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Hao Sun[a]; Corinne L. D. Gibb[a]; Bruce C. Gibb[a]
[a] Department of Chemistry, University of New Orleans, New Orleans, LA, USA

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Calorimetric Analysis of the 1:1 Complexes Formed between a Water-soluble Deep-cavity Cavitand, and Cyclic and Acyclic Carboxylic Acids

HAO SUN, CORINNE L. D. GIBB and BRUCE C. GIBB*

Department of Chemistry, University of New Orleans, New Orleans, LA 70148, USA

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Dedicated to Professor David Reinhoudt, for all his the outstanding achievements in supramolecular chemistry

A water-soluble cavitand was shown to form 1:1 complexes with a series of acyclic and cyclic aliphatic carboxylic acids. Isothermal titration calorimetry was used to determine the standard molar enthalpy change (ΔH°) and binding constant (K_a), and hence the Gibbs free energy (ΔG°) and entropy (ΔS°) change for the different complexes. The thermodynamic determinations were carried out from 288 to 318 K, allowing the standard molar heat capacity changes (ΔC_p°) also to be derived. Typical of the processes driven by the hydrophobic effect, ΔC_p° was observed to be proportional to the accessible (non-polar) surface area of the guest. The cyclic and acyclic guests displayed opposite trends; the heat capacity penalty upon binding increased with longer aliphatic chains, while the opposite was observed with the cyclic guests.

Keywords: Cavitand; Binding; Calorimetry

INTRODUCTION

Water is the most ubiquitous solvent, essential for life, but tantalisingly possesses attributes that remain poorly understood. In particular, the hydrophobic effect—the strong attraction between water molecules, which inhibits the mixing of oily compounds and water—is a highly complex phenomenon that displays dependence on both size and shape of the solute [1] or surface [2]. At the molecular level of scale, water-soluble hosts or receptors offer an ideal opportunity to study the hydrophobic effect, and in this regard the vanguard defined by the cyclodextrins [3–5] has been built upon by a range of synthetic hosts [6,7], including calixarenes [8–10], resorcinarenes [11], metal-organic cages [12–15], cucurbiturils [16–18] cavitands [19,20], and hemicarceplexes [21]. As accurate complexation data (ΔG°, ΔH°, ΔS° and ΔC_p°) is imperative if the subtleties of the hydrophobic effect are to be teased out, isothermal titration calorimetry (ITC) has been central to many such studies [5,22,23].

We have previously reported on the hydrophobically driven assembly of cavitand **1** (Fig. 1) [24–30]. This curved amphiphile possesses a hydrophobic, concave binding pocket and a hydrophilic convex outer surface. Additionally, it possesses a wide hydrophobic rim around its near nanometer-wide cavity, a feature believed to be important in the predisposition [31] of the molecule to dimerise in the presence of suitable guests and form supramolecular nanocapsules (Fig. 2). The hydrophobic effect promotes a tenacious capsule capable of storing molecules as large as steroids [24] and as flexible as straight chain alkanes [29]. Even small guests such as hydrocarbon gases bind strongly, a phenomenon that allows sequestration directly from the gas phase and separation of gas mixtures [27]. With this repertoire of encapsulation, it is perhaps not surprising that the capsule formed by **1** is also an ideal nanoscale reaction chamber [25,28,30], and a strong inhibitor of normally facile photochemical processes [26]. Much is still to be learned about the assembly of **1**, but as anticipated the capsules are denatured by co-solvents such as methanol [24] and stabilised by salting-out agents such as sodium chloride [27].

*Corresponding author. E-mail: bgibb@uno.edu

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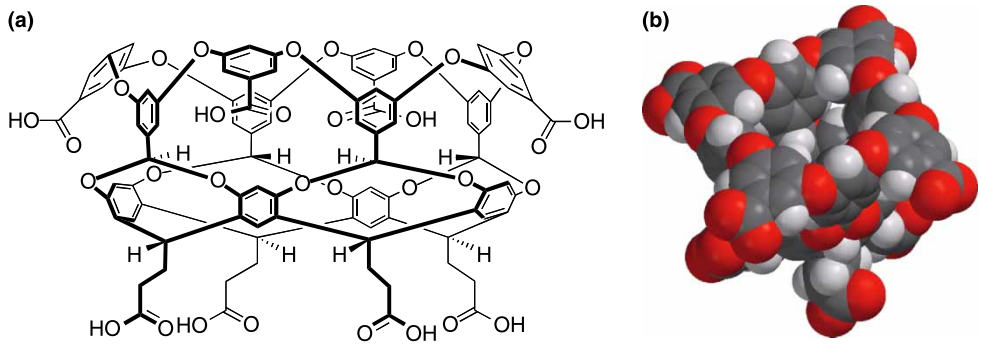

