Enthalpic and entropic contributions to the enhanced binding of pyridine ligands by cyclic metalloporphyrin hosts

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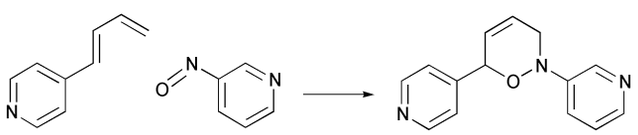
The binding constants between the pyridine ligands **1**–**3** and the metalloporphyrin hosts **4**, **6**, and **7** were measured at various temperatures in toluene. The binding constants and the thermodynamic parameters found for the various complexes indicate that the cyclic nature of hosts **6** and **7** enhances binding of the substituted pyridine ligands **1** and **2**, due to enthalpic factors with the smaller host **6**, or entropic factors with the larger host **7**. This enhanced binding is likely to lead to an increase in the reactive complex concentration in host-induced accelerated reactions; these cavity effects, which are not present in linear templates, could contribute to the greater efficiency of cyclic hosts. A plot of the enthalpic energetic gain *vs.* the entropic energetic cost measured for binding ligands **1**–**3** to hosts **4**, **6** and **7** shows an enthalpy–entropy compensation effect.

Introduction

An essential feature of the catalytic activity of many enzymes is their ability to bind two substrates in close proximity. Mimicking this ability is an important problem in supramolecular chemistry. Many examples of synthetic template molecules which are capable to various degrees of accelerating and even catalysing chemical reactions have appeared in the literature in recent years.[1] Recently, we showed that the regiospecific hetero Diels–Alder reaction of 1-(4-pyridyl)butadiene **1** with 3-nitrosopyridine **2** to give the oxazine **3** (Fig. 1) can be accelerated by various metalloporphyrin oligomers, including **5**–**7**, leading to rate accelerations of 12–1130 fold.[2] A combination of solution-state structure–activity relationships, crystallographic studies and quantum-mechanical calculations led us to conclude that (*a*) *both* host preorganisation and flexibility contribute to strong bidentate ligand binding and (*b*) it is the delicate balance between these structural features that leads to maximum transition-state stabilisation and high acceleration rates. In this paper we explore the ground-state, thermodynamic binding features of the same problem.

Each of the porphyrin units in the cyclic zinc–porphyrin hosts used, as in **5**–**7**, can bind one pyridine substrate (ligand) either inside or outside the cavity of the host through a predominantly electrostatic σ-bonding interaction of the nitrogen lone pair with the zinc centre.[3] Previous work in this laboratory has demonstrated that pyridine binds to monomers such as **4** and dimers and trimers such as **5** and **7**, respectively, with essentially the same microscopic binding constant in CH_2Cl_2 solutions.[4] This result indicated that binding of successive pyridines to different porphyrin subunits was independent and statistical and that binding on the inside and outside occurred randomly and to the same extent. However, various 4-substituted pyridine ligands bind selectively inside the cavity of the relatively small cyclic host **5**, enthalpic factors being the driving force for this preference.[5] If this is also the case for binding the substrates **1** and **2** to cyclic hosts such as **5**–**7**, then a preference to bind inside the cavity should contribute to the efficiency displayed by such cyclic hosts in accelerating the Diels–Alder reaction, because the concentration of the reactive complex (host and two substrates bound *inside* the cavity) will be higher than expected.‡ To examine this possibility we have now measured binding constants and thermodynamic parameters for binding the pyridine substrates **1** and **2** to the monomeric unit **4** and to the cyclic metalloporphyrin hosts **6** and **7** which possess a relatively small or large cavity, respectively. The results described below indeed demonstrate that enhanced binding does occur within the cavities; this could contribute to the efficiency of cyclic catalysts. However, the situation is complex: enhanced binding of pyridine ligands **1** and **2** to the smaller host **6** is enthalpy-driven, while it is entropy-driven with the larger host **7**. In addition, a plot of the enthalpic energetic gain *vs.* the entropic energetic cost measured for binding ligands **1**–**3** to hosts **4**, **6** and **7** shows an enthalpy–entropy compensation effect.



1 **2** **3**

Fig. 1 The hetero Diels–Alder reaction of substrates **1** and **2** to give adduct **3**.

