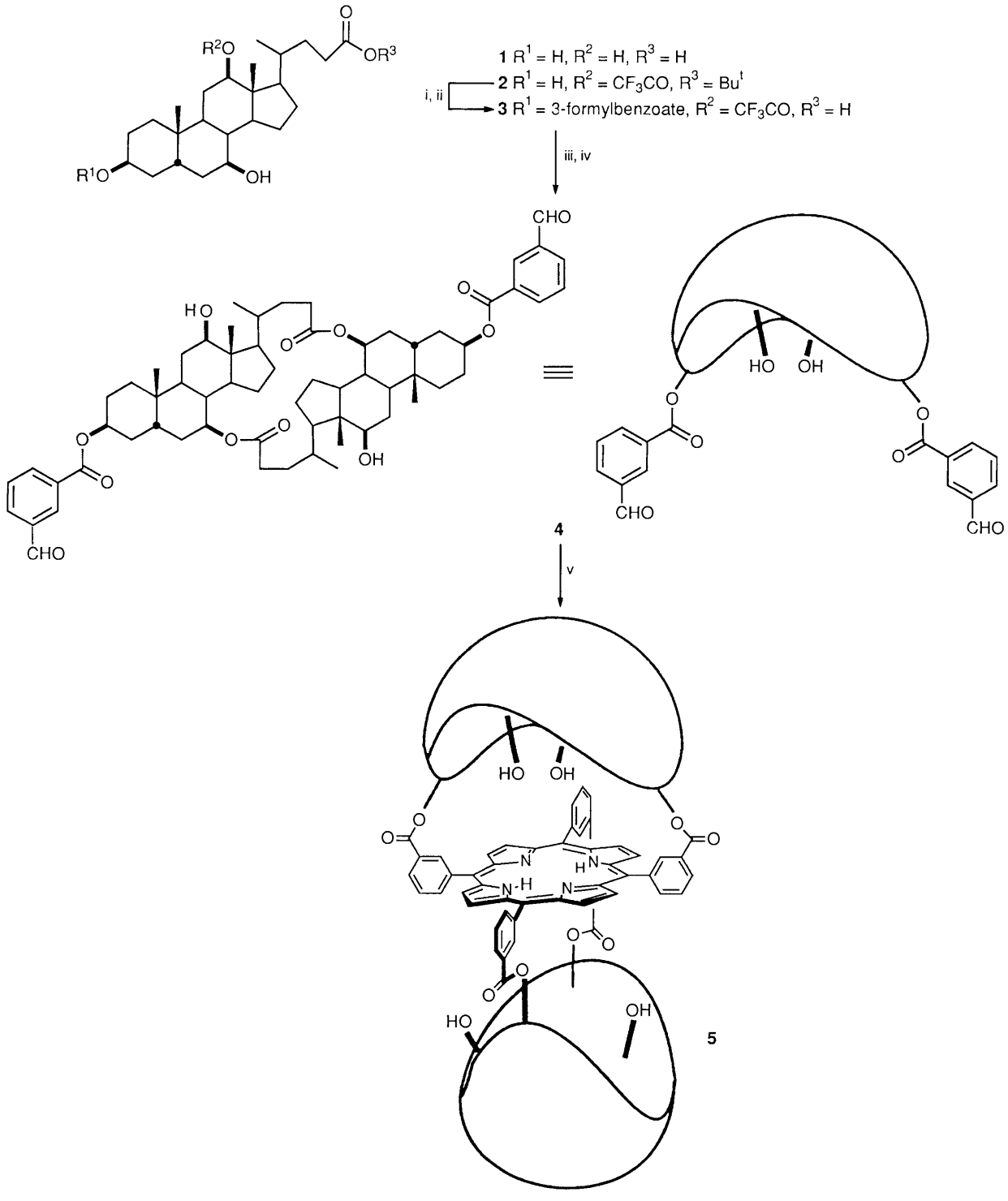
Synthesis, Binding Properties and Self-functionalization of a Steroid-capped Porphyrin

Richard P. Bonar-Law* and Jeremy K. M. Sanders

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

A porphyrin capped with a steroidal superstructure bearing convergent hydroxy groups has been synthesized and shown to bind a variety of functionalized amines *via* a combination of metal–amine and hydrogen-bonding interactions; the metal–ligand interaction was used to catalyse and control selective acylation of a single hydroxy group in the cap.