FIGURE 1 (a) Chemical structure of cavitand **1**. (b) Space-filling model of cavitand 1.

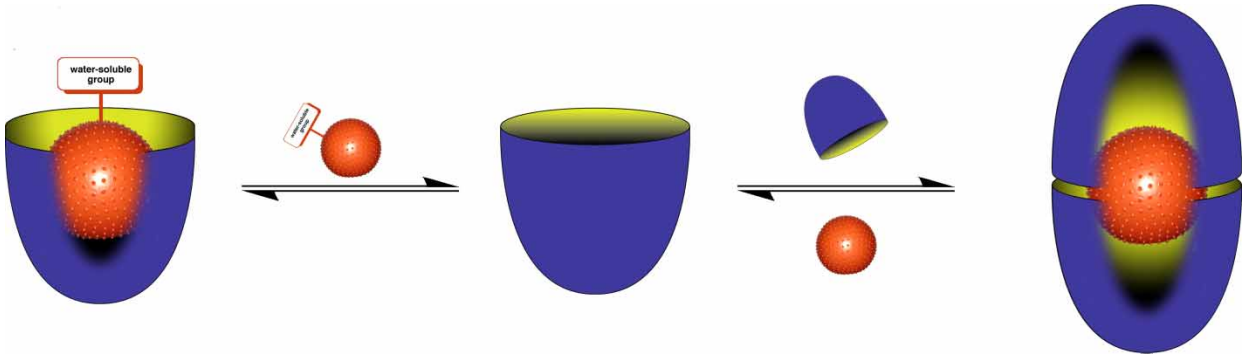

FIGURE 2 Schematic of the formation of 1:1 complexes or 2:1 assemblies using cavitand **1**.

Herein, we report that suitably amphiphilic guest molecules inhibit the self-assembly of the cavitand and lead to the formation of discrete 1:1 complexes (Fig. 2). The focus is on a variety of acyclic and cyclic aliphatic acids, which under basic conditions, bind with their hydrocarbon tail to the cavitand while leaving their carboxylate head group solvated. We report ΔG°, ΔH°, ΔS° and ΔC_p° values as derived by isothermal titration calorimetry (ITC).

EXPERIMENTAL

Cavitand **1** was synthesised and characterised following the literature procedure [24]. Sodium tetraborate, decanoic acid, octanoic acid, hexanoic acid, 1-adamantanecarboxylic acid, 3-noradamantanecarboxylic acid and cyclohexanecarboxylic acid were purchased from Sigma-Aldrich.

Microcalorimetric experiments were performed using a VP-ITC isothermal titration calorimeter from MicroCal, USA. Stock solutions of the host and guest in excess (50 mM sodium tetraborate, pH 8.9) were used for all experiments. The concentration of cavitand **1** was in the range of 0.2–1 mM, while the concentration of the guest acids was in the range of 3–20 mM (see Table 1 for specific concentrations used for each experiment). All solutions were degassed prior to each run following the procedures provided by MicroCal, Inc. Each run consisted of 25 consecutive (8 μl) injections of the solutions of guest into the ITC reaction cell charged with a solution of cavitand **1**. Computer simulations (curve fitting) were performed using ORIGIN 7.0 software adapted for the ITC data analysis. All data gave an excellent fit for a 1:1 complex model (Fig. 3). Each run was repeated at least twice with the experimental error between runs $<5\%$; the values provided in Table 1 being the averages of these runs.