Results

Syntheses of monomer **4**,[6] dimer **6**[2b] and trimer **7**[7] have been reported previously. In the earlier case of the ester-substituted dimeric host **5**, analysis of titration data was simplified by using a singly metallated version.[5] Unfortunately, separation of the singly metallated version of cyclic hosts **6** and **7**, where solubilising hexyl chains are used, proved unsuccessful so it was necessary to carry out titrations and analysis on fully metallated hosts. Experimental titrations were carried out in the temperature range 25–65 °C as described in the Experimental section and previously.[4b,5] Good isosbesticity was generally observed throughout the titration.

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‡ Molecular models indicate that the substrates **1** and **2** are in sufficiently close proximity to react only when both are bound within the cavity of the cyclic hosts.

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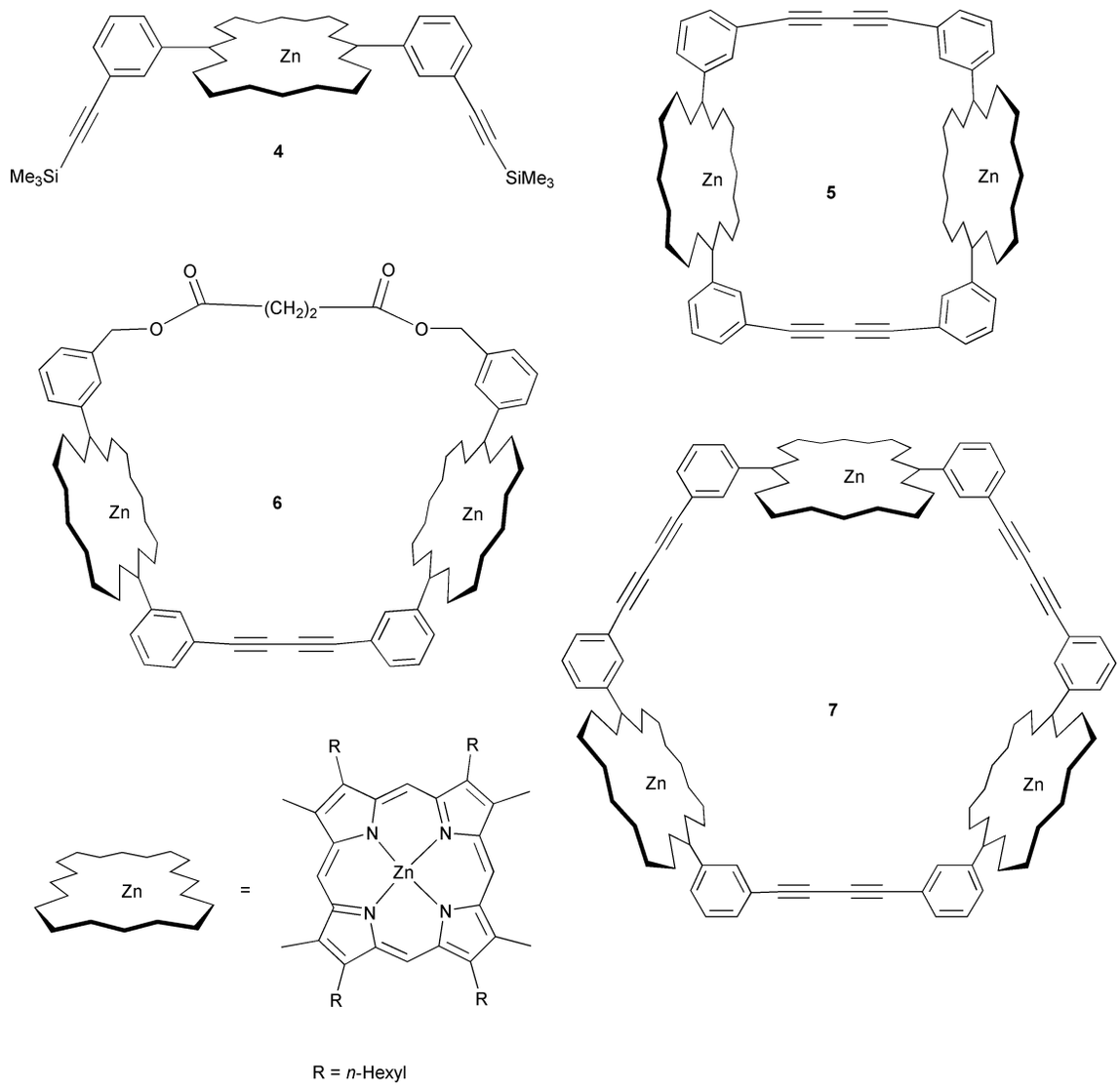

