Morphine Recognition by a Porphyrin–Cyclocholate Molecular Bowl

Richard P. Bonar-Law, Lindsey G. Mackay and Jeremy K. M. Sanders*

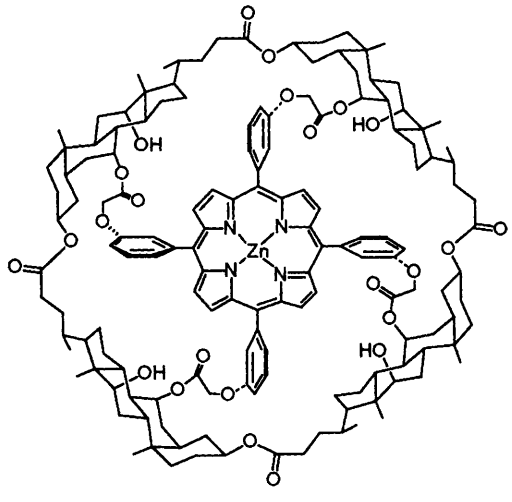
Cambridge Centre for Molecular Recognition, University Chemical Laboratory, Lensfield Road, Cambridge, UK CB2 1EW

A molecular bowl has been prepared by constructing a metalloporphyrin on one face of a tetrameric cyclocholate; the bowl selectively binds morphine by a combination of nitrogen–metal ligation and hydrogen bonding.

The emergence of supramolecular chemistry has led to the design and synthesis of many receptors for small molecules[1] but relatively few of these bind ligands larger than short peptides[2] or simple sugars.[3] We now report that the molecular bowl **1** selectively recognises alkaloids[4] of the morphine family by a combination of hydrogen bonding and nitrogen–metal ligation.

Bowl **1**† was prepared from the cholic acid derivative **2**[5] *via* linear dimer **3** as shown in Scheme 1. Macrolactonization of **3** under moderate-dilution conditions provided the tetrameric cyclocholate[6] **4** as the major product (55%) along with smaller quantities of cyclodimer (6%), cyclohexamer (12%) and cyclooctamer (3%).‡ Esterification of the hydroxy groups of **4** with 3-formylphenoxyacetic acid followed by cyclocondensation with pyrrole under Lindsey conditions,[8] metallation and removal of the trifluoroacetyl groups gave porphyrin bowl **1** in 4.5% yield. The low yield may reflect strain in the intermediate porphyrinogen, which is presumably just one of many pyrrole condensation products present at equilibrium.[8] For comparison, reference porphyrin **5** was prepared in 25% yield under similar conditions.

The porphyrin provides a floor to the bowl, and an electrophilic zinc atom which binds amines, while the four



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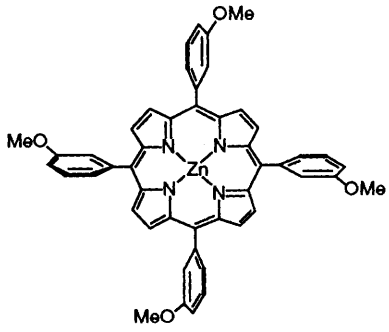

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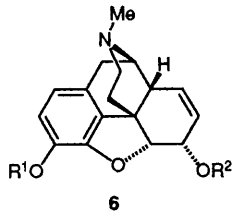

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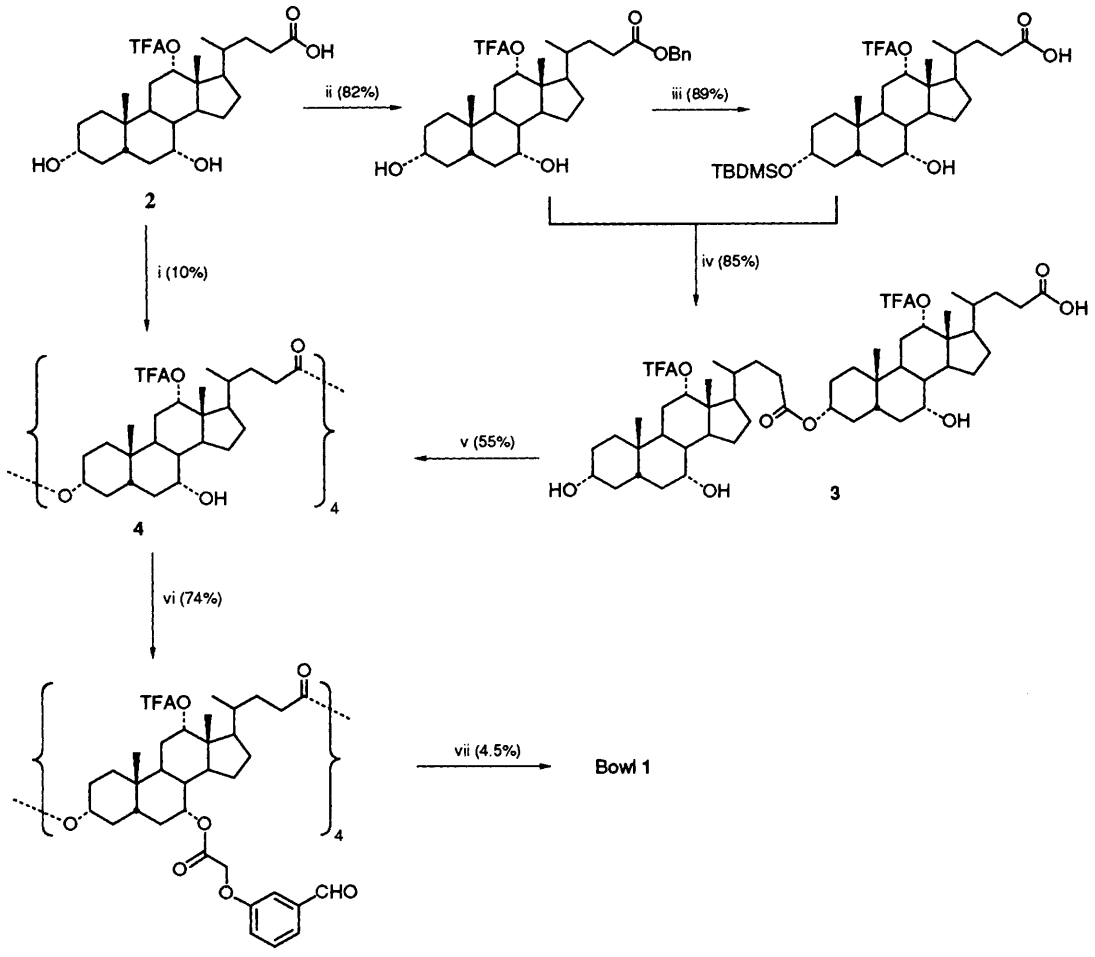
a; $R^1 = R^2 = Me$
b; $R^1 = Me$, $R^2 = H$
c; $R^1 = R^2 = H$

