Concerning the Thermodynamics of Molecular Recognition in Aqueous and Organic Media. Evidence for Significant Heat Capacity Effects†

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Received October 9, 1989

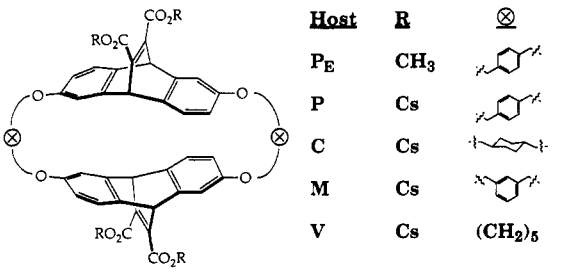
Variable-temperature binding studies are used to evaluate the thermodynamics of molecular recognition of a variety of guests by macrocyclic, cyclophane hosts. In both organic ($CDCl_3$) and aqueous media, significant heat capacity effects are evident. Curvature in the van't Hoff plots can be well-modeled by assuming a constant value for $\Delta C_p°$, and statistical analysis reveals a meaningful improvement in the correlation when $\Delta C_p°$ is included. Trends in the values for $\Delta H°_{298}$ and $\Delta S°_{298}$ reveal a predominantly enthalpic origin for the "cation-π" effect, which involves the stabilization of a positive charge by the electron-rich face of an aromatic ring.

As molecular recognition continues to develop into a major focus of modern chemistry, efforts to understand the fundamental forces involved in noncovalent binding are increasing. In abiotic, model systems[1] a large number of binding association constants (K_a) have been determined, and these lead naturally to the free energies of binding ($\Delta G°$). In principle, evaluation of K_a over a significant temperature range can lead, through standard relations, to the enthalpy ($\Delta H°$) and entropy ($\Delta S°$) of association. These latter terms can provide insights into the physical nature of the binding interaction. For example, classical "hydrophobic" binding is often associated with a large, favorable (positive) entropy change due to solvent ordering effects.[2-13] On the other hand, physical attraction between host and guest, i.e., true molecular recognition, should result in a favorable (negative) enthalpy change on binding.[14-16]

Such studies, however, are not always so straightforward. Firstly, experimental determinations often involve titration procedures that can be relatively imprecise, and such imprecisions can be amplified in a variable-temperature study. Nevertheless, in optimal cases, sufficiently accurate K_a values can be obtained. Another, potentially more severe, complication arises from the fact that $\Delta H°$ and $\Delta S°$ themselves need not be temperature-invariant. By definition, the variation of $\Delta H°$ with temperature is the heat capacity: $\Delta C_p° = (\partial \Delta H°/\partial T)_p$. If $\Delta C_p°$ is not negligible, the interpretation of $\Delta H°$ and $\Delta S°$ values can become substantially clouded.

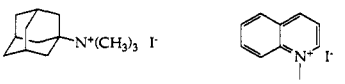
We describe herein the results of a series of variable-temperature (VT) binding studies performed on host–guest systems we have developed over the past several years. We previously reported binding studies in aqueous[17-19] and organic[20] media using electron-rich synthetic receptors. Preferential binding of electron-deficient (versus electron-rich) aromatic guests provided evidence for substantial donor–acceptor π-stacking interactions in water. Even higher affinities between host P and positively charged guests 1–4 identified favorable "cation-π" interactions[21] in both aqueous and organic media. It was from this perspective that VT binding studies were undertaken, in an effort to further define solvophobic, donor–acceptor, and cation-π interactions according to their respective $\Delta H°$ and $\Delta S°$ contributions. As before,[17-20] we emphasize *trends* in the data obtained from comparisons of closely related host–guest pairs, rather than focus on quantitative measurements of thermodynamic parameters. We find significant $\Delta C_p°$ effects in both aqueous and organic ($CDCl_3$) media.

Hosts



Host	R	⊗
P_E	CH_3	
P	Cs	
C	Cs	
M	Cs	
V	Cs	$(CH_2)_5$

Guests



1 (ATMA)

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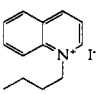

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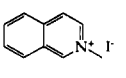

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† Contribution No. 8342.

‡ Department of Education Graduate Assistance in Areas of National Need Fellow, 1989.

(1) For recent reviews of the general area of molecular recognition, see: Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362-386. Franke, J.; Vögtle, F. *Top. Curr. Chem.* **1986**, *132*, 135-170. Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1039-1057. Saenger, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344-362. Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89-112. Rebek, J., Jr. *Science* **1987**, *235*, 1478-1484. Rebek, J., Jr. *Top. Curr. Chem.* **1988**, *149*, 189-210.