A host with multiple, identical, independent binding sites is indistinguishable from a simple monomeric host solely on the basis of titration data. However, two different models can be used for analysis of the data: if the model derived for a simple monomeric host [see Experimental section, eqn. (1)] is used to analyse ligand coordination to an oligomeric host, an apparent 1 : 1 binding constant K is measured. This is an empirical value and is the weighted average of the stepwise (stoichiometric) binding constants K_i. When the binding sites behave independently the distribution of bound species that form in the presence of a ligand is determined solely by statistical factors,[8] and for oligomeric hosts the microscopic binding constant is the apparent 1 : 1 binding constant K. Hence, for a dimeric host (as **6**) $K_1 = 2K$ and $K_2 = K/2$; for a trimeric host (as **7**) $K_1 = 3K$, $K_2 = K$ and $K_3 = K/3$. Obviously, when the host has only one binding site (as in **4**), $K = K_1$, and is also the microscopic binding constant. Therefore, in the absence of any differential binding effects, the same apparent binding constant is expected for both the cyclic and the monomeric hosts when a 1 : 1 binding model is used. Good curve fits were obtained using this simple model and revealed that the binding constants measured for ligands **1** and **2** are 1.3–6.9 times stronger with the cyclic hosts **6** and **7** than with monomer **4**; these data are not shown here as we chose to concentrate our analysis on a second, slightly more sophisticated model.

The second, stepwise, model avoids the assumption of independent binding [see Experimental section eqns. (2) and (3)] but involves fitting more parameters to the experimental data. In the event K_1 values for the first binding event led to the same qualitative results as the 1 : 1 binding model, *i.e.*, enhanced binding with the cyclic hosts; we will discuss here only the results obtained with the stepwise binding models. Excellent curve fits were obtained with these models and again, in all cases stronger binding of ligands **1** and **2** was found to the cyclic hosts than to monomer **4**.

Table 1 Binding constants, K^a [dm^3 mol^{-1}] of pyridine ligands **1**–**3** with Zn–porphyrin monomer **4** measured in toluene at various temperatures[b]

	K/dm^3 mol^{-1}		
T/°C	Diene **1**	Nitroso **2**	Oxazine **3**
25	7.0×10^3	1.0×10^3	8.2×10^3
35	3.8×10^3	5.9×10^2	4.6×10^3
45	2.2×10^3	3.5×10^2	2.7×10^3
55	1.1×10^3	1.8×10^2	1.5×10^3
65	6.8×10^2	1.0×10^2	9.4×10^2

[a] Eqn. (1) (Experimental section) was used to derive the binding constants. [b] Estimated experimental error <10%.

The 1 : 1 binding constants, K, in toluene at various temperatures for binding ligands **1**–**3** to monomer **4** and the 1 : 1 binding constants, K_1 for the first binding event of these ligands with hosts **6** and **7** are shown in Tables 1, 2 and 3, respectively. The temperature-dependent preferences for binding to the hosts relative to monomer **4** are summarised in Tables 4 and 5. Linear van't Hoff plots were obtained for binding ligands **1**–**3** to hosts

Table 2 Binding constants, K_1 [a] [dm^3 mol^{-1}] of pyridine ligands **1**–**3** with Zn–porphyrin dimer **6** measured in toluene at various temperatures [b,c]

	K_1/dm^3 mol^{-1}		
T/°C	Diene **1**	Nitroso **2**	Oxazine **3**
25	6.1×10^4	1.2×10^4	3.0×10^7
35	2.7×10^4	6.6×10^3	9.5×10^6
55	5.1×10^3	1.7×10^3	7.2×10^5
65	2.4×10^3	9.2×10^2	3.6×10^5

[a] First binding event (1 : 1 binding). Eqn. (2) (Experimental section) was used to derive the binding constants with **1** and **2**. The binding constant with oxazine **3** corresponds to the initial bidentate (1 : 1) interaction of the ligand with the host observed at low oxazine concentrations. For data analysis and binding constants with other bidentate ligands bound to porphyrin hosts see ref. 4*b*. [b] Estimated experimental error <10%. [c] For statistical reasons, in binding to hosts with multiple binding sites the first binding constants (in the first binding event) shown here, K_1, are expected to be twice as large as in the case of binding to monomer **4** (see text). Therefore, to obtain the effective enhanced binding due to the cyclic nature of host **6** (*vs.* monomer **4**) one needs to divide the binding constants for **1** and **2** by two.