† All new compounds shown gave satisfactory spectra and/or elemental analyses. Thus, **3** and **4** gave molecular ions in positive fast atom bombardment mass spectra (MH^+ 991 and 1946 respectively) and correct microanalyses (±0.3%). Bowl **1** gave a molecular ion (MH^+ 2462); its ^1H NMR spectrum showed the expected fourfold symmetry and small upfield shifts in the cholate residues due to porphyrin formation; and possessed the expected porphyrin colour and electronic spectrum (λ_{max} 422 nm).

‡ The tetrameric cyclocholate **4** can be isolated by direct oligomerization of **2** [see (i) in Scheme 1],[6] but it is more efficient on a large scale to combine two differentially protected monomers and then to cyclise the resulting linear dimer.[7]



Scheme 1 *Reagents and conditions*: i, 2,6-dichlorobenzoyl chloride, dimethylaminopyridine (DMAP), 2 mmol dm^{-3} in toluene at 100 °C; ii, benzyl alcohol, 2,6-dichlorobenzoyl chloride, DMAP; iii (a) *tert*-butyldimethylsilyl (TBDMS) chloride, triethylamine, DMAP, (b) H_2, 10% Pd/C; iv (a) 2,6-dichlorobenzoyl chloride, triethylamine, DMAP, 4Å sieves, (b) HF (aq), (c) H_2, 10% Pd/C; v, 2,6-dichlorobenzoyl chloride, DMAP, 4Å sieves, 2 mmol dm^{-3} in CH_2Cl_2 at room temp.; vi, 3-formylphenoxyacetic acid, dicyclohexylcarbodiimide, DMAP; vii (a) pyrrole, $BF_3{\cdot}Et_2O$ in CH_2Cl_2 then 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, (b) NH_3 (aq) then $Zn(OAc)_2$ (TFA = trifluoroacetyl; Bn = benzyl)

Table 1 Binding constants for bowl **1** and reference **5**

Ligands	Bowl 1[a]	Reference 5	$\Delta\Delta G$/kJ mol^{-1} [b]
Morphine, **6c**	2.3×10^5	60	−20.1
Codeine, **6b**	1.3×10^4	110	−11.6
Codeine methyl ether, **6a**	240	170	−0.8
N-Methylpiperidine	2.5×10^3	2.0×10^3	−0.5
Pyridine	1.4×10^4	1.0×10^4	−0.8
Brucine	9.0×10^4	1.7×10^5	+1.6

[a] Binding constants (dm^3 mol^{-1}) measured in CH_2Cl_2 at 293 K. Errors estimated ±10% for $K \geq 100$ and ±20% for $K < 100$. [b] Difference in binding energy between bowl and reference porphyrin: $\Delta\Delta G = -RT\ln(K_1/K_5)$.

cholates each contribute a wall and a potentially binding or catalytic hydroxy group which faces into the resulting cavity. The main driving force for ligand binding is interaction of the basic nitrogen atom with the zinc atom, so the recognition ability of **1** is most usefully analysed by comparison with reference porphyrin **5**. Amine-binding to the zinc leads to a shift in the main porphyrin Soret absorption from 422 to 431 nm which is readily monitored and analysed to yield binding constants.[9]

We have examined the recognition of several types of alkaloid by bowl **1**, the results being summarised in Table 1. In favourable cases metal–nitrogen binding is augmented by hydrogen bonding of polar functional groups on the ligand with the four converging hydroxy groups of the bowl. In the series codeine methyl ether, codeine and morphine (**6a**, **b** and **c**) it is seen that on sequentially changing the two OMe groups of codeine methyl ether to the two OH groups of morphine (which are now capable of both receiving and donating hydrogen bonds) the binding constant increases by almost three orders of magnitude. The relative affinities of **1** and **5** for *N*-methylpiperidine (a model ligand for the benzoisoquinoline alkaloids) and pyridine suggest that the zinc atom in bowl **1** is inherently slightly more electrophilic. Correcting for this factor it is seen that the extra hydrogen bonds present in the morphine complex contribute *ca.* 20 kJ mol^{-1} to the binding energy.

Size discrimination is evident in the binding properties of larger alkaloids such as brucine and strychnine. For brucine the recognition factor is +1.6 kJ mol^{-1}, corresponding to an intrinsic binding ratio of 0.5 between **1** and **5**. This is the result expected for a ligand unwilling to enter the bowl and hence only able to interact with the outside face of the porphyrin. The large absolute values of the binding constants for brucine reflects its less hindered nitrogen; all these alkaloids have essentially identical pK_a values.[10]

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