the data are as follows: cyclic alcohols, Rekharsky et al.[19] ($N_C = 6$) with the remaining data from this study; *n*-alkanols, Rekharsky et al.[15] ($N_C = 3$ and 4) and Matsui and Mochida[10] ($N_C = 5$ and 6); *sec*-alkanols, Rekharsky et al.;[15] aliphatic *n*-amines, ionized aliphatic *n*-acids, benzoate$^-$, phenylacetate$^-$, and 4-phenylbutanoate$^-$, this study; 3-phenylpropanoate$^-$, Rekharsky et al.[24]

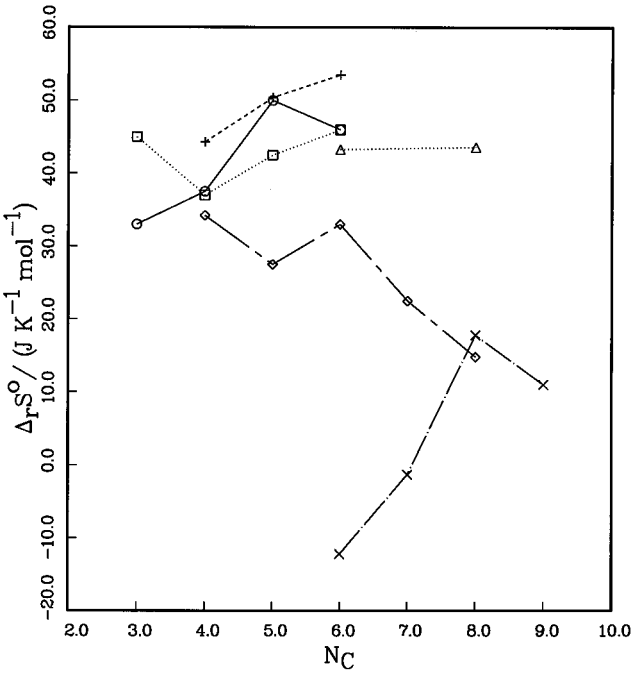

Figure 8. Standard molar entropies $\Delta_r S°$ for the reactions of various classes of ligands with β-cyclodextrin as a function of N_C, the number of hydrocarbon carbon atoms in the chemical formula of the ligand; that is, the carbon in the carboxylate group is not counted. The symbols and their significance are as follows: (○ connected with —) *n*-alkanols; (△ connected with ···), aliphatic *n*-amines; (+ connected with ---) ionized aliphatic *n*-acids; (× connected with — · —) benzoate$^-$, phenylacetate$^-$, 3-phenylpropanoate$^-$, and 4-phenylbutanoate$^-$; (□ connected with ···), *sec*-alkanols; (◇ connected with — - —) cyclic alcohols. The values of $\Delta_r S°$ were calculated from the values of $\Delta_r G°$ and $\Delta_r H°$ used, respectively, in Figures 6 and 7.

equilibrium constant for the complexation of the charged ligand and the cyclodextrin. A ligand having less charge would bind more strongly to the cyclodextrin.

4.7. Unsaturated Compounds. The equilibrium constants for the reactions of *trans*-3-hexenoate$^-$ and of 6-heptenoate$^-$ with α-cyclodextrin are approximately half those for the respective reactions of hexanoate$^-$ and heptanoate$^-$. Comparison of the respective values of $\Delta_r H°$ and $\Delta_r S°$ for these reactions shows that this is an entropic effect. It is possible that when these substances are bound in the cyclodextrin cavity, the unsaturated acid has a greater loss of freedom of motion than the saturated acid. A *possible* explanation for the anomalous behavior of the *trans*-2-hexenoate$^-$ could be delocalization of the charge on this ligand due to conjugation. This delocalization could result in enhanced van der Waals interactions as well as a lowering of the charge density on the carboxyl group. As pointed out above, a lower charge would probably lead to a larger value of the binding constant.

4.8. Cyclic Alcohols. The thermodynamics of the reactions of the cyclic alcohols with α- and β-cyclodextrin exhibit some interesting patterns. We first consider the reactions involving β-cyclodextrin and note that the corresponding thermodynamic quantities for the reactions of cyclobutanol and 1-butanol are comparable. However, as the number of carbon atoms N_C in the cyclic alcohol increases, there is a rapid decrease in the values of $\Delta_r H°$ as well as some decrease in the values of $\Delta_r S°$. In contrast, this behavior is not found for the reactions of the *n*-alkanols with β-cyclodextrin. These observations are consistent with the view that, as N_C increases, the cyclic alcohols are being more snugly accommodated within the cyclodextrin cavity. This could lead to increased van der Waals interactions and an increase in the exothermicity of the reaction.