RESULTS AND DISCUSSION

Three acyclic guests (hexanoic acid, octanoic acid and decanoic acid) and three cyclic guests (cyclohexanecarboxylic acid, 3-noradamantanecarboxylic acid and adamantanecarboxylic acid) were examined for their ability to complex with host **1**. The NMR spectrometry confirmed that under the conditions examined, all guests formed 1:1 complexes, and that as had been seen previously in the binding of adamantanecarboxylic acid [32], the guests bound functional group 'up' (Fig. 2) with their carboxylate groups at the entrance of the binding site. This orientation maximises the solvation of the carboxylate and inhibits capsule formation by reducing the overall hydrophobicity of the 'upper' face of the complex.

The thermodynamic quantities for these different complexations, from 288 K to 318 K, are reported in Table I. Figs. 4–6 show how ΔG°, ΔH° and $T\Delta S^\circ$ of complexation vary as a function of N_c, the number

TABLE I Thermodynamic quantities for binding of the conjugate base of aliphatic acid derivatives to cavitand **1** in dilute aqueous solutions.*

Guest carboxylate	Temp (K)	K_a (M^{-1})	$\Delta G°$ (kcal mol^{-1})	$\Delta H°$ (kcal mol^{-1})	$\Delta S°$ (cal mol^{-1} K^{-1})	$\Delta C_p^{\circ}\beta$(cal mol^{-1} $^{-}$ K^{-1})
Decanoate†	288	1.49×10^5	−6.81	−3.84	10.3	−170
	298	1.09×10^5	−6.87	−5.57	4.4	
	308	8.60×10^4	−6.95	−7.41	−1.5	
	318	6.00×10^4	−6.94	−8.88	−6.1	
Octanoate‡	288	3.61×10^4	−6.00	−4.27	6.0	−126
	298	2.63×10^4	−6.02	−5.60	1.4	
	308	1.83×10^4	−6.00	−6.82	−2.7	
	318	1.22×10^4	−5.94	−8.05	−6.6	
Hexanoate§	288	5.01×10^3	−4.87	−4.29	2.0	−85
	298	3.64×10^3	−4.85	−5.24	−1.3	
	308	2.83×10^3	−4.86	−6.02	−3.7	
	318	2.10×10^3	−4.83	−6.86	−6.4	
1-Adamantane carboxylate¶	288	1.40×10^6	−8.09	−7.05	3.2	−102
	298	1.14×10^6	−8.25	−8.52	−0.8	
	308	7.70×10^5	−8.29	−9.22	−3.5	
	318	5.40×10^5	−8.33	−10.23	−6.8	
3-Noradamantane carboxylate‖	288	3.90×10^5	−7.36	−6.29	3.76	−106
	298	2.80×10^5	−7.42	−7.40	−0.11	
	308	1.75×10^5	−7.38	−8.35	−3.12	
	318	1.27×10^5	−7.42	−9.43	−6.31	
Cyclohexanecarboxylate#	288	5.86×10^3	−4.96	−3.05	6.65	−111
	298	5.02×10^3	−5.04	−4.16	2.96	
	308	4.41×10^3	−5.13	−5.23	−0.58	
	318	2.71×10^3	−4.99	−6.41	−4.42	

* All data gave an excellent fit for a 1:1 complex model (Figure 3). Each run was repeated at least twice with the experimental error between runs <5%; the quoted values are the averages of these runs; † [cavitand **1**] = 0.1 mM, [decanoic acid] = 1.5 mM; ‡ [cavitand **1**] = 0.5 mM, [octanoic acid] = 7.7 mM; § [cavitand **1**] = 1.0 mM, [hexanoic acid] = 15 mM; ¶ [cavitand **1**] = 0.1 mM, [1-adamantane carboxylic acid] = 1.5 mM; ‖ [cavitand **1**] = 0.1 mM, [3-noradamantane carboxylic acid] = 1.5 mM; # [cavitand **1**] = 1.0 mM; [cyclohexanecarboxylic acid] = 1.5 mM.