(2) The hydrophobic effect has been extensively reviewed, and continues to be the topic of much study and discussion. The classic introduction to the field is: Tanford, C. *The Hydrophobic Effect*, 2nd ed.; Wiley: New York, 1980. References 3-13 constitute a variety of more recent contributions to the topic. The list is not meant to be exhaustive.

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Table I. Thermodynamic Data for $\Delta G°_{298}$ = -6.82 kcal/mol; $\Delta H°_{298}$ = -4.44 kcal/mol; $\Delta S°_{298}$ = +8.0 cal/mol K

T, K	$\Delta G°$ [a]	$\Delta H°$ [a]	$\Delta S°$ [b]	$-T\Delta S°$ [a]
	Case I: $\Delta C_p°$ = -500 cal/mol K			
278	-6.3	+5.6	+43	-12
298	-6.8	-4.4	+8.0	-2.4
318	-6.7	-14	-24	+7.8
	Case II: $\Delta C_p°$ = -100 cal/mol K			
278	-6.6	-2.4	+15	-4.2
298	-6.8	-4.4	+8.0	-2.4
318	-6.7	-6.4	+1.5	-0.5

[a] In kcal/mol. [b] In cal/mol K.

Expectations from Studies of Biological Receptors

It has been amply demonstrated that large $\Delta C_p°$ effects are common in protein chemistry.[11,12] Invariably, binding events (e.g., between enzyme and substrate) show $\Delta C_p° <$ 0, with typical values in the range -100 to -1000 cal/mol K. In contrast, protein unfolding reactions show $\Delta C_p° \gg$ 0, with typical values in the range of 1000–3000 cal/mol K. Several factors have been invoked to rationalize these effects, including conformational, vibrational, and hydrophobic contributions.[23] The trends are consistent with small molecule studies that find $\Delta C_p° > 0$ for dissolution of organic molecules in water. For example, $\Delta C_p°$ for dissolution of 1-pentanol in water is 83.5 cal/mol K.[5]

Thus, heat capacity effects should be expected to occur in studies of molecular recognition in water. Some feeling for the potential magnitude of these effects can be obtained from a hypothetical model calculation. The relevant equations are 1–6

$$\Delta G° = -RT \ln K_a \quad (1)$$

$$\Delta G° = \Delta H° - T\Delta S° \quad (2)$$

$$\Delta H° = \Delta H_0 + T\Delta C_p° \quad (3)$$

or

$$\Delta H° = \Delta H°_{298} + (T - 298)\Delta C_p° \quad (4)$$

$$\Delta S° = \Delta S_0 + \Delta C_p° \ln T \quad (5)$$

or

$$\Delta S° = \Delta S°_{298} + \Delta C_p° \ln (T/298) \quad (6)$$

Table II. Comparison of Binding Constants for "Single-Point" and "Complete" VT Binding Studies of Host P_E and Guest 2 in $CDCl_3$

T, K	"single-point" K_a,[a,b] M^{-1}	"complete" K_a, M^{-1}	D value,[b] ppm
234.2	1230	1220	2.87
296.4	380	410	2.65
334.6	190	190	2.80

[a] D = 2.65 ppm. [b] For N-CH_3.

where ΔH_0 and ΔS_0 are constants of integration. Combining these equations gives:

$$R \ln K_a = -\left(\frac{\Delta H_0}{T}\right) + \Delta C_p° \ln T + (\Delta S_0 - \Delta C_p°) \quad (7)$$

If heat capacity is neglected:

$$R \ln K_a = -\Delta H_0\left(\frac{1}{T}\right) + \Delta S_0 \quad (8)$$

which is the typical van't Hoff analysis.

Consider an association process with $K_a = 10^5$ M^{-1} at 298 K. Table I summarizes two scenarios for the same combination of $\Delta H°$ and $\Delta S°$ at 298 K. In the first, $\Delta C_p°$ = -500 cal/mol K, typical of a biological association; in the second, $\Delta C_p°$ = -100 cal/mol K, perhaps more typical of small molecule binding, given the 1-pentanol result. Although the effect is, of course, more dramatic when $|\Delta C_p°|$ is larger, both cases produce the same qualitative conclusion. A process for which entropy is the primary driving force for complexation evolves into one for which enthalpy is the major force over the relatively modest temperature range of 5–45 °C. Note that while $\Delta H°$ and $\Delta S°$ vary widely, $\Delta G°$ remains nearly constant.

Of course, these effects have been appreciated for some time, and this simple illustration is only meant to dramatize the conclusion that in biological systems "enthalpy usually dominates in association reactions at high temperatures, while the entropy is more important at low temperatures".[24] If one accepts such values of $\Delta H°$ and $\Delta S°$, one is left with the unsavory situation of the identical physical process completely changing its character over a narrow temperature range. It is not certain how to attach a physical significance to such parameters.