There is no similar decrease in the values of $\Delta_r H°$ for the reactions of the cyclic alcohols with α-cyclodextrin. Instead, the values of the corresponding thermodynamic quantities in the range $N_C = 4$ to $N_C = 7$ show no drastic changes and they are not too different from each other. However, there is a remarkable increase in the values of both $\Delta_r H°$ (8.6 kJ mol^{-1}) and $\Delta_r S°$ (38.7 J K^{-1} mol^{-1}) in going from cycloheptanol to cyclooctanol. Thus, it is likely that the nature of the complexation of cyclooctanol with α-cyclodextrin is quite different than for the cyclic alcohols containing fewer carbons.

4.9. Methyl and Methoxy Groups. In this study, a series of ligands were systematically selected (see Figure 1 and Table 2) so as to allow for the examination of differences in thermodynamic quantities attributable to the addition of a methyl group to cyclohexanol. These systematic variations involved the reactions of these ligands with β-cyclodextrin. The thermodynamic quantities for the reaction of cyclohexanol with β-cyclodextrin were taken from the study of Rekharsky et al.[19] In this series, one expects the effective radius of the cyclohexane part of the ligand in the β-cyclodextrin cavity to be unchanged by the addition of a methyl group in either the 1 or 4 position. However, this effective radius will be changed by the addition of a methyl group in either the 2 or 3 position. Thus, changes in the position of the methyl group could involve a subtle combination of both steric effects and van der Waals interactions, and a simple picture was not anticipated. Interestingly, however, the average value of the quantity {$\Delta_r H°$(methylcyclohexanol derivative) − $\Delta_r H°$(cyclohexanol)} is very constant; it is −2.6 kJ mol^{-1} (s = 0.2 kJ mol^{-1}). Also, the

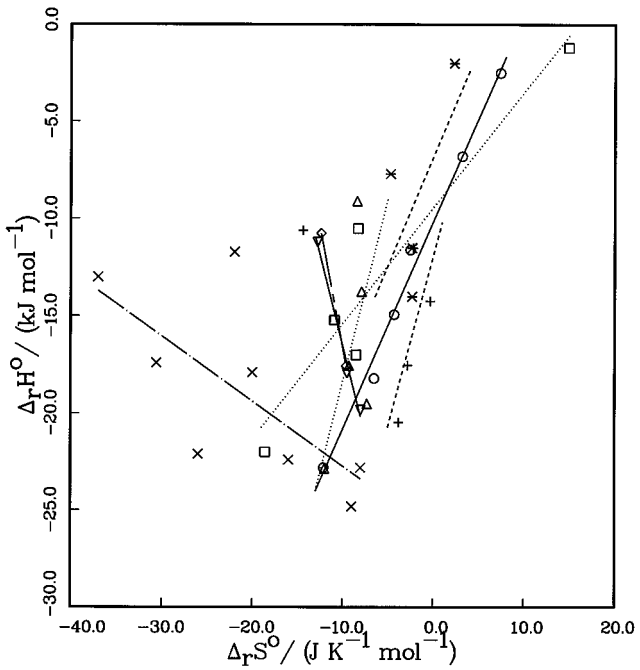

Figure 9. Standard molar enthalpies $\Delta_r H°$ as a function of the standard molar entropies $\Delta_r S°$ for the reactions of various ligands with α-cyclodextrin. The symbols and their significance are as follows: (○ and —) *n*-alkanols; (△ and ···) aliphatic *n*-amines; (+ and ---) ionized aliphatic *n*-acids; (× and — · —) alkane-1,ω-diols; (◇ and — - —) *N*-methylbutylamine$^+$ and *N*-methylhexylamine$^+$; (▽ and —) aliphatic *sec*-amines; (□ and ···), *sec*-alkanols; (* and ---) alkane-1,2-diols. The straight lines are least-squares fits to the data.