of aliphatic carbon atoms in the alkane chain or ring of each guest [7]. The weakest binding guest in these two series was hexanoic acid. Indeed, butanoic acid was not observed to bind significantly with host **1**; apparently, the hydrophobicity of a propyl chain cannot compete against the hydrophilicity of the carboxylate group. In contrast, adamantanecarboxylic acid was the strongest binding guest releasing over 8 kcal mol^{-1} of free energy at room temperature ($K_a = 1.14 \times 10^6 M^{-1}$). This value is considerably higher than the binding of the same guest to similarly sized β-cyclodextrin (5.47 kcal mol^{-1}, pH 8.6) [33]. This stronger binding is enthalpic in nature ($\Delta H = -8.52$ and -5.45 kcal mol^{-1}, respectively), suggesting that C–H···π bonds play an important role in the complexation of aliphatic guests to **1**. Packing coefficients ($V_{aliphatic}/V_{cavity}$) for each guest (Table II) are such that $\Delta G°$ values become more favourable with increasing number of N_c (Fig. 4), and the gradients $d\Delta G°/dN_c$ for each series are calculated to be -0.65 and -0.93 kcal mol^{-1} per aliphatic carbon for the acyclic acids and cyclic acids, respectively. These values are similar to those obtained for the transfer of hydrocarbons from water to organic solvents (-0.71 to -0.96 kcal mol^{-1} per aliphatic carbon) [34].

Examining how the enthalpy and entropy changes for complexation vary as a function of N_c provides further details (Figs. 5 and 6). As shown in Fig. 5, $\Delta H°$ values for the complexation of cyclic guests are more dependent on N_c than the acyclic guests ($d\Delta H°/dN_c = -1.08$ versus -0.20 kcal mol^{-1} per aliphatic carbon atom). On the other hand, as the chain of the acyclic guests increases in length, the values of $T\Delta S°$ become more favourable for binding (Fig. 6). In other words, at room temperature, entropy disfavours hexanoate binding, but as the chain length increases complexation becomes promoted by entropy. The opposite trend is observed for cyclic guests. In this case, binding cyclohexanecarboxylate is promoted by entropy, whereas tricyclic binding is marginally penalised in entropic terms.

A comparison between Figs. 5 and 6 reveals that as the acyclic guest size increases, both the enthalpy and entropy change with binding becomes more favourable; all of these processes are enthalpically driven, but it is only the larger guests where, as is often observed in complexations driven by the hydrophobic effect, the $T\Delta S°$ term is favourable. In contrast, the cyclic guests demonstrate enthalpy–entropy compensation. As the guest increases in volume, it can make more contacts with the sides of the cavity, but movement within the cavity is increasingly restricted; the largest guest, adamantanecarboxylate, is essentially restricted to rotation around the C_4 axis of the host. Complexation is therefore slightly entropically disfavoured, whereas complexation of cyclohexanecarboxylate is promoted by entropy.

In general terms, how $\Delta G°$, $\Delta H°$, and $T\Delta S°$ vary as a function of N_c is highly dependent on the hydrophilic group of the guest, and so the aforementioned results

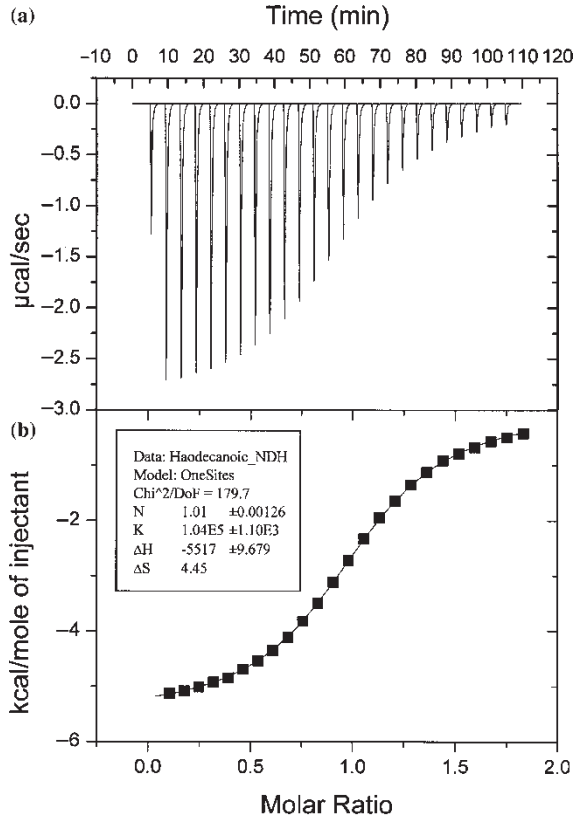

FIGURE 3 (a) Raw data obtained for 25, 8 µl injections of a guest solution (1.5 mM decanoic acid in 50 mM sodium tetraborate buffer) into the sample cell containing cavitand **1** (0.1 mM and 50 mM sodium tetraborate buffer) at 298 K. (b) Plot of heat evolution per injection (ΔQ) against molar ratio of host and guest (curve fitting using a 1:1 binding model).