As mentioned above, we have seen significant heat capacity effects in the present work. For the purpose of comparison with other sytems, we will focus on the values at 298 K ($\Delta H°_{298}$ and $\Delta S°_{298}$). We find the *trends* in these values are interpretable and produce useful insight into the binding process.

Results and Discussion

Single-Point VT Binding Analysis. As described in our earlier work,[17-20] protons for guests encapsulated by our hosts experience substantial upfield shifting in their ^1H NMR spectra. We have used an iterative, nonlinear, least-squares method called MULTIFIT[17] to evaluate these time-averaged shifts from a series of host and guest concentrations at room temperature. From each analysis, we ascertain values for the binding affinity, K_a, and, for each guest proton, the maximum upfield shifts, *D*.

We sought to take advantage of our knowledge of the *D* values to reduce the time and effort required to carry out a VT binding study. The binding constant can be

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(20) Stauffer, D. A.; Dougherty, D. A. *Tetrahedron Lett.* **1988**, *29*, 6039–6042.
(21) In our previous work[17,18,20] we described this interaction as an "ion–dipole" effect. Although the term was intended to be descriptive only, we now believe it has an overly specific connotation. The stabilization of a positive charge by an electron-rich π system is no doubt a complex phenomenon, involving charge–dipole, charge–quadrupole, charge-induced dipole, π-polarization, and other effects. "Ion–dipole" implies, for example, a definite distance dependence ($1/r^2$) which may not be appropriate here. For a recent discussion of these various interactions as applied to protein chemistry, see ref 22.
(22) Burley, S. K.; Petsko, G. A. *Adv. Prot. Chem.* **1988**, *39*, 125–189.
(23) Sturtevant, J. M. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 2236–2240.
(24) Reference 11, p 222.

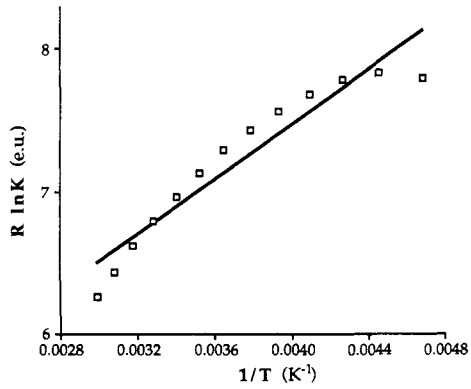

Figure 1. Van't Hoff plot with best fit straight line for host P_E and guest 1 (ATMA) in $CDCl_3$.

calculated simply from *single* host and guest concentrations at each temperature according to eqs 9 and 10 where

$$K_a = \left(\frac{1}{[H]_0 - (P[G]_0)}\right)\left(\frac{P}{1-P}\right) \quad (9)$$

$$P = \frac{\text{observed upfield shift}}{D} \quad (10)$$

$[H]_0$ and $[G]_0$ are total concentrations of host and guest, respectively; P is the fraction guest bound; and the D value for a given guest proton is assumed to be temperature-invariant.

To assess the validity of the assumption of a temperature-invariant D value, we performed complete binding studies with MULTIFIT analysis for host P_E and guest 2 in $CDCl_3$ at three different temperatures. We also conducted a "single-point" analysis (D = 2.65 ppm for N-CH_3), wherein binding constants were calculated according to eqs 9 and 10. The results for the "single-point" and "complete" (i.e., full binding studies at each temperature) studies are shown in Table II. The agreement between the two methods is quite good; the calculated D values show less than 10% deviation from each other. All parameters reported in this study were obtained with this "single-point" method using room-temperature, MULTIFIT-calculated D values.

Regression Analysis. The variable-temperature data were fit to the linear van't Hoff equation (eq 8) and to the adjusted equation allowing for the effect of a temperature-invariant heat capacity change (eq 7).[25] The fits were obtained using a general least-squares procedure with two and three adjustable parameters, respectively.

It is important in regression analysis to critically test the inclusion of additional parameters to fit a data set, since the fit is expected to improve even if the new parameters have no relation to the actual distribution of the data, or if the deviation without the new parameters is entirely due to random error. An F test for significance of regression[26] has been employed in each case to evaluate the null hypothesis that the two-parameter fit is as justified as that with three parameters.[27] The null hypothesis can be rejected if the improvement in the fit is convincingly better than expected. In the present work, it typically can

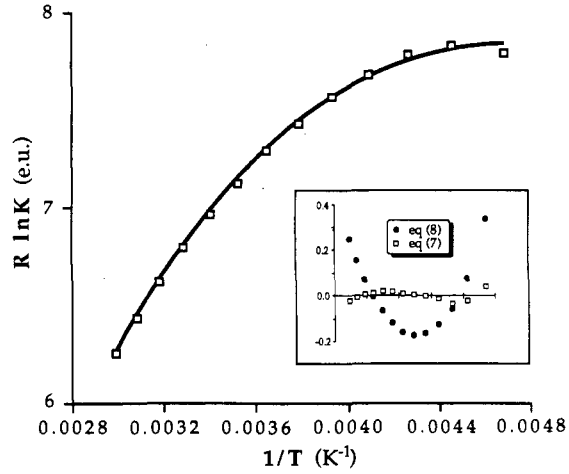

Figure 2. Van't Hoff plot with best fit curve following eq 7 for host P_E and guest 1 (ATMA) in $CDCl_3$. Inset: residuals from fits to the data using eqs 7 and 8. The horizontal axis is $1/T$, with hatches at the same values as the main graph.