Table 3 Binding constants, K_1 [a] [dm^3 mol^{-1}] of pyridine ligands **1**–**3** with Zn–porphyrin trimer **7** measured in toluene at various temperatures [b,c]

	K_1/dm^3 mol^{-1}		
T/°C	Diene **1**	Nitroso **2**	Oxazine **3**
25	4.6×10^4	4.7×10^3	5.6×10^7
35	3.2×10^4	3.3×10^3	2.2×10^7
45	2.0×10^4	2.2×10^3	7.5×10^6
55	1.2×10^4	1.4×10^3	2.2×10^6
65	8.7×10^3	1.0×10^3	1.0×10^6

[a] First binding event (1 : 1 binding). Eqn. (3) (Experimental section) was used to derive the binding constants with **1** and **2**. The binding constant with oxazine **3** corresponds to the initial bidentate (1 : 1) interaction of the ligand with the host observed at low oxazine concentrations. For data analysis and binding constants with other bidentate ligands bound to porphyrin hosts see ref. 4*b*. [b] Estimated experimental error <10%. [c] For statistical reasons, in binding to hosts with multiple binding sites the first binding constants (in the first binding event) shown here, K_1, are expected to be three times stronger than in the case of binding to monomer **4** (see text). Therefore, to obtain the effective enhanced binding due to the cyclic nature of host **7** (*vs.* monomer **4**) one needs to divide the binding constants for **1** and **2** by three.

4, **6** and **7**, and led to the thermodynamic parameters shown in Tables 6–8.

Discussion

The enthalpic and entropic contributions to binding simple pyridine ligands to monomer **4** found in this work (Table 6) are in good agreement with those reported by others.[9] The additional stabilisation in forming complexes with the cyclic hosts is presumably related to the presence of the cavity. To gain insight into the features that might be responsible for this enhanced binding, the binding constants were measured at various temperatures. It is striking that the preference for ligands **1** and **2** to bind to the cyclic hosts *decreases* substantially with increasing temperature for the dimer **6**, while it *increases* with increasing temperature for the trimer **7** (Tables 4, 5). Comparison of the thermodynamic parameters obtained for binding ligands **1** and **2** to monomer **4** (Table 6) with those obtained with the cyclic hosts **6** and **7** (Tables 7 and 8, respectively), reveals that enthalpic factors are responsible for the enhanced binding with **6**, while entropic factors are responsible for the enhanced binding with **7**. For example, binding diene **1** to dimer

Table 4 Binding constants ratio, $K_{1dimer}/K_{monomer}$, [a] for ligands **1** and **2** measured in toluene at various temperatures [b]

	$K_{1dimer}/K_{monomer}$	
T/°C	Diene **1**	Nitroso **2**
25	8.7	12.0
35	7.1	11.2
55	4.6	9.4
65	3.5	9.2

[a] K_{1dimer} are the 1 : 1 binding constants of ligands **1** and **2** with dimer **6** (see Table 2). $K_{monomer}$ are the 1 : 1 binding constants of ligands **1** and **2** with monomer **4** (see Table 1). [b] To obtain the effective enhanced binding with the cyclic host **6** (*vs.* monomer **4**) one needs to correct for the statistical factor in binding to hosts with multiple binding sites (see text) and therefore, the numbers in the table should be divided by 2.

Table 5 Binding constants ratio, $K_{1trimer}/K_{monomer}$, [a] for ligands **1** and **2** measured in toluene at various temperatures [b]

	$K_{1trimer}/K_{monomer}$	
T/°C	Diene **1**	Nitroso **2**
25	6.6	4.7
35	8.4	5.6
45	9.1	6.3
55	10.9	7.8
65	12.8	10.0

[a] $K_{1trimer}$ are the 1 : 1 binding constants of ligands **1** and **2** with trimer **7** (see Table 3). $K_{monomer}$ are the 1 : 1 binding constants of ligands **1** and **2** with monomer **4** (see Table 1). [b] To obtain the effective enhanced binding with the cyclic host **7** (*vs.* monomer **4**) one needs to correct for the statistical factor in binding to hosts with multiple binding sites (see text) and therefore, the numbers in the table should be divided by 3.

6 is 4.0 kcal mol^{-1} more favourable enthalpically and 3.2 kcal mol^{-1} less favourable entropically, than binding to monomer **4**. However, the reverse is found with trimer **7** which, relative to **4**, shows a 3.3 kcal mol^{-1} less favourable binding enthalpy for **1** and a 4.2 kcal mol^{-1} more favourable binding entropy.