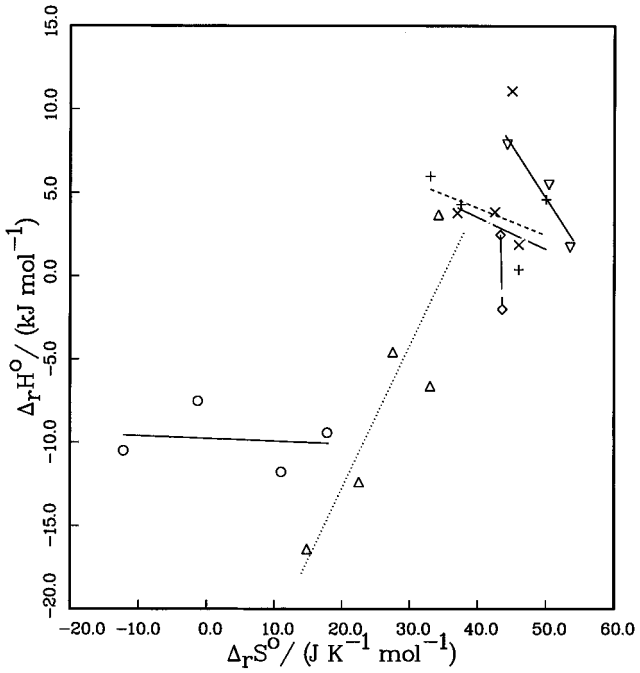

Figure 10. Standard molar enthalpies $\Delta_r H°$ as a function of the standard molar entropies $\Delta_r S°$ for the reactions of various ligands with β-cyclodextrin. The symbols and their significance are as follows: (○ and —) benzoate$^-$, phenylacetate$^-$, 3-phenylpropanoate$^-$, and 4-phenylbutanoate$^-$; (△ and ···) cyclic alcohols; (+ and ---) *n*-alkanols; (× and — · —) *sec*-alkanols; (◇ and — - —) aliphatic *n*-amines; (▽ and —) ionized aliphatic *n*-acids. The straight lines are least-squares fits to the data.

average value of the quantity {$\Delta_r S°$(methylcyclohexanol derivative) − $\Delta_r S°$(cyclohexanol)} is also very constant; it is −5.5 J K^{-1} mol^{-1} (s = 1.3 J K^{-1} mol^{-1}). While the value of −2.6 kJ mol^{-1} for the enthalpy difference is very close to the average

TABLE 6: Standard Molar Gibbs Energies $\Delta_r G°$, Enthalpies $\Delta_r H°$, and Entropies $\Delta_r S°$ for the Exchange Reaction *sec*-Ligand(aq) + Cyclodextrin·*n*-Ligand(aq) = *n*-Ligand(aq) + Cyclodextrin·*sec*-ligand(aq)[a]

N_C[b]	$\Delta_r G°$ (kJ mol^{-1})	$\Delta_r H°$ (kJ mol^{-1})	$\Delta_r S°$ (J K^{-1} mol^{-1})
	Aliphatic Alcohols + α-Cyclodextrin		
3	2.12	5.6	11.7
4	2.92	1.1	−5.8
5	1.70	−0.3	−6.6
6	1.78	1.2	−2.0
7	2.74	0.8	−6.5
8	3.71		
	Aliphatic Amines + α-Cyclodextrin		
5	4.00	2.5	−4.9
7	2.31	1.6	−2.2
8	1.84	3.0	4.0
	Aliphatic Acids + α-Cyclodextrin		
3	3.1	−1.0	−13.5
	Aliphatic Alcohols + β-Cyclodextrin		
3	1.36	5.1	12
4	0.31	−0.5	−0.5
5	1.67	−0.75	−7.5
6	1.49	1.5	0
8	0.22		

[a] The values of $\Delta_r G°$ for the reactions involving the alcohols are from Rekharsky et al.[15] and the references cited therein. The data for the reactions involving the aliphatic acids and amines are from this study. [b] N_C is the number of hydrocarbon carbon atoms (CH, CH_2, and CH_3 groups) in the chemical formula of the ligand; that is, the carbon in the carboxylate group is not counted.

value of $d\Delta_r H°/dN_C$ (−2.5 kJ mol^{-1}) found for the reactions of the various classes of ligands with β-cyclodextrin, the difference in the $\Delta_r S°$'s is not close to the corresponding average value of $d\Delta_r S°/dN_C$. It is also noted that small structural changes in a ligand can cause substantive changes in thermodynamic quantities. For example the equilibrium constant for the reaction of *trans*-4-methylcyclohexanol with β-cyclodextrin is almost twice as large as that of *cis*-4-methylcyclohexanol.

A similar systematic variation involving the reactions of these ligands with β-cyclodextrin was also performed for the addition of methyl and methoxy groups to phenylacetate$^-$. The most striking result obtained from these variations is that the addition of a methyl or methoxy groups in the 2 position on these substances correlates with a significantly lower value of the equilibrium constant for the formation of the β-cyclodextrin·-ligand complex. A similar destabilization has been observed[24] for methoxy derivatives of phenethylamine$^+$. It is very likely that these destabilizations are due to steric effects. It was also found that addition of a methyl group in either the 3 or 4 position of phenylacetate$^-$ or of a methoxy group in the 3 position of phenylacetate$^-$ lowers $\Delta_r H°$ by ∼4.5 kJ mol^{-1}. However, addition of a methoxy group in the 4 position of phenylacetate$^-$ lowers $\Delta_r H°$ by only 0.7 kJ mol^{-1}. A possible explanation for this anomalous result is that the methoxy group in 4-methoxyphenylacetate$^-$ is not contained in the β-cyclodextrin cavity.