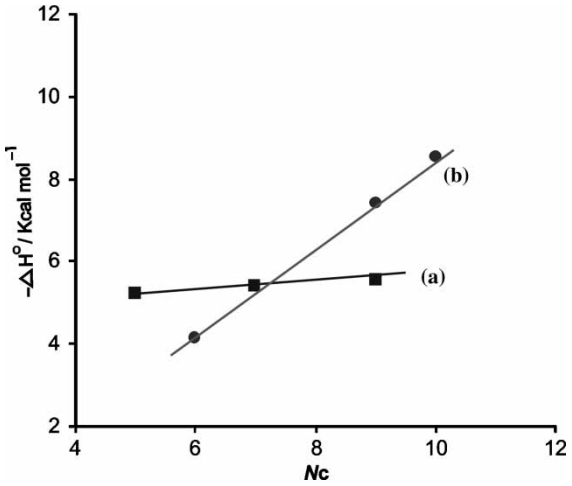

FIGURE 5 Plot of ΔH° for guest binding to host **1** as a function of the number of aliphatic carbon atoms (N_c) in the guest (298 K). (a) Acyclic guests. (b) Cyclic guests.

can only be compared to the cyclodextrins literature that deals with the binding of carboxylates under basic conditions. Although a systematic study of the binding of cyclic carboxylates to cyclodextrins has not been reported, the binding of acyclic alkanoates to α- and β-cyclodextrins has been previously reported [35,36]. Unfortunately, the data on binding to β-cyclodextrins is limited to three examples, one of which has a large associated error. In the case of binding to α-cyclodextrins, the values of $d\Delta G^\circ/dN_c = -0.55$ kcal mol^{-1} per aliphatic carbon and $d\Delta H^\circ/dN_c = -0.86$ kcal mol^{-1} at 298 K can be calculated. Thus, host **1** ($d\Delta G^\circ/dN_c = -0.65$kcal mol^{-1}, $d\Delta H^\circ/dN_c = -0.20$ kcal mol^{-1} per aliphatic carbon) is able to accommodate increasing guest sizes more readily than the cyclodextrin, a phenomenon that is primarily promoted by entropy rather than enthalpy. This can be interpreted in terms of greater guest desolvation through the more enveloping cavity of **1**.

The effects of temperature upon guest binding are portrayed in Figs. 7–9. As shown in Fig. 7, the effect of temperature change upon ΔG° is negligible for both the acyclic and the cyclic guests. Beneath this result is (near perfect) enthalpy–entropy compensation which is the 'trademark' of the hydrophobic effect (Figs. 8 and 9); with increasing temperature the enthalpy component becomes more favourable,

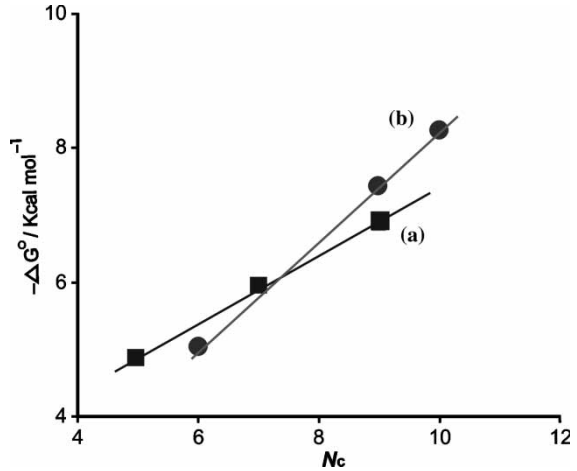

FIGURE 4 Plot of ΔG° for guest binding to host **1** as a function of the number of aliphatic carbon atoms (N_c) in the guest (298 K). (a) Acyclic guests. (b) Cyclic guests.