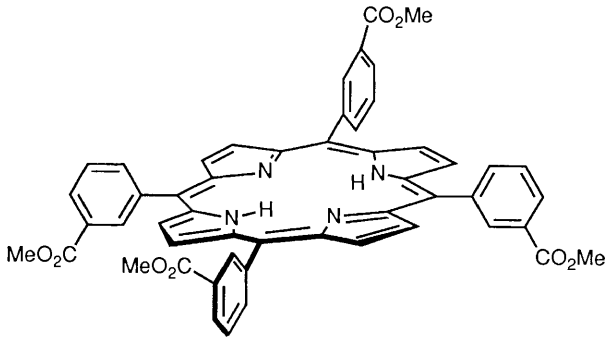
Since metalloporphyrins mediate ligand and electron transport and catalyse several types of reaction[1,2] there has been much interest in the development of artificial porphyrin-based host molecules and catalysts; most attention has focused on the development of chiral catalysts for reactions such as asymmetric hydroxylation,[2] for which there is little existing synthetic methodology. The majority of porphyrin-based catalysts reported to date recognize the shape of their substrates by hydrophobic[3] or van der Waal forces[4] (and possibly ππ-stacking interactions), which are geometrically



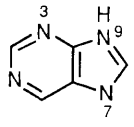
Scheme 1. *Reagents and conditions*: i, 3-formylbenzoic acid, DCC (dicyclohexylcarbodiimide), DMAP; ii, TFA; iii, 2,4,6-trichlorobenzoyl chloride, triethylamine, DMAP; iv, aqueous NaOH, MeOH, THF; v, pyrrole, $BF_3.Et_2O$, [substrate] = 1 mmol dm^{-3}, then DDQ

rather non-specific. While several porphyrin-based receptor molecules bearing polar functional groups as recognition elements have been prepared,[5] none of them display the truly three-dimensional array of convergent functionality that is responsible for the rate and selectivity of enzymic catalysis. Our approach has been to use steroids as naturally-occurring building blocks[6–8] to erect an enveloping chiral superstructure over the porphyrin ring, positioning functionality capable of binding substrates right over the active site. We report here the synthesis and preliminary binding studies of a chiral doubly-capped porphyrin **5** bearing convergent hydroxy groups as recognition elements, and show how ligand binding can be used to direct selective acylation of a single hydroxy group in the cap.

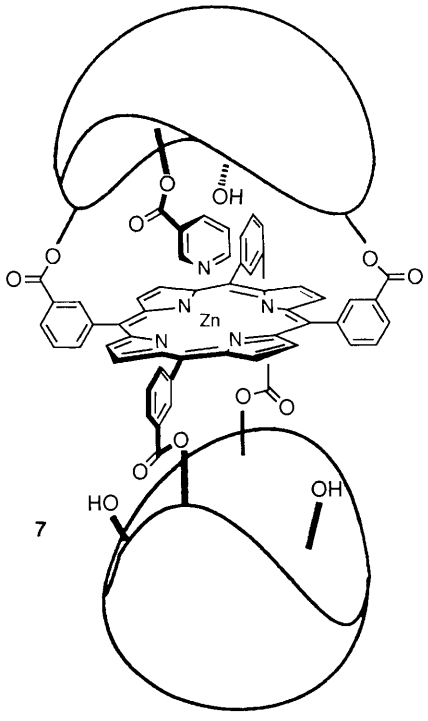
The basic framework of **5** was built from cholic acid **1**, a readily available steroid which has previously been deployed in the construction of host molecules.[8] Thus, selective acylation of protected cholic acid derivative[9] **2** with 3-formylbenzoic acid and cleavage of the *tert*-butyl ester gave hydroxy acid (**3**, 60% from **2**). Macrodilactonization under Yamaguchi[10] conditions (51%) followed by mild basic hydrolysis of the trifluoroacetate protecting groups furnished crystalline dilactone (**4**, 88%). Molecular models suggested that this dilactone should have a hemispherical cup-shaped conformation, shown