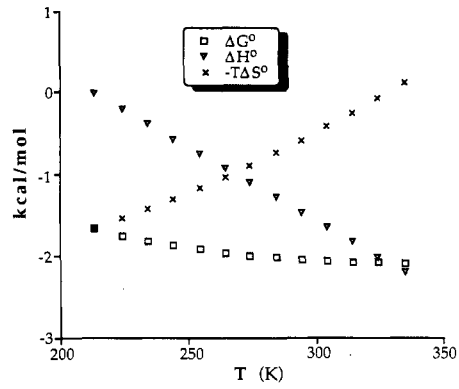

Figure 3. Plot of $\Delta G°$ and calculated $\Delta H°$ and $-T\Delta S°$ values vs T for host P_E and guest 1 (ATMA) in $CDCl_3$.

be rejected with "six nines" (99.9999%) confidence or better, and with 94% confidence in the worst case (see Figures 2, 4, and 5).

We have made no attempt to model a $\Delta C_p°$ that changes with temperature, although such variability has been observed for similar processes.[7,28] The use of a constant $\Delta C_p°$ gives good fits to our data, and it is doubtful that including a temperature dependence in $\Delta C_p°$ as yet another parameter would provide a meaningful improvement. Furthermore, reported and theoretical $\Delta C_p°$ values have complex temperature dependences, so it is not clear what functional form such a fitted dependence should take.[29]

Organic VT Binding Studies. In recent work, we interpreted the complexation between tetraester host P_E and a series of positively charged onium guests (1–4) in chloroform as evidence for substantial cation-π interactions in organic media.[20] We sought in the present study to characterize such interactions as being enthalpic or entropic in origin. Figure 1 shows the van't Hoff plot for the VT binding study of host P_E and guest 1 in $CDCl_3$. If we fit the plot according to eq 8, in which $\Delta C_p° = 0$, $\Delta H°$ (-1.0 kcal/mol) and $T\Delta S°$ (1.1 kcal/mol) make roughly the same

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(27) $F = (SSR^* - SSR)/(SSR/(n-3))$, where SSR is the sum of the squares of the residuals between the data and the three-parameter fit, SSR* is the sum of the squares of the residuals between the data and the two-parameter fit, and n is the number of data points. If the null hypothesis is true, F should follow the F (1, n - 3) distribution.

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(29) A pattern is apparent in the residuals from fits to eq 7 shown in Figures 2, 4, and 5, and in other fits we have done. While we are not certain that the quality of our data is sufficient to interpret this effect, we note that the general shape is qualitatively similar to that expected if $\Delta C_p°$ varies linearly with temperature.

Table III. Thermodynamic Parameters for Host P_E and Guests 1–4 in $CDCl_3$

guest[a]	$\Delta G°_{298}$[d]	$\Delta H°_{298}$[d]	$\Delta S°_{298}$[e]	$\Delta C_p°$[e]
1[b]	−2.1	−1.5	+1.8	−18
2[c]	−3.5	−3.3	+0.4	−24
3[c]	−2.5	−3.6	−3.8	−24
4[c]	−2.4	−2.4	0.0	−19

[a] VT binding study covering: [b] 214–334 K; [c] 234–334 K. [d] In kcal/mol. [e] In cal/mol K.

contribution to $\Delta G°$ (−2.1 kcal/mol) at 298 K. However, this plot clearly exhibits curvature over its 120-deg temperature range, such that $\Delta C_p°$ cannot be neglected. The fitted curve for this same data using eq 7 is shown in Figure 2: $\Delta C_p° = -18$ cal/mol K. According to this analysis, the binding force at 298 K is composed primarily of a strong enthalpic contribution (−1.5 kcal/mol) with a slightly favorable $T\Delta S$ term (0.52 kcal/mol).

The varying contributions of entropy and enthalpy to the free energy for this process are shown in Figure 3. As alluded to above, biological association processes with large $|\Delta C_p°|$ values exhibit compensation of enthalpic and entropic contributions to afford a relatively temperature-invariant $\Delta G°$.[12] Although $\Delta C_p°$ is smaller in the present work ($CDCl_3$), we still find the expected compensation behavior. Entropy is the sole contributor to $\Delta G°$ at −60 °C, while enthalpy completely dominates at +60 °C. The free energy for complexation changes less than 0.5 kcal/mol over 120 °C!

