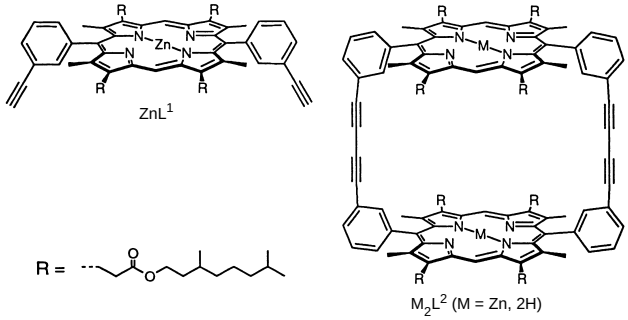
Unexpectedly selective ligand binding within the cavity of a cyclic metalloporphyrin dimer

R. Stephen Wylie, Esther G. Levy and Jeremy K. M. Sanders*

Cambridge Centre for Molecular Recognition, University Chemical Laboratory, Lensfield Road, Cambridge, UK CB2 1EW

4-Substituted pyridines of an appropriate size show a remarkable preference for binding inside the cavity of a cofacial butadiyne-linked zinc porphyrin dimer; the origin of the effect is not entirely clear but may be related to solvent release or favourable host–guest contacts

We report here that the binding of a pyridine ligand to a zinc porphyrin dimer can occur selectively on the inner face of a cavity rather than on the more accessible but otherwise apparently equivalent outer face.



Previous work in this laboratory had demonstrated that pyridine binds to monomers such as ZnL^1 and dimers such as Zn_2L^2 with essentially the same microscopic binding constant in CH_2Cl_2 solution;[1,2] each individual zinc porphyrin can form only a 1:1 complex with amines. For larger oligomers such as trimers, which have spacious cavities, we interpreted the results to indicate that binding of successive pyridines to different porphyrin subunits was independent and statistical; we also concluded that binding on the inside and outside occurred randomly and to the same extent. However, the small cavity associated with dimer Zn_2L^2 does not allow for the same independence of inner binding: ligation of a 4-substituted pyridine to the inner face of one porphyrin might tend to inhibit binding to the internal face of the other. We therefore expected that a careful study of the binding of pyridines to Zn_2L^2 [eqns. (1) and (2)] would demonstrate negative cooperativity: K_1

$$Zn_2L^2 + X \overset{K_1}{\rightleftharpoons} Zn_2L^2{\cdot}X \quad (1)$$

$$Zn_2L^2{\cdot}X + X \overset{K_2}{\rightleftharpoons} Zn_2L^2{\cdot}2X \quad (2)$$

should be twice as large as for binding to ZnL^1 (K_{mon}) due to the presence of two binding sites, each with the possibility of inner and outer binding, while K_2 should be less than half the size as inner binding of the second ligand would be hindered. The results for spectrophotometric titrations in toluene solution were very different from those expected. Pyridine itself has a K_1/K_{mon} value (Table 1) of 3.2, which differs from the expected value of 2.0 by slightly more than the experimental error. The discrepancy is larger for 4-methylpyridine (4-Mepy), while the first 4-*tert*-butylpyridine (4-Bu^{t}py) binds some 50 times more strongly to the dimer than to the monomer.

Table 1 Equilibrium constants (dm^3 mol^{-1}) for binding of ligands X to ZnL^1 and Zn_2L^{2a} (X = NC_5H_4R)

R	Zn_2L^2 (K_1)	ZnL^2 (K_2)	ZnL^1 (K_{mon})	K_1/K_{mon}	K_2/K_{mon}
H	1.6×10^4	2.9×10^3	5.0×10^3	3.2	0.6
4-Me	6.2×10^4	1.1×10^4	1.1×10^4	5.6	1.0
4-Bu^t	7.3×10^5	3.0×10^4	1.4×10^4	*ca.* 50	2.1

[a] In toluene at 25 °C using electronic spectroscopy;[2] estimated uncertainties 7–10%.