The effects of methyl and methoxy groups can be further explored by a comparison of the values of the thermodynamic quantities for the exchange reactions

R-phenethylamine$^+$(aq) + R-phenylacetate$^-$·β-cyclodextrin(aq) = (5)

R-phenethylamine$^+$·β-cyclodextrin(aq) + R-phenylacetate$^-$(aq)

Here, "R-" is a methyl or methoxy group (and its position) in either phenethylamine$^+$ or in phenylacetate$^-$. If there is no substituent group, reaction 5 pertains to the exchange reaction involving phenethylamine$^+$ and phenylacetate$^-$. Values of the thermodynamic quantities for reaction 5 were calculated with the results obtained in this study together with the results previously reported by Rekharsky et al.[24] It was found that the values of $\Delta_rG°$ for reaction 5 fall in a narrow range (0.7−1.9 kJ mol^{-1}). However, the values of $\Delta_rH°$ and $\Delta_rS°$ are less constant and their respective ranges are (−5.3 to −0.1 kJ mol^{-1}) and (−24 to −3 J K^{-1} mol^{-1}).

4.10. Estimation of Thermodynamic Quantities. Empirical observations such as those discussed above can be very useful for the estimation of thermodynamic quantities. For example, the equilibrium constant for the complexation reaction of 1-heptylamine$^+$ with β-cyclodextrin could not be measured with titration calorimetry because the standard molar enthalpy of this reaction was near zero. However, we can estimate $\Delta_rG° = -12.7$ kJ mol^{-1}, corresponding to $K \approx 168$, for this reaction from the β-cyclodextrin results for 1-hexylamine$^+$ and 1-octylamine$^+$. Combined with our measured value of $\Delta_rH°$, this leads to $\Delta_rS° \approx 43$ J K^{-1} mol^{-1}. The interpolated value of $\Delta_rH°$ (0.3 kJ mol^{-1}) from Table 2 is close to the measured value (∼0.2 kJ mol^{-1}). As a second example, the literature does not contain a result for the equilibrium constant for the complexation of neutral 2-methylpropanoic acid with α-cyclodextrin. However, extrapolation of the data for the neutral aliphatic *n*-acids (see Figure 3) leads to $\Delta_rG° = -12.2$ kJ mol^{-1} for the reaction of neutral 1-butanoic acid ($N_C = 3$) with α-cyclodextrin. We then use $\langle\Delta_rG°\rangle = 2.6$ kJ mol^{-1} for the exchange reaction (4) involving the branched and unbranched ligands to obtain an estimated $\Delta_rG° \approx -9.6$ kJ mol^{-1} and $K \approx 48$ for the complexation of neutral 2-methylpropanoic acid with α-cyclodextrin. Clearly, many additional estimates for substances can be made using the results obtained in this study.

4.11. NMR. Several interesting features are seen in an examination of the profiles of the changes in chemical shifts (see Figures 11−14) determined in this study. Most significantly, it is seen that all of the normal and branched hexylamines and heptylamines have very similar profiles, independent of the presence of an extra 1-methyl or *N*-methyl group. Furthermore, the values of $\Delta\delta$ for the 1-methyl and *N*-methyl protons are relatively small (−0.02 to −0.05). On this basis, it is concluded that these 1-methyl and *N*-methyl groups lie outside the α-cyclodextrin cavity and make no significant contribution to the stabilization of the cyclodextrin·ligand complex. This finding is consistent with the calorimetric results.

The concentrations *c* of α-cyclodextrin and ligand were kept approximately equal ($c = 0.005$ mol dm^{-3}) in the NMR experiments. Under these conditions, the fractions α of ligand and α-cyclodextrin that are complexed will not be unity. Using the equilibrium constants given in Table 1, the following values of α are calculated: 1-pentylamine$^+$, 0.27; 1-hexylamine$^+$, 0.50; 1-methylhexylamine$^+$, 0.52; N-methylhexylamine$^+$, 0.49; 1-heptylamine$^+$, 0.65; 1-methylheptylamine$^+$, 0.66; 1-octylamine$^+$, 0.75; pentanoate$^-$, 0.23; hexanoate$^-$, 0.45; heptanoate$^-$, 0.62; and octanoate$^-$, 0.75. It was found that the quantity $\Sigma N_H(\Delta\delta)$, defined as the sum of the $\Delta\delta$'s for a given ligand weighted by the number of hydrogens N_H in a given position (see Table 4), was found to correlate well with the α values. This correlation is in accord with expectations.