Thermodynamic parameters derived from the VT binding studies in $CDCl_3$ for host P_E and guests 1–4 are summarized in Table III. The corresponding van't Hoff plots (not shown) all display distinct curvature. The heat capacities for binding in chloroform are consistent with biological association processes in that all $\Delta C_p°$ values are negative, although their magnitudes are smaller, as would be expected for a nonaqueous environment.[12,23]

Based upon the values for $\Delta H°$ and $\Delta S°$ at 298 K, the origin of the cation-π effect for binding onium guests in organic media is primarily enthalpic, as expected. Additionally, the lower affinity of guest 3 versus 2 is clearly the result of an unfavorable entropic term, which we attribute to the necessity to orient the butyl group upon encapsulation in host P_E. These findings bolster our previous conclusion[20] that the binding of such structures in chloroform is not due to solvophobic effects. A surprising result, however, is the near-zero entropic contribution to the binding force, in light of results obtained in related host–guest systems. Association processes involving other highly preorganized hosts with *neutral* guests in organic solvents[16,30] have been found to exact a substantial entropic cost attributed to the order necessary to bring two species together as one. We do not know why a similar effect is not seen in our systems, but we can suggest two possible explanations. Perhaps the near-zero $\Delta S°_{298}$ reflects the presence of the counterion, such that two species are in equilibrium with two:

$$\text{host} + \text{guest}^+\cdot X^- \rightleftharpoons \text{host}\cdot\text{guest}^+ + X^-$$

In this model, the recognition of the onium guest by host P_E would be equivalent to breaking a tight-ion pair (such salts are known to be completely associated in chloroform) into a "host-separated" ion pair. Alternatively, we cannot rule out the possibility that, to some extent, the near-zero $\Delta S°_{298}$ reflects "solvophobic" effects, analogous to hydrophobic binding. Perhaps the charged guest causes an entropically unfavorable ordering of solvent dipoles that is released upon binding. The fact that $\Delta C_p° < 0$ in chloroform would appear to be consistent with this explanation. We emphasize, however, that at present these are simply speculations that attempt to rationalize the anomalous entropy we observe.

(30) Cram, D. J.; Stewart, K. D.; Goldberg, I.; Trueblood, K. M. *J. Am. Chem. Soc.* **1985**, *107*, 2574–2575.

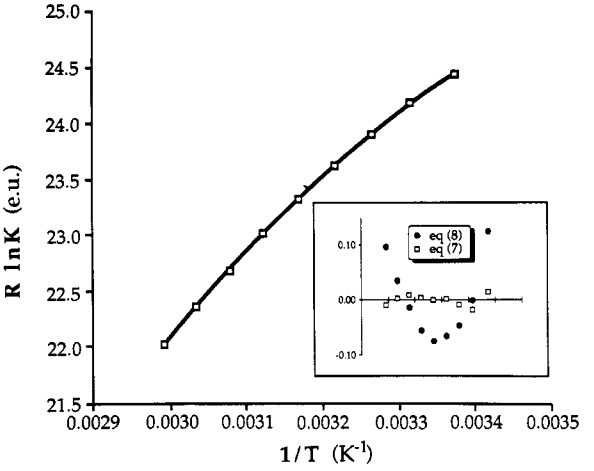

Figure 4. Van't Hoff plot with best fit curve following eq 7 for host P and guest 1 (ATMA) in borate-*d*. Inset: residuals, as in Figure 2.

Table IV. Thermodynamic Parameters for Guest 1 and Several Hosts in Borate-*d*[a]

host	$\Delta G°_{298}$[b]	$\Delta H°_{298}$[b]	$\Delta S°_{298}$[c]	$\Delta C_p°$[c]
P	−7.3	−4.7	+8.6	−100
M	−6.4	−3.4	+10	−130
C	−5.6	−1.3	+14	−110
V	−5.5	−4.9	+2.2	−34

[a] VT binding studies covering 294–334 K. [b] In kcal/mol. [c] In cal/mol K.

Aqueous VT Binding Studies: Guest ATMA. We begin our evaluation of the thermodynamics of binding in aqueous media by considering guest 1 with a series of hosts in which the linker groups (⊗) are varied. Because we are comparing data for a single guest, guest–solvent interactions are factored out. A typical set of experimental data along with the fit from eq 7 are shown in Figure 4 for host P. The relevant thermodynamic parameters are listed in Table IV. As expected, $\Delta C_p°$ effects in water are generally much larger than in chloroform, with the sign and magnitude completely consistent with expectation.