6



8



7

schematically, with the aromatic esters projecting downwards and approximately parallel to each other. Treatment of **4** with pyrrole under Lindsey conditions[11] followed by oxidation with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) afforded doubly-capped porphyrin **5** in a 7% recrystallized yield.†‡ The ^{1}H NMR spectrum of **5** is consistent with C_2 symmetry and the steroid resonances show upfield shifts compared to dilactone **4** due to the porphyrin ring current; the magnitudes of the upfield shifts (*e.g.* 0.2 ppm for the steroid angular methyl groups) suggest[12] that the cap is held in a fully-extended conformation enclosing a spacious cavity. The UV–VIS absorptions of **5** are red-shifted by 5 nm compared to reference porphyrin **6**, which may be due to distortion of the porphyrin ring by the tight-fitting caps.[13]

The binding affinity of the zinc derivative of **5**, Zn(**5**) for a variety of simple and functionalized amines was measured to assess the recognition ability of the convergent OH groups, and map out the topography of the underside of the dilactone cap. Association constants were measured by ^{1}H NMR or UV titration[14] of Zn(**5**) with ligand in $CDCl_3$ or $CHCl_3$ and some representative results are given in Table 1, along with data for reference porphyrin Zn(**6**) for comparison. In all cases the dominant binding process is coordination of one ligand to the zinc atom forming a 1 : 1 complex.

Not surprisingly, ligands that are too big to fit under the cap when coordinating in the normal fashion (Zn–ligand nitrogen bond perpendicular to porphyrin plane) bind weakly *e.g.* $K < 1$ for 4-*tert*-butylpyridine. Information about the coordination geometry can be obtained from the limiting ^{1}H NMR chemical shifts of the bound species. For example, the limiting chemical shift changes of the porphyrin Zn(**5**) on titration with 3,5-lutidine suggest that this ligand is bound more strongly than pyridine because it is held in an orientation such that the methyl groups project up to form favourable van der Waals interactions with pockets in the cap.§

Ligands bearing functionality capable of accepting or donating hydrogen bonds are particularly strongly bound. Thus, the binding of 3-hydroxypyridine, which is likely to form only one H-bond to the cap for geometric reasons, is enhanced by 6 kJ mol^{-1}. 4-Hydroxypyridine can potentially both donate and accept H-bonds by bridging the cap hydroxys and is consequentially bound more tightly.[15] The remarkable selectivity for purine **8** seems to be a consequence of a favourable H-bonded network; ^{1}H NMR studies on deuteriated analogues of **8** suggest that the ligand coordinates to the zinc atom through N-7 of the imidazole ring, allowing simultaneous donation and acceptance H-bonds by N-9(H) and N-3 respectively.

Metalloporphyrins with covalently attached axial ligands are efficient catalysts for oxygen transfer reactions.[16] It was, thus, of interest to use the affinity of Zn(**5**) for functionalized amines to prepare a 'ligand-tailed' version, such as **7**.

† We have also prepared an analogous singly-capped diarylporphyrin in good (50%) yield *via* a different route. Its binding affinity for non-amine substrates is currently being investigated.