It is a reasonable assumption that ligand binding to the outer side of the host cavity is similar to binding to monomer **4**: the crystal structures of the porphyrin units in the product-free host **6** are qualitatively planar,[2b] as in monomeric units such as **4**.[10] It follows that the enhanced binding observed with the cyclic hosts is due to a preference to bind **1** and **2** inside the cavity. It was possible to prove this assumption very easily by NMR spectroscopy in the earlier case of **5**: the rigid cavity forced the two porphyrin units to be held close together and cofacial, leading to very large upfield shifts for ligands bound within the cavity. The Zn–Zn distance in **6** is calculated to be only 0.4 Å larger than in **5**, but the angle between porphyrins and the greater flexibility mean that there is a less dramatic difference between the shifts of inside and outside ligands. This is even more the case for the trimer. It has not been possible therefore to rigorously and independently confirm the common-sense conclusion that preferred binding does indeed occur within the cavity.

If the enhanced binding does indeed enforce preferred binding of the Diels–Alder substrates inside the cavity, it would increase the concentration of the reactive complex (host and two substrates *inside* the cavity) compared with a purely statistical distribution of the ligands. This would imply an obvious advantage in constructing cyclic, rather than linear, zinc–porphyrin templates. A simple calculation shows that cyclic dimers like **6** or cyclic trimers like **7** form 14 or 34, respectively, distinct complexes when present in a solution of two different substrates like **1** and **2**. As no results are available as to possible cooperative effects in ternary complexes where two different ligands are bound in the cavity, we have made no attempt to

Table 6 Thermodynamic parameters for 1 : 1 binding of ligands **1**–**3** with Zn–porphyrin monomer **4**[a,b]

Ligand	ΔH/kcal mol^{-1}	ΔS/cal mol^{-1} K^{-1}	$-T\Delta S$/kcal mol^{-1} (at 25 °C)	ΔG/kcal mol^{-1} (at 25 °C)
Diene **1**	−12	−22	6.6	−5.4
Nitroso **2**	−12	−25	7.5	−4.5
Oxazine **3**	−11	−19	5.7	−5.3

[a] Derived from the linear van't Hoff plots obtained with the data in Table 1. The *r* factors found for these linear plots are: 0.999, 0.998 and 0.999 for binding ligands **1**, **2** and **3**, respectively. Standard deviation <5%. [b] Non-SI unit used: 1 kcal mol^{-1} = 4.184 kJ mol^{-1}.

Table 7 Thermodynamic parameters for 1 : 1 binding of ligands **1**–**3** with Zn–porphyrin dimer **6**[a,b]

Ligand	ΔH/kcal mol^{-1}	ΔS/cal mol^{-1} K^{-1}	$-T\Delta S$/kcal mol^{-1} (at 25 °C)	ΔG/kcal mol^{-1} (at 25 °C)
Diene **1**	−16	−33	9.8	−6.2
Nitroso **2**	−13	−25	7.5	−5.5
Oxazine **3**	−23	−43	13	−10

[a] Derived from the linear van't Hoff plots obtained with the data in Table 2. The *r* factors found for these linear plots are: 0.999, 0.999 and 0.998 for binding ligands **1**, **2** and **3**, respectively. Standard deviation <5%. [b] Non-SI unit used: 1 kcal mol^{-1} = 4.184 kJ mol^{-1}.

Table 8 Thermodynamic parameters for 1 : 1 binding of ligands **1**–**3** with Zn–porphyrin trimer **7**[a,b]

Ligand	ΔH/kcal mol^{-1}	ΔS/cal mol^{-1} K^{-1}	$-T\Delta S$/kcal mol^{-1} (at 25 °C)	ΔG/kcal mol^{-1} (at 25 °C)
Diene **1**	−8.7	−7.9	2.4	−6.3
Nitroso **2**	−7.8	−9.3	2.8	−5.0
Oxazine **3**	−21	−34	10	−11

[a] Derived from the linear van't Hoff plots obtained with the data in Table 3. The *r* factors found for these linear plots are: 0.996, 0.998 and 0.998 for binding ligands **1**, **2** and **3**, respectively. Standard deviation <5%. [b] Non-SI unit used: 1 kcal mol^{-1} = 4.184 kJ mol^{-1}.

quantify the possible increase in concentration of the reactive complex relative to the case of a purely statistical distribution.