Extending the conclusion from the organic VT binding studies that the cation-π effect is of enthalpic origin suggests that what is left over, i.e., the positive $\Delta S°_{298}$ term, results from hydrophobic interactions, consistent with "classical" views of hydrophobic binding. We have previously invoked the cation-π effect to account for the different binding capabilities of hosts P and C, which possess similar binding site dimensions and comparable degrees of preorganization. Indeed, host P, with its fully aromatic binding site, shows a more favorable $\Delta H°_{298}$, in line with our view that the cation-π effect is enthalpic in origin. The more favorable entropy term for host C indicates classical hydrophobic interactions, since cyclohexyl is more hydrophobic than phenyl.[6] Apparently, binding also diminishes the amount of *host* surface area that is exposed to water, as well as guest surface area. We find that for hosts P and M, which both contain aromatic linkers, stronger cation-π interactions are evident by the more favorable $\Delta H°_{298}$ versus host C. These findings are consistent with the binding of adamantyl ammonium and carboxylate derivatives by β-cyclodextrin: $\Delta C_p°$ values are

Table V. Thermodynamic Parameters for Hosts P and C with Guests in Borate-d^a

guest	$\Delta G°_{298}$[b]	$\Delta H°_{298}$[b]	$\Delta S°_{298}$[c]	$\Delta C_p°$[c]
		Host P		
5	-6.0	-11	-17	-12
6	-6.4	-9.8	-11	-25
7	-7.1	-9.8	-9.1	-130
8	-4.0	-1.6	+8.1	-120
		Host C		
5	-6.4	-7.5	-3.8	-39
6	-6.3	-2.9	+11	-61
7	-6.3	+1.0	+24	-190
8	-5.0	+0.3	+18	-120

[a] VT binding studies covering 294–334 K. Guest solubilities (M^{-1})[17] in borate-*d*: 5 (0.078); 6 (0.037); 7 (0.014); 8 (0.0032). [b] In kcal/mol. [c] In cal/mol K.

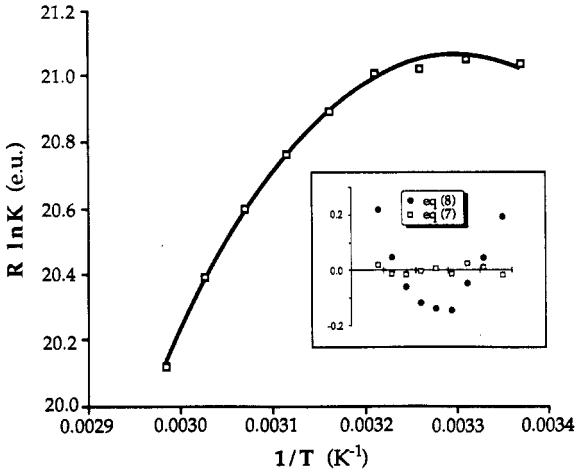

Figure 5. Van't Hoff plot with best fit curve following eq 7 for host C and guest 7 in borate-*d*. Inset: residuals, as in Figure 2.

comparable (~−100 cal/mol K), and complexation is enthalpically driven at room temperature.[15] Host V shows a less favorable $\Delta S°_{298}$, as anticipated[17] for this less preorganized host. The value of $\Delta H°_{298}$ is surprisingly negative and suggests that V can adopt a conformation that allows significant cation-π interactions. Detailed comparisons are risky, however, because it is known[17,19] that V binds 1 in a significantly different orientation than does P.

Aqueous VT Binding Studies: Hosts P and C with Neutral Guests. Table V compares thermodynamic parameters for hosts P and C determined from VT binding studies with neutral, aromatic guests 5–8.[31] Our previous work indicated substantial donor–acceptor π-stacking interactions[17,18] between these electron-rich hosts and the electron-deficient guests (5–7). Figure 5 depicts the fit of eq 7 to the van't Hoff plot for host C and guest 7. The compensation of $\Delta H°$ and $\Delta S°$ contributions to $\Delta G°$ is shown in Figure 6.

In comparing hosts P and C, VT binding studies reveal two important features. First, enthalpic and entropic contributions identify donor–acceptor and hydrophobic interactions, respectively. Second, methylation of the guests appears to affect the magnitude of the heat capacities for association with both hosts in aqueous media.

With respect to hydrophobic and donor–acceptor interactions, as discussed above for the binding of guest 1,

(31) We have found that for host–guest pairs with very high K_a's (>2 × 10^5 M^{-1}), our stock solution concentrations and/or D values are not accurate enough for "single-point" analysis with eqs 9 and 10, such that we cannot obtain meaningful VT binding data for host P and guests 2–4 in aqueous media.