As can be seen from Figures 11 and 13, the $|\Delta\delta|$ values of the ligands increase constantly up to four methylene groups and reach a plateau in the region G4 to G6 for the amines and G3 to G6 for the acids. These $|\Delta\delta|$ values then decrease rapidly

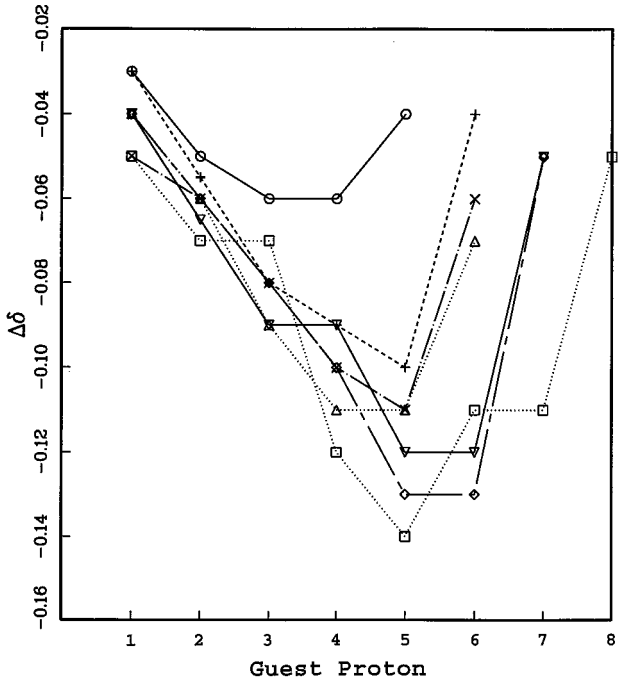

Figure 11. Profiles of complexation induced changes in chemical shifts $\Delta\delta$ in protons of pentylamine$^+$ (○ connected with —); hexylamine$^+$ (△ connected with •••); 1-methylhexylamine$^+$ (+ connected with ---); *N*-methylhexylamine$^+$ (× connected with — • —); heptylamine$^+$ (◇ connected with — - —); 1-methylheptylamine$^+$ (▽ connected with —); and octylamine$^+$ (□ connected with ...).

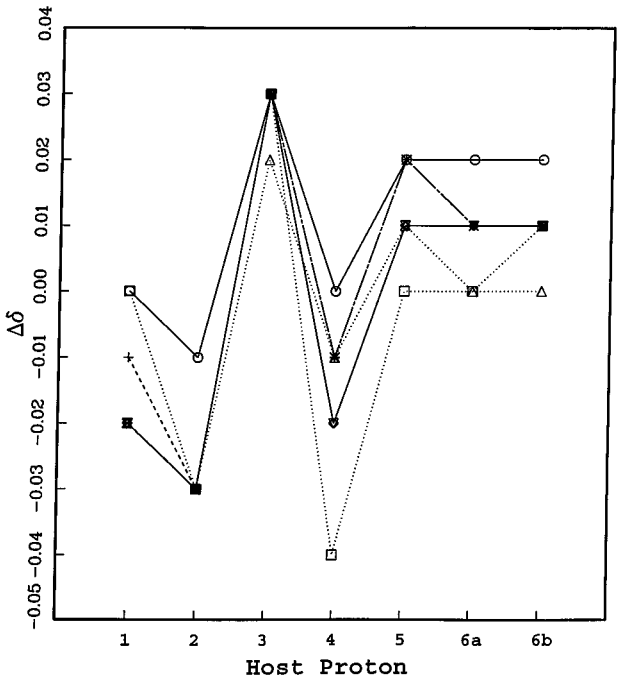

Figure 12. Profiles of complexation-induced changes in chemical shifts $\Delta\delta$ in α-cyclodextrin protons upon inclusion of amines. The symbols and connecting lines correspond to the same amines as in Figure 11.

for the terminal methyl group. While the maximum values of $|\Delta\delta|$ are comparable for the amines and acids, the $|\Delta\delta|$ plateau appears earlier for the acids. This indicates that the mode of accommodation of the acids and amines is similar and suggests that the alkyl chain of the *n*-alkanoates is embedded slightly deeper in the cyclodextrin cavity than the corresponding *n*-amines. This would be consistent with the finding from the calorimetry that, for the same value of N_C, the acids bind more