Additional stabilisation upon formation of a 1 : 1 complex in which the ligand binds inside the cavity could result from solvation effects or from ligand interaction with the face of the second porphyrin. Molecular models suggest that when **1** binds through the pyridine nitrogen to one of the porphyrin units in **6**, the other end of the ligand is in close contact with this second, apparently passive, porphyrin unit. Ideally this should be tested crystallographically, but growing single crystals of these large host molecules as complexes with guests such as **1** or **2** is not trivial. Despite many attempts using a range of solvents and temperatures we were unable to obtain crystals suitable even for X-ray crystallography using a synchrotron source.

Nevertheless, the X-ray structure determined for the product-free host **6**,[2b] allows a reasonable estimate of the possible contacts between the ligand and the cavity faces when **1** is modelled in a constrained structure of **6** based on the crystal structure. A favourable van der Waals contact within the cavity could lead to an enthalpic contribution to binding, but is also expected to lead to an additional entropic cost. Indeed, if monomer **4** is used as a model for binding outside the cavity, then comparing the thermodynamic parameters found for binding **1** to **6** *vs.* those found when binding to **4** supports this explanation. In accord with this, the smaller ligand **2**, for which molecular models suggest no contact with the other porphyrin face, shows the same thermodynamic parameters, within experimental error, for binding to the cyclic host **6** and to monomer **4**.

Molecular models suggest that when ligands **1** or **2** bind inside the cavity of the larger host **7**, no contact with other porphyrin faces is likely, so no enthalpic gain is expected, and indeed no such gain is observed compared with binding to **4**. In fact, the enthalpy of binding to the cyclic trimer **7** is less favourable than binding to monomer **4**. It is possible that solvation effects could account for this observation. Two immobilised molecules of toluene were found in the crystal structure of **6**;[2b] as the cavity of trimer **7** is larger than that in **6**, the binding of a ligand such as **1** or **2** could displace more toluene molecules, leading to an entropic gain.[11] This is consistent with the relatively low negative entropic change found for binding **1** and **2** to host **7** (see Table 8). However, at the same time, the complex should now be less well solvated than in the case where the ligand binds outside the cavity (or to monomer **4**), a situation where fewer localised solvent molecules are expected to be displaced upon binding. This could account for the relatively low enthalpic gain observed in binding ligands **1** and **2** to host **7** (see Table 8).

Entropic gain due to solvent displacement does not necessarily have to lead to an overall positive entropic change upon complexation. Rather the complexation could of course be driven by enthalpy, and the entropic contributions control the complex's ultimate stability. It is difficult to predict the extent of such possible entropic gain in such a complex process as many factors are involved simultaneously. For example, in different host cavities, a whole spectrum of solvent–host and solvent–solvent interactions could lead to a range of degrees of freedom for the solvent molecules in these cavities, all of which are expected to be different from those of the bulk solvent. In addition, the solvent molecules are replaced with a pyridine ligand which forms a well defined and relatively strong bond with the Zn–porphyrin and which therefore is expected to lead to an entropic cost upon binding. Obviously, release of solvent molecules from the surface of the guest upon complex formation should also contribute to an increase in enthalpy and entropy. These possible processes are complex and generally unpredictable so the conclusions above are not unequivocal but they seem to be consistent with the experimental results.

The high enthalpic gain and entropic cost of binding bidentate ligands such as **3** inside the cavity of cyclic hosts **6** and **7** (see Tables 7 and 8) is broadly as expected. However, the binding enthalpy and entropy found for the **6·3** complex are both more negative than in the **7·3** complex, implying a tighter complex in the former case. The X-ray structures of hosts **6** and **7** and of the **6·3** complex support this: the Zn–Zn distance in **6** (of 10.6 Å) is closer to that found in a host–product (**6·3**) complex (of 11.7 Å), than in the case of **7** for which the Zn–Zn distance is 15.6 Å.[2]

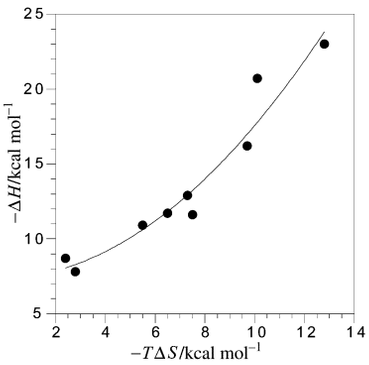

Fig. 2 Plot of the enthalpic energetic gain *vs.* the entropic energetic cost (at T = 298 K) found in forming the various complexes between ligands **1**, **2** and **3** and hosts **4**, **6** and **7** (see Tables 6–8). The curve drawn is for visual guidance only.