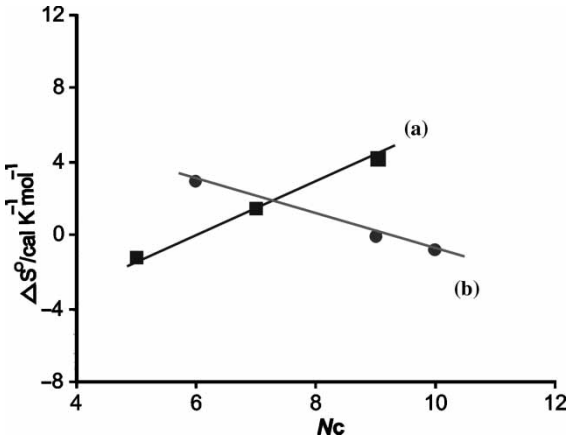

FIGURE 6 Plot of $T\Delta S^\circ$ for guest binding to host **1** as a function of the number of aliphatic carbon atoms (N_c) in the guest (298 K). (a) Acyclic guests. (b) Cyclic guests.

TABLE II Accessible surface areas of guests in this study

Guest carboxylate	N_c	ASA* (Å^2)	ASA$^{\dagger}_{\text{non-pol}}$ (Å^2)	$V_{\text{aliphatic}}$‡ (Å^3)	PC§ %
Decanoate	9	245	210	180	72
Octanoate	7	205	170	144	58
Hexanoate	5	165	130	107	43
1-Adamantane carboxylate	10	196	161	159	64
3-Noradamantane carboxylate	9	185	150	144	58
Cyclohexanecarboxylate	6	161	126	112	45

* Total accessible surface area. † Non-polar accessible surface area; ‡ Volume of aliphatic moiety of guest; § Packing coefficient $V_{\text{aliphatic}}/V_{\text{cavity}} \times 100$, based on the volume of non-polar region of guest and a cavity volume of 250 Å^3.

while the entropy contribution becomes less so [37]. The increase in the exothermicity of binding as temperature increases corresponds to the telltale negative heat capacity change (ΔC_p°) of the hydrophobic effect, and the ΔC_p° values for each guest are reported in Table I. To our knowledge, there have been no reports of ΔC_p° determinations for the binding of alkanoates to cyclodextrins under basic conditions. However, comparisons with alkanoates binding to cyclodextrins under neutral conditions suggest that the values obtained here (ΔC_p° from -85 to -170 cal mol^{-1} K^{-1}) are generally equal to and/or greater than those seen with the cyclic amyloses [7].

The negative change in ΔC_p° for binding events driven by the hydrophobic effect has been explained—at least at a general level—by the loss of the water solvation shell around the solute. This solvation shell consists of an ensemble of water molecules that can each adopt different orientation states, the higher energy and therefore less populated