‡ *Selected spectroscopic data* for: Zn(**5**); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 9.37 (4H, s, porphyrin β), 9.13 (4H, dt, *J* 7.7, 1.5 Hz, Ar-H), 8.75 (4H, s, porphyrin β), 8.44 (4H, dt, *J* 7.7, 1.5 Hz, Ar-H), 8.29 (4H, t, *J* 1.5 Hz, Ar-H), 8.05 (4H, t, *J* 7.7 Hz, Ar-H), 4.95 (4H, tt, *J* 11, 5 Hz, 3-H), 4.56 (4H, brq, *J* 3 Hz, 7-H), 3.57 (4H, brq, *J* 3.5 Hz, 12-H), 0.78 (12H, s, 19-Me), 0.60 (12H, d, *J* 6.6 Hz, 21-Me), 0.59 (4H, d, *J* 4 Hz, O*H*), 0.43 (12H, s, 18-Me); λ_{max} (CH_2Cl_2) 424.8, 552.5 and 589.1 nm; *m/z* (FAB, *m*-nitrobenzyl alcohol) 2344 (MH_2^+). **7** ^{1}H NMR δ ($CDCl_3$, 400 MHz) 9.32, 9.30, 9.25, 9.21 (4 × 1H, 4 × d, *J* 4.75 Hz, porphyrin β), 9.19, 9.11, 9.08, 9.05 (4 × 1H, 4 × dt, *J* 7.7, 1.5, Ar-H), 8.83, 8.79, 8.73, 8.59 (4 × 1H, 4 × d, *J* 4.68 Hz, porphyrin β), 8.45, 8.43, 8.36, 8.34 (4 × 1H, 4 × dt, *J* 7.7, 1.5 Hz, Ar-H), 8.40, 8.39, 8.35, 7.79 (4 × 1H, 4 × t, *J* 1.5 Hz, Ar-H), 8.08, 8.03, 8.02, 8.00 (4 × 1H, 4 × t, *J* 7.7 Hz, Ar-H), 6.83 (1H, dt, *J* 8, 1.7 Hz, ligand 4-H), 5.98 (1H, dd, *J* 8, 5.4 Hz, ligand 5-H), 4.95 (4H, m, 3-H), 4.63 and 4.56 (1H and 3H, 2 × brs, 7-H), 4.61 (1H, brt, *J* 3 Hz, 12-H), 3.65, 3.60, 3.55 (3 × 1H, 3 × brq, *J* 3.5 Hz, 12-H), 3.0 (1H,d, *J* 1.8 Hz, ligand 2-H), 2.93 (1H, dd, *J* 5.4, 1.7 Hz, ligand 6-H), 0.80, 0.79, 0.78, 0.77 (4 × 3H, 4 × s, 19-Me), 0.53, 0.46, 0.44, 0.42 (4 × 3H, 4 × s, 18-Me); λ_{max} (CH_2Cl_2) 432.4, 566.3 and 605.4 nm; *m/z* (FAB, *m*-nitrobenzyl alcohol) 2450 (MH_2^+).

§ At present we believe that the reduced binding affinity of Zn(**5**) for pyridine relative to reference Zn(**6**) is due primarily to heavy solvation of Zn(**5**) by $CHCl_3$. The value of $\Delta\Delta G$ for pyridine is very solvent dependent; in cyclohexane, where solvent effects should be small, $\Delta\Delta G = -1.1$ (±0.1), $\Delta\Delta H = 1.2$ (±2) and $T\Delta\Delta S = 2.3$ (±2) kJ mol^{-1}. Thus, the $\Delta\Delta G$ values for functionalized pyridines are minimum values.

Table 1 Binding constants for porphyrins Zn(**6**) and Zn(**5**)

Ligand	Zn(**6**)[a]	Zn(**5**)	$\Delta\Delta G$ (kJ mol^{-1})[b]
Pyridine	1.1×10^4	3.0×10^3	3.2
4-Ethylpyridine	2.4×10^4	540	9.2
3,5-Dimethylpyridine	1.4×10^4	4.7×10^4	−3.0
3-Hydroxypyridine	1.2×10^4	1.4×10^5	−6.0
4-Hydroxypyridine	1.3×10^3	4.4×10^4	−8.7
Pyrazine-*N*-oxide	720	1.1×10^4	−6.7
Imidazole	3.2×10^4	7.0×10^4	−1.9
Purine **8**	4.1×10^3	2.1×10^6	−15.2
Tropine	50	350	−4.6

[a] Binding constants (dm^3 mol^{-1}) measured in $CHCl_3$ or $CDCl_3$ at 293 K. Reproducibility in most cases is better than 10%. [b] Difference in binding energy between capped and reference porphyrin. $\Delta\Delta G = -RT\ln(K_{Zn(5)}/K_{Zn(6)})$.

Treatment of Zn(**5**) in toluene with an excess (10 equiv.) of the mixed anhydride formed from 3-carboxypyridine and 2,6-dichlorobenzoic acid followed by the addition of 4-*N*,*N*-dimethylaminopyridine (DMAP, 2 equiv.) resulted in rapid (<5 min) acylation of *one* of the OH groups in Zn(**5**) to give **7**. No further reaction occurred (24 h). By contrast, in a direct competition experiment no reaction of the zinc-free porphyrin **5** was observed under the same conditions. Thus, the Zn-amine interaction is positioning the active species (presumably an acylpyridinium salt) for rapid intramolecular reaction; only one hydroxy is acylated since the Zn atom in **7** is now pentacoordinate and shows no tendency to bind another ligand.

In summary, we have developed a concise synthetic route to doubly-capped chiral functionalized porphyrins and demonstrated both cooperative multipoint binding, and metalloporphyrin-directed catalysis of an intramolecular reaction. Work is now in progress to examine enantioselective complexation with a view to chiral catalysis.