The plot of the enthalpic energetic gain against the entropic energetic cost involved in forming the various complexes between ligands **1**, **2** and **3** and hosts **4**, **6** and **7** (Tables 6–8) shows an enthalpy–entropy compensating effect (see Fig. 2).[9,12,13] § The origin of the correlation found in Fig. 2 could be rationalised in terms of the different depths of the wells in the electrostatic potentials, corresponding to the associated states in the various complexes, and in the density of the states within these wells.[12] For a deep well, corresponding to a strong bond with large enthalpy change upon binding, the vibrational energy levels of the complex are widely spaced and the vibrational entropy is small (*e.g.*, in binding the bidentate ligand **3** within the cavity of the cyclic hosts **6** and **7**); on the other hand, a shallow well corresponds to many closely spaced vibrational levels and therefore to a larger vibrational entropy (*e.g.*, in monodentate binding of the ligands to hosts **4**, **6** and **7**).

Conclusions

In this study we have explored possible cavity effects on binding of the Diels–Alder substrates **1** and **2** to the cyclic hosts **6** and **7**. We found that enthalpic and entropic factors lead to enhanced binding by the cyclic metalloporphyrin hosts **6** and **7**. This might imply an obvious advantage in constructing cyclic metalloporphyrin hosts *vs.* linear ones, as enhanced binding could be the result of a preference to bind within the cavity of the cyclic metalloporphyrin hosts, and which should lead to an increase in the concentration of the reactive complex in host-induced accelerated Diels–Alder reactions. In addition, the thermodynamic parameters found for binding ligand **1**–**3** to hosts **4**, **6** and **7** show an enthalpy–entropy compensating effect, as expected by theory.[12]

Experimental

Binding studies

In order to measure the affinity of ligands **1**–**3** to the hosts **4**, **6** and **7**, a series of UV–VIS titrations were carried out at various temperatures in toluene using a Hewlett-Packard 8452A diode array spectrometer fitted with a temperature-controlled jacket (estimated error in temperature ±0.1 °C). Other experimental details and data analysis were as described previously[4b] and as described below. (a) Eqns. (1) and (2)–(3) were employed for calculating the binding constants K and K_1, respectively, through nonlinear curve-fitting plots for the changes in absorbance of the porphyrin's Soret bands (λ_{max} = 412 nm for free porphyrin, λ_{max} = 426 nm for bound porphyrin) as a function of the ligand added. The ligand absorbance is negligible in the wavelength range of interest (Soret bands region). For general

§ Qualitatively a similar graph was obtained when eqn. (1) (see Experimental section) was used to calculate the binding constants for **1** and **2**.

$$A = A_0 + \frac{(A_f - A_0)KL}{1 + KL} \quad (1)$$

$$A = A_0 + (A_f - A_0)\left(\frac{\frac{1}{2}K_1L + K_1K_2L^2}{1 + K_1L + K_1K_2L^2}\right) \quad (2)$$

$$A = A_0 + (A_f - A_0)\left(\frac{\frac{1}{3}K_1L + \frac{2}{3}K_1K_2L^2 + K_1K_2K_3L^3}{1 + K_1L + K_1K_2L^2 + K_1K_2K_3L^3}\right) \quad (3)$$

binding equations for various types of complex see ref. 14. (b) Eqn. (1) was used to model the 1 : 1 binding of the ligands to the monomeric unit **4**. (c) To avoid the assumption of independent binding sites in the oligomeric hosts **6** and **7** and to concentrate on the first binding event in these hosts, eqns. (2) and (3) were used for binding **1** and **2** with dimer **6** and trimer **7**, respectively. This was achieved by modelling the system studied which considers the species H, L, HL and HL_2 for host (H) **6** and the ligand (L), and species H, L, HL, HL_2 and HL_3 for binding to trimer **7**. This allows estimation of the values of the stepwise association constants K_1, K_2 (for **6**) and K_1, K_2 and K_3 (for **7**). To simplify the function, the molar absorption coefficients of the intermediates, *i.e.*, ε_{HL} and ε_{HL_2}, are approximated by linear combination of the absorption coefficients of the free and fully bound host. Therefore, these models [eqns. (2) and (3)] assume that the molar absorption coefficients, ε_{HL} in **6**, and ε_{HL} and ε_{HL_2} in **7**, are linear combinations of ε_H and ε_{HL_2} or ε_H and ε_{HL_3}, respectively. The good curve fits obtained for these systems with the simple 1 : 1 binding model [eqn. (1)] make this a reasonable assumption. This assumption was proved to be valid with similar systems; the molar absorption coefficients of the partially bound species (measured directly for a singly or singly and doubly metallated ester-substituted porphyrin dimer, like **5**, or trimer, like **7**, respectively) were found to correspond to linear combinations of the molar absorption coefficients of the free and fully bound species.[15] In addition, these models gave excellent curve fits for the systems studied here.