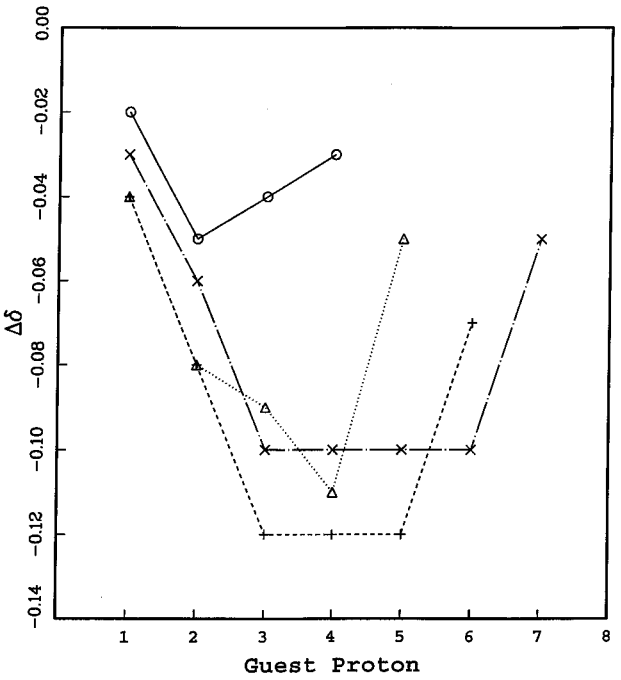

Figure 13. Profiles of complexation-induced changes in chemical shifts Δδ in protons of pentanoate⁻ (○ connected with —); hexanoate⁻ (△ connected with ...); heptanoate⁻ (+ connected with ---); and octanoate⁻ (× connected with — · —).

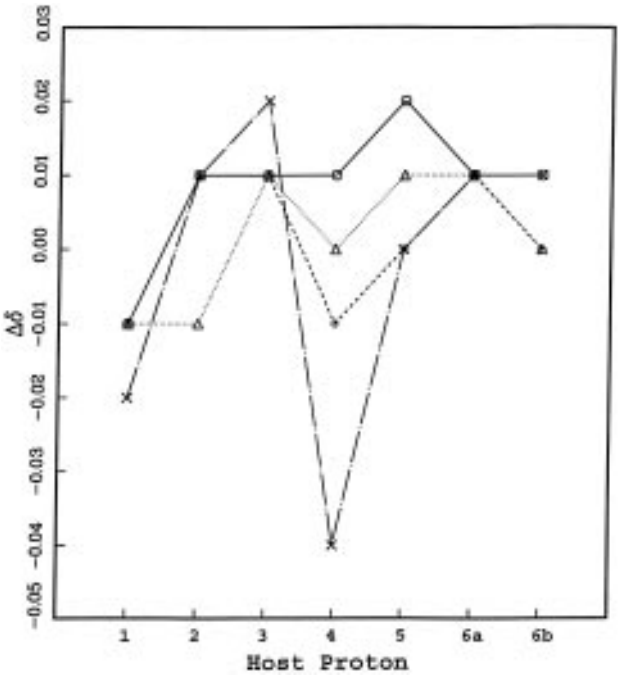

Figure 14. Profiles of complexation-induced changes in chemical shifts Δδ in α-cyclodextrin protons upon inclusion of acids. The symbols and connecting lines correspond to the same acids as in Figure 13.

tightly than the amines. This difference in depth of penetration could be attributable to charge delocalization at the carboxylate group.

The profiles of the cyclodextrin protons are shown in Figures 12 and 14. As a rule, the H3 and H5 protons, located inside the CD cavity, are most influenced by the inclusion of ligand molecules, while the H1, H2, and H4 protons, located outside the CD cavity, are unaffected. Thus, in our previous study,[24] the induced shifts of the H3 and H5 protons were found to be particularly large upon inclusion of aromatic ligands, and the ratio Δδ(H5)/Δδ(H3) was used as a quantitative measure of the depth of ligand penetration. Also, the |Δδ|'s of the H1, H2, and H4 cyclodextrin protons located outside the cavity were found[24] to be negligible (≤0.02). In this context, the small but steady downfield shifts of the H1, H2, and H4 protons found in this study, particularly upon inclusion of the amines, are unusual. These H1, H2, and H4 protons are located outside the cavity and cannot interact directly with that part of the ligand molecule located in the cyclodextrin cavity. Therefore, the downfield shifts of these outside protons can be attributed to hydrogen bonding of the amine's ammonium protons to the cyclodextrin's ethereal and alcoholic oxygens connected, respectively, to [C1/C4′] and C2. This, in turn, indirectly reduces the electron density of the H1, H2, and H4 protons and leads to the small but steady downfield shifts that are observed.