We thank the SERC for financial support.

Received, 23rd January 1991; Com. 1/00336D

References

1 See for example, D. W. Bartley and T. J. Kodadek, *Tetrahedron Lett.*, 1990, **31**, 6303; K. Konishi, K. Makita, T. Aida and S. Inoue, *J. Chem. Soc., Chem. Commun.*, 1988, 643; Y. Aoyama, Y. Tanaka, Y. Yoshida, H. Toi and H. Ogoshi, *J. Organomet. Chem.*, 1987, **329**, 251.

2 T. J. McMurry and J. T. Groves in *Cytochrome P-450: Structure, Mechanism and Biochemistry*, ed. P. R. Ortiz de Montellano, Plenum: New York, 1986, p. 1.

3 Y. Kuroda, T. Hiroshige and H. Ogoshi, *J. Chem. Soc., Chem. Commun.*, 1990, 1594; D. R. Benson, R. Valentekovich and F. Diederich, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 191.

4 Y. Naruta, F. Tani and K. Maruyama, *J. Chem. Soc., Chem. Commun.*, 1990, 1378; J. T. Groves and P. Viski, *J. Org. Chem.*, 1990, **55**, 3628; S. O'Malley and T. Kodadek, *J. Am. Chem. Soc.*, 1989, **111**, 9116.

5 See for example, J. S. Lindsey, P. Kearney, R. J. Duff, P. Tjivikua and J. Rebek, *J. Am. Chem. Soc.*, 1988, **110**, 6575; R. Breslow, A. B. Brown, R. D. McCullough and P. W. White, *J. Am. Chem. Soc.*, 1989, **111**, 4517; Y. Aoyama, J. Uzawa, K. Saita, Y. Tanaka, H. Toi and H. Ogoshi, *Tetrahedron Lett.*, 1988, **29**, 5271.

6 Steroid derivatives have been used previously as biomimetic catalysts; J. P. Guthrie, J. Cossar and B. A. Dawson, *Can. J. Chem.*, 1986, **64**, 2456.

7 Cholesterol was recently employed to anchor a tetraarylporphyrin in vesicle lipid bilayers for the catalysis of regioselective oxygen transfer reactions; J. T. Groves and R. Neumann, *J. Am. Chem. Soc.*, 1989, **111**, 2900.

8 R. P. Bonar-Law and A. P. Davis, *J. Chem. Soc., Chem. Commun.*, 1989, 1050; R. P. Bonar-Law, A. P. Davis and B. A. Murray, *Angew. Chem. Int. Ed., Engl.*, 1990, **29**, 1407; C. J. Burrows and R. A. Sauter, *J. Incl. Phenom.*, 1987, **5**, 747; J. McKenna, J. M. McKenna and D. W. Thornthwaite, *J. Chem. Soc., Chem. Commun.*, 1977, 809.

9 R. P. Bonar-Law, A. P. Davis and J. K. M. Sanders, *J. Chem. Soc., Perkin. Trans.* 1, 1990, 2245.

10 J. Inanaga, K. Hirata, H. Saeki, T. Katsuki and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1989.

11 J. S. Lindsey, I. C. Schreiman, H. C. Hsu, P. C. Kearney and A. M. Marguerettaz, *J. Org. Chem.*, 1987, **52**, 827.

12 R. J. Abraham, G. R. Bedford, D. McNeillie and B. Wright, *Org. Magn. Reson.*, 1980, **14**, 418.

13 U. Simonis, F. A. Walker, P. L. Lee, B. J. Hanquet, D. J. Meyerhoff and W. R. Scheidt, *J. Am. Chem. Soc.*, 1987, **109**, 2659.

14 C. A. Hunter, P. Leighton and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans.* 1, 1989, 547.

15 The measured binding constants for this ligand represent minimum values since 4-hydroxypyridine exists in chloroform solution largely as aggregates of the pyridone tautomer; P. Beak, J. B. Covington, S. G. Smith, J. M. White and J. M. Zeigler, *J. Org. Chem.*, 1980, **45**, 1354.

16 F. Montanari, M. Penso, S. Quici and P. Vigano, *J. Org. Chem.*, 1985, **50**, 4888; B. Meunier, M.-E. de Carvalho, O. Bortolini and M. Momenteau, *Inorg. Chem.*, 1988, **27**, 161.