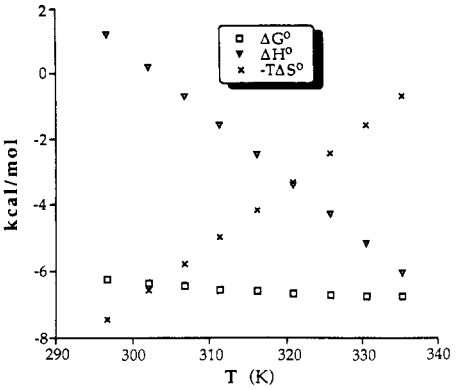

Figure 6. Plot of $\Delta G°$ and calculated $\Delta H°$ and $-T\Delta S°$ values vs T for host C and guest 7 in borate-*d*.

the more hydrophobic host C displays a more positive $\Delta S°_{298}$. In contrast, the binding of electron-deficient guests by host P is clearly more enthalpic in origin. Thus, hosts P and C show comparable affinities for guests 5 and 6, but apparently for different reasons, as was anticipated.[18] The result for host P nicely complements a recent study by Diederich and co-workers wherein host complexation of benzene-type guests was driven by a strong enthalpic component in water and in methanol.[14] Additionally, in our work, the trend in $\Delta S°_{298}$ for host P matches the guest solubilities in the borate buffer: the least soluble (and hence most hydrophobic) guest, 8, has the most favorable $\Delta S°_{298}$ contribution to the binding force.

The magnitudes of $\Delta C_p°$ values for both hosts are distinguished by whether the guest is methylated, independent of the electronic structure of the aromatic π-system. Methylated guests 7 and 8 have significantly larger values for $|\Delta C_p°|$ compared to 5 and 6. This result is consistent with trends in heat capacities for dissolution of aromatic versus alkylaromatic solutes in water:[32] $|\Delta C_p°|$ is significantly larger when alkyl groups are added.

Conclusion

Variable-temperature binding studies in both aqueous and organic media have revealed significant heat capacity effects. Consequently, the origin of the binding force changes from entropic at lower temperatures to enthalpic at higher temperatures. The magnitudes of $\Delta C_p°$ in the present work reflect a dependence on solvent as well as on electronic and structural properties of guests: $|\Delta C_p°|$ tends to be greater in water than in chloroform; and $|\Delta C_p°|$ is found to be larger for methylated guests in aqueous media. From the trends in $\Delta H°_{298}$ and $\Delta S°_{298}$, we find that solvophobic binding is evident by a positive $\Delta S°$ term, and we conclude that donor–acceptor and cation-π interactions are enthalpically driven.

Experimental Section

Variable-temperature (VT) ^{1}H NMR spectra were recorded on a JEOL JNM GX-400 spectrometer. The probe temperature was calibrated against either a methanol or an ethylene glycol standard. Pulse delays used during integration of the organic and aqueous stock solutions (15–20 s) were at least 5 times the measured T_1 for the species involved. Enantiomerically pure hosts were used in all binding studies, except for V, which was racemic. Concentration ranges and fitting techniques used were as in previous studies.[17,20]

Organic VT Binding Studies. Organic binding spectra were referenced at all temperatures to the residual proton signal of

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$CDCl_3$ (7.24 ppm). Guest stock solutions were prepared in volumetric flasks (2 mL) with deuteriochloroform. Concentrations of host and guest were quantified separately via NMR integrations against a standardized solution of a carefully tared amount of adamantyltrimethylammonium iodide (1) in $CDCl_3$ (2 mL, 19.1 mM). Volumetric measurements were made using Hamilton microliter syringes. Volumes were corrected for thermal expansion of solvent according to: $v_t = v_o(1 + \alpha t_o)$; where v_t = volume at the corrected probe temperature; t_o = difference between probe and room temperatures; v_o = volume measured at room temperature; and $\alpha = 0.001\,26$ cm^3/deg, the coefficient of thermal expansion for $CHCl_3$.[33]

(33) Riddick, J. A.; Bunger, W. B. *Organic Solvents*, 3rd ed.; Wiley: New York, 1970.

Aqueous VT Binding Studies. Aqueous binding spectra were referenced at all temperatures to internal 3,3-dimethylglutarate (DMG, 1.09 ppm vs TSP) in a standard 10 mM deuterated cesium borate buffer[17] at pD ~9 (borate-*d*). Concentrations of host and guest stock solutions were determined via NMR integrations against a stock solution of DMG (4.20–4.23 mM). Volumeric measurements were made using adjustable volumetric pipets. Volumes were corrected for density changes from a plot of densities of H_2O versus temperature (10–65 °C),[33] which fit the following equation: $y = a + bx + cx^2$; where y = density at corrected probe temperature, x (°C); $a = 1.0011$; $b = -6.7589 \times 10^{-5}$; $c = -3.8471 \times 10^{-6}$.

Acknowledgment. We thank the Office of Naval Research for support of this work. D.A.S. was an NSF predoctoral fellow, 1983–86.