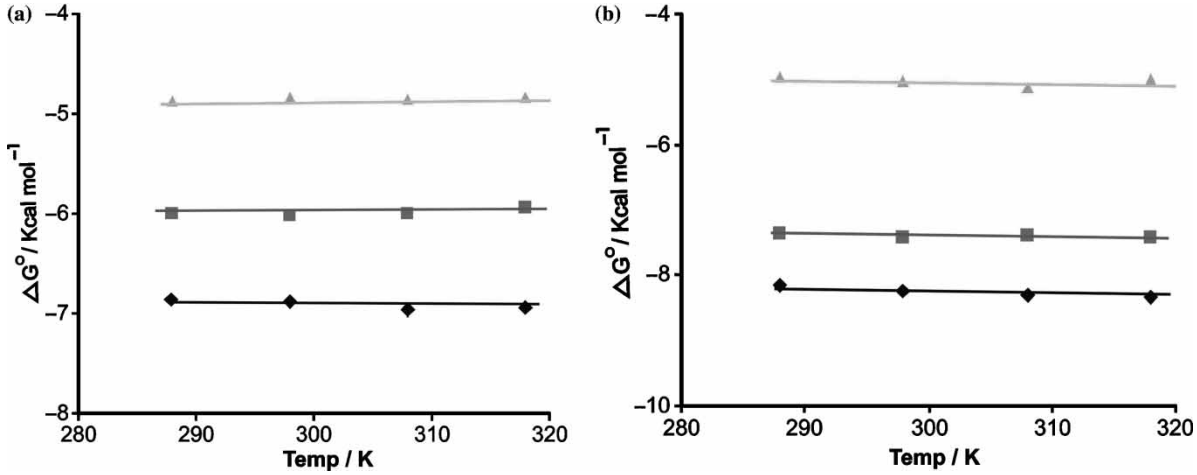

FIGURE 7 Plot of ΔG° for the binding of aliphatic carboxylates to cavitand **1** as a function of temperature. (A) Acyclic guests: ◆ decanoate, ■ octanoate, ▲ hexanoate. (B) Cyclic guests: ◆1-adamantanecarboxylate, ■ 3-noradamantanecarboxylate and ▲ cyclohexanoate.

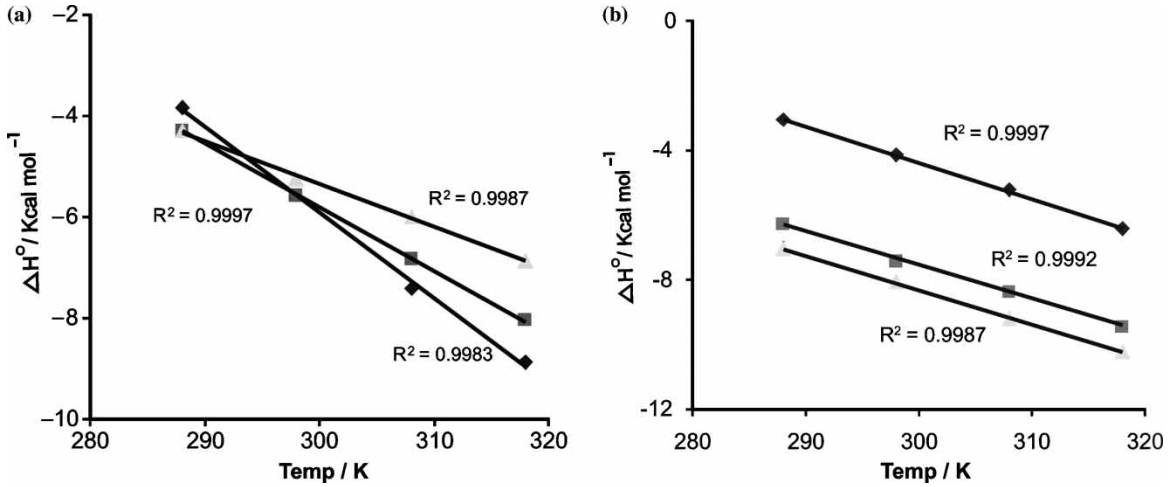

FIGURE 8 Plot of ΔH° for the binding of aliphatic carboxylates to cavitand **1** as a function of temperature. (A) Acyclic guests: ◆ decanoate, ■ octanoate, ▲ hexanoate. (B) Cyclic guests: ◆ cyclohexanoate, ■ 3-noradamantanecaboxylate and ▲1-adamantanecarboxylate.