To rigorously exclude the possibility of problems that can easily arise from the analysis of multiple binding equilibria, the free-base dimer H_4L^2 was partially metallated, and the singly metallated $Zn(H_2L^2)$ species was isolated by chromatography. Now only a single ligand can be bound, and data analysis is simpler. Table 2 summarises the results for a wider range of ligands, the *f* value (= K_{dim}/K_{mon}) giving a direct comparison of binding strength. The trends are similar to those seen for the doubly metallated host, the maximum effect of 25-fold being for *R* = 4-Bu^t in toluene. Preferential binding is not restricted to alkyl substituents, as is apparent in the results for 4-hydroxymethylpyridine. Only when the substituent is so large that the ligand cannot comfortably fit inside the cavity is the *f* value less than 1. Similar trends were seen for titrations in dichloromethane (Table 2, results in italics), although the absolute size of the effect is smaller, and now pyridine itself is bound less well by the dimer than by the monomer.†

The larger *f* values for some ligands imply that binding occurs preferentially to one face of the porphyrin, presumably the intracavity one. One explanation for these results might be that molecules of solvent toluene are more strongly associated with the dimer cavity than with the open faces of the monomer,[3] and that binding of an appropriately sized ligand within the cavity would then lead to entropically favourable solvent release. Where one ligand releases more than one solvent molecule this can lead to entropy-driven binding.[4] However there is no

Table 2 Equilibrium constants (dm^3 mol^{-1}) for binding of ligands X to ZnL^1 and $Zn(H_2L^2)^a$ (X = NC_5H_4R)

R	$Zn(H_2L^2)$ (K_{dim})	ZnL^1 (K_{mon})	$f = K_{dim}/K_{mon}$
H	8.0×10^3	5.0×10^3	1.6
	(*3.1* × *10^3*)	(*4.1* × *10^3*)	(*0.8*)[b]
4-Me	2.9×10^4	1.1×10^4	2.6
4-Pr^i	8.3×10^4	8.3×10^3	10
4-Bu^t	3.5×10^5	1.4×10^4	25
	(*3.6* × *10^4*)	(*9.2* × *10^3*)	(*3.9*)[b]
4-(1-Adamantyl)	2.1×10^4	1.1×10^4	1.9
4-$CHBu_2$	3.8×10^4	8.3×10^3	4.6
4-Ph	1.1×10^4	8.8×10^3	1.2
4-CH_2OH	1.0×10^5	9.5×10^3	11
	(*2.0* × *10^4*)	(*5.4* × *10^3*)	(*3.7*)[b]
3-Me, 5-Me	9.5×10^3	6.3×10^3	1.5
4-Y[c]	1.1×10^4	1.5×10^4	0.7

[a] In toluene at 25 °C using electronic spectroscopy; [2] estimated uncertainties 7–10%. [b] In CH_2Cl_2 at 25 °C. [c] Y = *trans*-(4-Pyridyl)ethenyl.

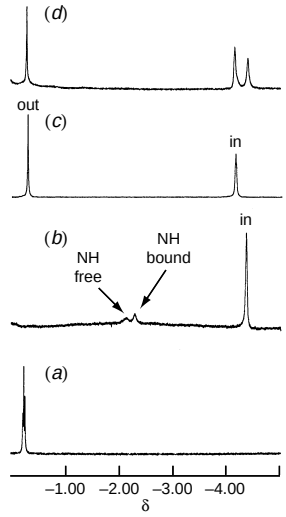


Fig. 1 Partial 400 MHz ^{1}H NMR spectra at −60 °C in [$^2H_8$]toluene of (*a*) ZnL^1 in the presence of 0.5 equiv. 4-Bu^{t}py, indicating that three complexes are formed (Fig. 2); (*b*) $Zn_2(H_2L^2)$ in the presence of 0.5 equiv. 4-Bu^{t}py, demonstrating exclusively inside cavity binding; (*c*) $Zn_2L^2{\cdot}2$(4-Bu^{t}py), showing inside and outside binding; and (*d*) Zn_2L^2 in the presence of 1.0 equiv. 4-Bu^{t}py showing the co-existence of 1 : 1 and 1 : 2 complexes

evidence for such an effect in this system: Van't Hoff plots (25–55 °C) for 4-Bu^{t}py binding in the temperature range 25–55 °C give very similar values for $-T\Delta S$ [24 kJ mol^{-1} at 298 K for ZnL^1 and 23 kJ mol^{-1} for $Zn(H_2L^2)$] in toluene. The major difference in driving force is in $-\Delta H$, which is 47 kJ mol^{-1} for ZnL^1 and 54 kJ mol^{-1} for $Zn(H_2L^2)$. Solvent-dependent binding within cavities has been reported in many other systems, but these can be usually be rationalised in terms of optimising host–guest or disrupting host–solvent interactions.[5]