Intermediate in Sommelet–Hauser Rearrangement of *N,N*-Dimethylbenzylammonium *N*-Methylides

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Received August 18, 1989

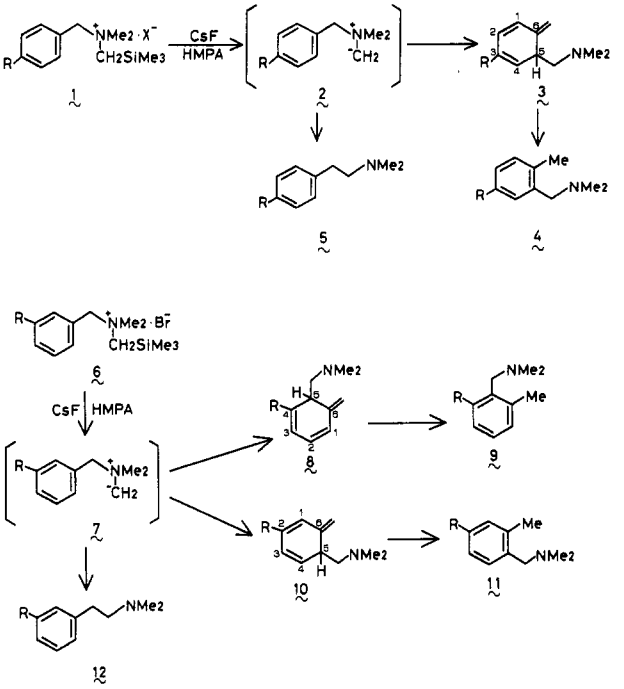
Formation of benzylammonium *N*-methylides by fluoride anion induced desilylation of dimethyl(4-substituted benzyl)[(trimethylsilyl)methyl]ammonium halides (**1**) and 3-substituted benzyl analogues (**6**) was examined to isolate 5-[(dimethylamino)methyl]-6-methylene-1,3-cyclohexadienes (isotoluene intermediates, **3**, **8**, and **10**) in the Sommelet–Hauser rearrangement. Some isotoluenes were isolated and their structures were confirmed by ^{1}H NMR analysis. The stability of the isotoluenes was dependent on the electron-donating effects of the substituents on the conjugated bonds, and 3-methoxy-substituted isotoluene **3a** was the most stable compound studied.

Introduction

The base-induced ylide formation reaction of (substituted benzyl)trimethylammonium halides gives mainly *N,N*-dimethyl-2-methylbenzylamine derivatives (Sommelet–Hauser rearrangement). This rearrangement has been thought to proceed via unstable intermediates, 5-[(dimethylamino)methyl]-6-methylene-1,3-cyclohexadienes (isotoluene derivatives), which are difficult to isolate because they are easily aromatized to the final products.[1] Hauser and Van Eenam isolated 5-[(dimethylamino)methyl]-1,3,5-trialkyl-6-methylene-1,3-cyclohexadienes from *N,N*-dimethyl-2,4,6-trialkylbenzylammonium *N*-methylide; however, these compounds do not have the hydrogen atom needed to restore ring resonance by proton migration.[2]

We previously reported that the fluoride anion induced desilylation of (substituted benzyl)dimethyl[(trimethylsilyl)methyl]ammonium halides gives the *N*-methylide intermediates exclusively and that they are isomerized to *N,N*-dimethyl-2-methylbenzylamines (Sommelet–Hauser rearrangement products) in high yields.[3] Similar desilylation of *N*-methyl-*N*-[(trimethylsilyl)methyl]-2-phenylpiperidinium iodide, however, gave 2-methyl-1,3,4,5,6,11a-hexahydro-2*H*-2-benzazonine (an isotoluene derivative) instead of the expected 2-methyl-2,3,4,5,6,7-hexahydro-1*H*-2-benzazonine (Sommelet–Hauser rearrangement product).[4] This isotoluene derivative is unexpectedly stable in a neutral medium and is aromatized to the Sommelet–Hauser rearrangement product only in the presence of a strong base. This result suggests that 5-[(dimethylamino)methyl]-6-methylene-1,3-cyclohexadienes (isotoluene intermediates) might also be stable in a nonbasic medium. Here, we report the reexamination of the ylide formation reaction from benzyldimethyl[(trimethylsilyl)methyl]ammonium halides in order to determine the possible isolation of 5-[(dimethylamino)-

Scheme I



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(3) (a) Nakano, M.; Sato, Y. *J. Org. Chem.* **1987**, *52*, 1844. (b) Shirai, N.; Sato, Y. *J. Org. Chem.* **1988**, *53*, 194.
(4) Shirai, N.; Sumiya, F.; Sato, Y.; Hori, M. *J. Chem. Soc., Chem. Commun.* **1988**, 370; *J. Org. Chem.* **1989**, *54*, 836.

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