5. Conclusions

The interactions of the acids, amines, and alcohols and the related substances studied herein with α- and β-cyclodextrin can be qualitatively understood in terms of van der Waals forces and hydrophobic effects. Hydrogen bonding and steric effects also play a role in selected instances. Enthalpy−entropy compensation is evident when individual classes of substances are considered, but does not hold when these various classes of ligands are considered collectively. The values of the CH_2 increment $d\Delta_r G°/dN_C$ for the reactions of a variety of ligands with both α- and β-cyclodextrin are remarkably constant (average value = −3.2 kJ mol^{-1}) and are consistent with the presence of hydrophobic effects. However, the corresponding increments for the enthalpy and entropy show less regularity. In general, the values of thermodynamic quantities, $\Delta_r G°$ in particular, correlate well with structural features (branching, charge number, double bonds, and methyl and methoxy groups) in the ligands. Thermodynamic quantities for appropriately formulated exchange reactions are useful in summarizing the differences characteristic of these structural features and can be very useful for the estimation of thermodynamic quantities. The NMR results indicate that the mode of accommodation of the acids and amines in the α-cyclodextrin cavity is very similar, but that the 1-methyl groups in 1-methylhexylamine and in 1-methylheptylamine and the *N*-methyl group in *N*-methylhexylamine lie outside the cavity. These findings are consistent with the calorimetric results. The downfield shifts of the α-cyclodextrin's protons that are located outside the cavity can be attributed to hydrogen bonding of the amine's ammonium protons to the cyclodextrin's ethereal and alcoholic oxygens connected, respectively, to [C1/C4′] and C2.

Acknowledgment. We thank Dr. David Vanderah for his careful reading of this paper.

Supporting Information Available: One table (3 pages) containing information on the principal substances used in this study. Ordering information is given on any current masthead page.

References and Notes

(1) Szejtli, J. In *Inclusion Compounds. Volume 3: Physical Properties and Applications*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Academic Press: New York, 1984; pp 331−390.

(2) Szejtli, L. *Cyclodextrin Technology*; Kluwer Academic Publishers: Dordecht, The Netherlands, 1988.

(3) Schurig, V.; Jung, M. In *Recent Advances in Chiral Separations. Proc. Chromatogr. Soc. Int. Symp. Chiral Sep., 2nd Meeting;* Stevenson, D., Wilson, I. D., Eds.; Plenum: New York, 1991; pp 117−133.

(4) Amato, M. E.; Djedaini-Pilard, F.; Perly, B.; Scarlata, G. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2065.

(5) Berthod, A.; Li, W.; Armstrong D. W. *Anal. Chem.* **1992**, *64*, 873.