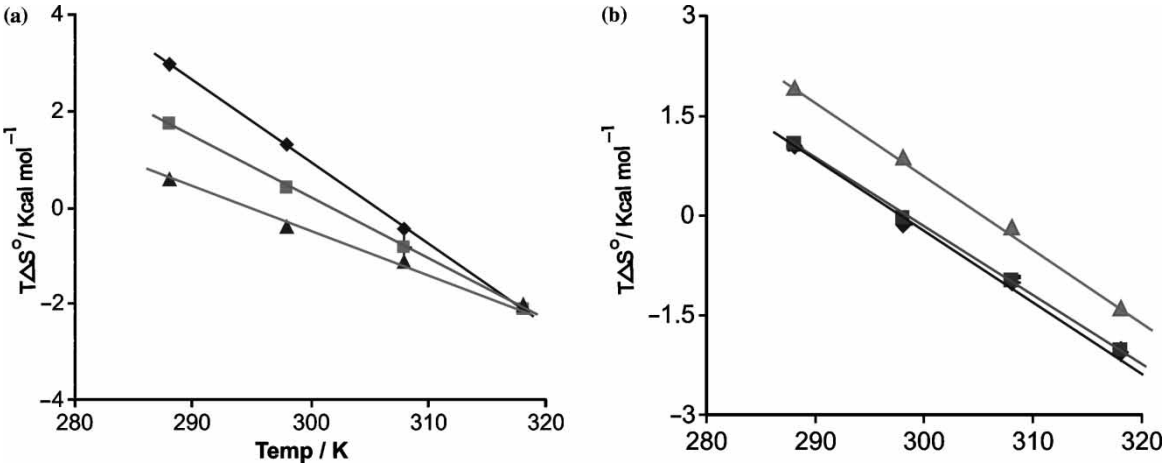

FIGURE 9 Plot of $T\Delta S^{\circ}$ for the binding of aliphatic carboxylates to cavitand **1** as a function of temperature. (A) ◆ decanoate, ■ octanoate, ▲ hexanoate. (B) ◆ Cyclohexanoate, ■ 3-noradamantanecaboxylate and ▲1-adamantanecarboxylate.

states amounting to an energy storage mechanism that is not available when the guest is bound. This model is based in part on the observation that binding or solvation events dominated by the hydrophobic effect show a proportional relationship between ΔC_p° and the non-polar accessible surface area (ASA_{np}) of the guest/solute in question. This phenomenon is confirmed here (Table 2; Fig. 10). However, whereas ΔC_p° intuitively becomes increasingly negative with longer alkyl chains, the reverse is true for the cyclic guests; the change in heat capacity is less dependent on the ASA_{np} value of these guests, but there is a distinct decrease in the heat capacity penalty for the larger guests. Why is this so? For now, we can only point to likely suspects. First, there are significant differences in the shape and form of the solvation shells that form around thread-like alkyl chains and rotund cycles. Shape and size are the important factors in the hydrophobic effect [1,2]. Additionally, a contributor to the overall change in ΔC_p° are the changes in the conformational states of guests when bound versus free in solution. Thus, bound in a preorganised bowl-like cavity the ensemble of different states that alkyl chains can engender is much smaller than in free solution, and there are therefore fewer mechanisms by which energy can be stored. More rigid cyclic guests are constrained less by complexation. A related point, and also a possible contributing factor, must be the packing coefficients ($V_{aliphatic}/V_{cavity} \times 100$; Table 2). The more space a guest has to move inside the cavity relates to both entropy and heat capacity. Considering the strong attraction that water molecules have for each other, these constraining and space issues of a bound guest may be minor components in the overall ΔC_p°, but further studies are necessary to tease out precisely how the hydrophobic effect influences the molecular structures at hand. In this regard, an interesting line of study would be to more closely compare the binding properties of cavitand **1** and β-cyclodextrin.

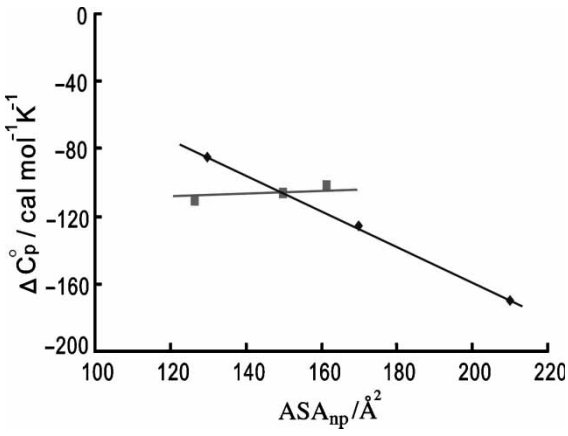

FIGURE 10 Plot of $-\Delta C_p^{\circ}$ of binding as a function of the accessible surface area of the hydrophobic region of the guest: acyclic acids (◆) and cyclic acids (■).

In summary, the binding of amphiphilic guests to host **1** leads to distinct 1:1 complexes. The polar head group of the amphiphile is located at the entrance of the binding site, and hence inhibits dimerisation and capsule formation. The major driving force in these complexations is the hydrophobic effect, and with a highly enveloping host the hydrophobic effect manifests itself strongly, both in terms of the changes to the free energy of complexation and the changes to the heat capacity of the system. The size of the host and the generally observed strong binding allows many different sized guests to be bound, and hence host **1** offers a new (reductionist) viewpoint on the hydrophobic effect. In this regard, we will report further studies in due course.

Acknowledgements

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