In eqns. (1)–(3), A is the absorbance at a given wavelength, A_0 is the initial absorbance, A_f is the final absorbance at the completion of the titration, L is the total ligand concentration, K is the 1 : 1 binding constant and K_1, K_2 and K_3 are the first, second and third stepwise binding constants, respectively, with the oligomeric hosts.

In general, no, or weak, negative cooperative effect was found for the second binding event with ligands **1** and **2**, K_2 being 0–60% weaker than that expected due to statistical factors. This could result from a weak repulsive interaction between the two ligands in the cavity or due to a reduction, in the second binding event, of the positive effects that enhances binding with the cyclic hosts **6** and **7** (see text).

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References

1 For recent reviews on catalytic host–guest systems see: (*a*) J. K. M. Sanders, *Chem. Eur. J.*, 1998, **4**, 1378; (*b*) A. J. Kirby, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 707; (*c*) Y. Murakami, J-i. Kikuchi, Y. Hisaeda and O. Hayashida, *Chem. Rev.*, 1996, **96**, 721.
2 (*a*) M. Nakash and J. K. M. Sanders, *J. Org. Chem.*, 2000, **65**, 7266; (*b*) M. Nakash, Z. Clyde-Watson, N. Feeder, J. E. Davies, S. J. Teat and J. K. M. Sanders, *J. Am. Chem. Soc.*, 2000, **122**, 5286.
3 G. C. Vogel and J. R. Stahlbush, *Inorg. Chem.*, 1977, **16**, 950.
4 (*a*) J. K. M. Sanders, *Comprehensive Supramolecular Chemistry*, eds. J. L. Atwood, J. E. D. Davies, D. D. Macnicol and F. Vögtle, Elsevier, Oxford, 1996, vol. 9, pp. 131–164; (*b*) H. L. Anderson, S. Anderson and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2231 and following papers.

5 R. S. Wylie, E. G. Levy and J. K. M. Sanders, *Chem. Commun.*, 1997, 1611.
6 L. J. Twyman and J. K. M. Sanders, *Tetrahedron Lett.*, 1999, **40**, 6681.
7 (*a*) M. Marty, Z. Clyde-Watson, L. J. Twyman, M. Nakash and J. K. M. Sanders, *Chem. Commun.*, 1998, 2265; (*b*) the general route for cyclic dimers (as **5**) and trimers (as **7**) is described in H. L. Anderson, S. Anderson and J. K. M. Sanders, *J. Chem. Soc. Perkin Trans. 1*, 1995, 2223 and following papers.
8 K. A. Connors, *Binding Constants*, John Wiley & Sons, New York, 1987, pp. 51–54.
9 T. Mizutani, K. Wada and S. Kitagawa, *J. Org. Chem.*, 2000, **65**, 6097 and references therein.
10 For crystal structures of various porphyrin monomeric units see: W. R. Scheidt and Y. Lee, *Struct. Bond.*, 1987, **64**, 1.
11 In some systems, the displacement of solvent molecules has been suggested as the driving force for binding and acceleration: (*a*) J. Kang and J. Rebek, Jr., *Nature (London)*, 1996, **382**, 239; (*b*) J. Kang, J. Santamaria, G. Hilmersson and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1998, **120**, 7389.
12 (*a*) J. D. Dunitz, *Chem. Biol.*, 1995, **2**, 709; (*b*) B. R. Peterson, P. Wallimann, D. R. Carcanague and F. Diederich, *Tetrahedron*, 1995, **51**, 401; (*c*) M. S. Searle, M. S. Westwell and D. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1995, 141.
13 For other examples of enthalpy–entropy compensating effects found in complexation with cyclodextrins see: M. V. Rekharsky and Y. Inoue, *Chem. Rev.*, 1998, **98**, 1875.
14 K. A. Connors, *Binding Constants*, John Wiley & Sons, New York, 1987.
15 E. G. Levy, Ph.D. Thesis, University of Cambridge, UK, 1996.