(6) Yamashoji, Y.; Ariga, T.; Asano, S.; Tanaka, M. *Anal. Chim. Acta* **1992**, *268*, 39.
(7) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: Berlin, 1978.
(8) Wishnia, A.; Lappi, S. J. *J. Mol. Biol.* **1974**, *82*, 77.
(9) Tucker, E. E.; Christian, S. D. *J. Am. Chem. Soc.* **1984,** *106*, 1942.
(10) Matsui, Y.; Mochida, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2808.
(11) Barone, G.; Castronuovo, G.; Del Vecchio, P.; Elia, V.; Muscetta, M. *J. Chem. Soc., Faraday Trans. 1* **1986**, *82*, 2089.
(12) Sasaki, K. J.; Christian, S. D.; Tucker, E. E. *Fluid Phase Equilib.* **1989**, *49*, 281.
(13) Andini, S.; Castronuovo, G.; Elia, V.; Gallotta, E. *Carbohydr. Res.* **1991**, *217*, 87.
(14) Hallén, D.; Schön, A.; Shehatta, I.; Wadsö, I. *J. Chem. Soc., Faraday Trans.* **1992**, *88*, 2859.
(15) Rekharsky, M. V.; Schwarz, F. P.; Tewari, Y. B.; Goldberg, R. N. *J. Phys. Chem.* **1994**, *98*, 10282.
(16) Bastos, M.; Briggner, L.-E.; Shehatta, I.; Wadsö, I. *J. Chem. Thermodyn.* **1990**, *22*, 1181.
(17) Lin, S.-F.; Connors, K. A. *J. Pharm. Sci.* **1983**, *72*, 1333.
(18) Bertrand, G. L.; Faulkner, J. R.; Han, S. M.; Armstrong, D. W. *J. Phys. Chem.* **1989**, *93*, 6863.
(19) Rekharsky, M. V.; Schwarz, F. P.; Tewari, Y. B.; Goldberg, R. N.; Tanaka, M.; Yamashoji, Y. *J. Phys. Chem.* **1994**, *98*, 4098.
(20) Inoue, Y.; Hakushi, T.; Liu, Y.; Tong, L.-H.; Shen, B.-J.; Jin, D.-S. *J. Am. Chem. Soc.* **1993**, *115*, 475.
(21) Connors, K. A.; Lin, S.-F.; Wong, A. B. *J. Pharm. Sci.* **1982**, *71*, 217.
(22) Wong, A. B.; Lin, S.-F.; Connors, K. A. *J. Pharm. Sci.* **1983**, *72*, 388.
(23) Connors, K. A.; Paulson, A.; Toledo-Velasquez, D. *J. Org. Chem.* **1988**, *53*, 2023.
(24) Rekharsky, M. V.; Goldberg, R. N.; Schwarz, F. P.; Tewari, Y. B.; Ross, P. D.; Yamashoji, Y.; Inoue, Y. *J. Am. Chem. Soc.* **1995**, *117*, 8830.
(25) Casu, B.; Grenni, A.; Naggi, A.; Torri, G.; Virtuani, M.; Focher, B. *Carbohydr. Res.* **1990**, *200*, 101.
(26) Watanabe, M.; Nakamura, H.; Matsuo, T. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 164.
(27) Wiseman, T.; Williston, S.; Brandts, J. F.; Lin, L.-N. *Anal. Biochem.* **1989**, *179*, 131.
(28) Certain commercial materials and products are identified in this paper to specify adequately the experimental procedure. Such identification does not imply recommendation or endorsement by the National Institute of Standards and Technology.
(29) Yang, C. P. *Omega Data Analysis in Origin*; Microcal: Northampton, MA, 1990.
(30) Murray, K.; May, P. M. *Joint Expert Speciation System*; Murdoch University: Murdoch, Western Australia, 1992.
(31) Martell, A. E.; Smith, R. M.; Motekaitis, R. J. *NIST Critical Stability Constants of Metal Complexes Database*; NIST Standard Reference Database 46; National Institute of Standards and Technology: Gaithersburg, MD, 1993.
(32) Siimer, E.; Kurvits, M.; Köstner, A. *Thermochim. Acta* **1987**, *116*, 249.
(33) Germain, P.; Bilal, M.; de Brauer, C. *Thermochim. Acta* **1995**, *259*, 187.
(34) Ross, P. D.; Rekharsky, M. V. *Biophys. J.* **1996**, *71*, 2144.
(35) Kauzmann, W. *Adv. Protein Chem.* **1959**, *14*, 1.
(36) Gill, S. J.; Nichols, N. F.; Wadsö, I. *J. Chem. Thermodyn.* **1976**, *8*, 445.
(37) Gill, S. J.; Dec, S. F.; Olofsson, G.; Wadsö, I. *J. Phys. Chem.* **1985**, *89*, 3758.
(38) Martin, P. J.; Morss, L. R.; Strauss, U. P. *J. Phys. Chem.* **1980**, *84*, 577.
(39) Frank, H. S.; Evans, M. W. *J. Chem. Phys.* **1945**, *13*, 507.
(40) Pimentel, G. C.; McClellan, A. L. *The Hydrogen Bond*; Freeman: San Francisco, 1960; p 220.
(41) Tanford, C. *The Hydrophobic Effect: Formation of Micelles and Biological Membranes*; Wiley-Interscience: New York, 1980.
(42) Eftink, M. R.; Andy, M. L.; Bystrom, K.; Perlmutter, H. D.; Kristol, D. S. *J. Am. Chem. Soc.* **1989**, *111*, 6765.
(43) Voet, D.; Voet, J. G. *Biochemistry*; John Wiley: New York, 1990; pp 175−181.
(44) Gelb, R. I.; Schwartz, L. M.; Johnson, R. F.; Laufer, D. A. *J. Am. Chem. Soc.* **1979**, *101*, 1869.
(45) Gelb, R. I.; Schwartz, L. M.; Cardelino, B.; Fuhrman, H. S.; Johnson, R. F.; Laufer, D. A. *J. Am. Chem. Soc.* **1981**, *103*, 1750.
(46) Rymdén, R.; Carlfors, J.; Stilbs, P. *J. Inclusion Phenom.* **1983**, *1*, 159.
(47) Siimer, E.; Kõbu, M.; Kurvits, M. *Thermochim. Acta* **1990**, *170*, 89.