To prove that preferential binding occurs within the cavity we turned to ^{1}H NMR spectroscopy at a temperature low enough to ensure slow ligand exchange; the large ring current associated with the porphyrin π system leads to particularly marked shielding of ligands sandwiched inside the cavity of a dimer.[1, 2] At – 60 °C in [$^2H_8$]toluene, the Bu^t resonance in the complex of 4-Bu^{t}py with ZnL^1 appears as three very close singlets at δ –0.2 [Fig. 1(*a*)], a shift of 1.2 ppm on binding; the three signals result from the slow exchange between three isomeric complexes (Fig. 2).[6] By contrast, when 0.5 equiv. 4-Bu^{t}py are added to $Zn(H_2L^2)$ at −60 °C in [$^2H_8$]toluene, a single Bu^t resonance due to the complex of 4-Bu^{t}py appears at δ −4.3 [Fig. 1(*b*)], a binding shift of 5.3 ppm that is consistent only with the ligand being bound within the cavity as shown in Fig. 3(*a*); no externally bound ligand is seen. It is notable that the NH resonances of the free-base porphyrin are sensitive to the presence of the ligand within the cavity, shifting from δ −2.1 to −2.3 upon ligation of the other porphyrin unit. The ^{1}H NMR spectrum of the $ZnL^2{\cdot}2$(4-Bu^{t}py) complex [Fig. 1(*c*)] contains

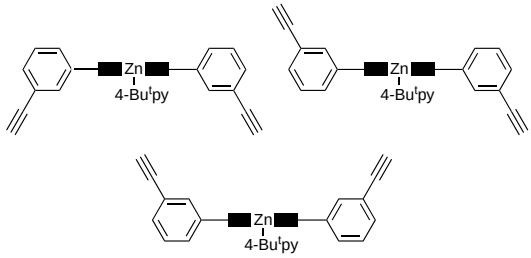


Fig. 2 Three isomeric forms of the complexes of 4-Bu^{t}py with ZnL^1. The *trans*-atropisomer complex is statistically twice as abundant as either of the individual *cis*-atropisomer complexes.

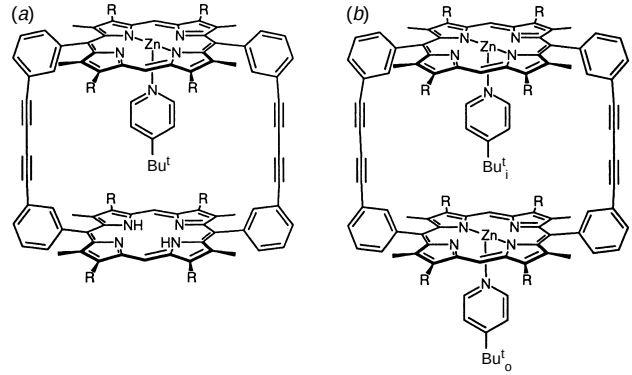


Fig. 3 Geometries of (*a*) $Zn(H_2L^2){\cdot}$4-Bu^{t}py and (*b*) $Zn_2L^2{\cdot}2$(4-Bu^t-py)

two signals in a 1 : 1 intensity ratio and with shifts that show one ligand bound inside and one outside the cavity [Fig. 3(*b*)], while a deficiency of the ligand yields a mixture of the 1 : 2 complex with the inside-only 1 : 1 complex [Fig. 1(*d*)]. The results described here show that cavity effects can have unpredictable influences on the strength and position of binding. The dependence of the first binding constant on ligand size may reflect a direct van der Waals enthalpic contribution from ligand contact with the non-binding porphyrin,‡ but this explanation seems hard to reconcile with the similarity of effect between $Zn(H_2L^2)$ and Zn_2L^2, and between polar and non-polar substituents on the ligand. It seems more likely that the effect is an unpredictable outcome of the delicate changes in host and guest solvation that occur on complex formation. The corresponding cyclic porphyrin trimer in toluene displays small but measurable preferences for binding some ligands within its cavity, and this may influence the rate of host-catalysed reactions within the cavity. Details will be reported elsewhere.

We thank Dr Nick Bampos for the methyl ester analogue of $Zn(H_2L^2)$, NSERC Canada (R. S. W.), the Cambridge Commonwealth Trust and New Zealand Vice-Chancellors' Committee (E. G. L.) for financial support, and the EPSRC Mass Spectrometry Service for FAB spectra.

Footnotes and References

* E-mail: jkms@cam.ac.uk

† Control experiments with the toluene-insoluble methyl ester analogues of ZnL^1 and $Zn(H_2L^2)$ (R = $CH_2CH_2CO_2Me$) in dichloromethane show no significant difference in binding behaviour, ruling out effects due to interaction with the long alkyl side-chains.

§ The small but probably real increase of K_2 for Zn_2L^2 with ligand size may reflect subtle geometry changes in the second porphyrin as the first ligand binds within the cavity and contacts the second porphyrin.

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Received in Basel, Switzerland, 28th April 1997; 7/02901B