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Urea porphyrins as simple receptors for sugars

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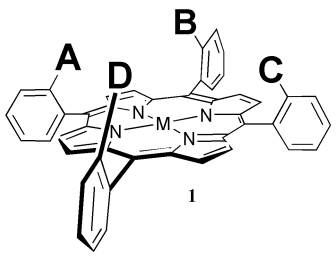
Urea-functionalised porphyrins with amino acid substituents bind sugar derivatives strongly in non-polar solution.

Given the importance of sugar recognition in biological chemistry, the design of low molecular weight artificial receptors for sugars is of fundamental interest, and may also have practical applications.[1] Sugar-binding proteins surround the ligand with functional groups capable of both hydrogen bonding to the sugar hydroxyls and solvating less polar areas of the ligand.[2] A synthetic receptor presumably needs to operate in the same fashion, and several biomimetic receptors with appreciable affinity in non-polar solvents have been developed,[3] although solvent competition usually makes recognition in polar solvents much less effective.[4]

Our initial goal was to make receptors of general structure **1**, where A to D represent 'recognition functionality'. The tetraarylporphyrin base was chosen because it is large enough to span a monosaccharide and provides a sensitive chromophore for monitoring the binding process.[5] Since sugar receptors are difficult to design from scratch, groups A to D were to be attached simultaneously to the porphyrin, screening the resulting mixture of receptors for sugar binding. However before embarking on the combinatorial approach it seemed wise to prepare simple symmetrical derivatives to check the basic design. Here we report preliminary binding properties of a series of receptors **2a**–**d** with four identical amino acid esters linked to the porphyrin by urea groups.[6] Similar urea-functionalised porphyrins have recently been shown to be effective receptors for anions.[7]

Porphyrins **2a**–**d** were prepared from the α,α,α,α-atropisomer of 5,10,15,20-*meso*-tetrakis(*o*-aminophenyl)porphyrin and the appropriate amino acid methyl ester, using Collman's *in situ* isocyanate method.[8] Equilibrium constants (*K* values) for typical organic soluble pyranosides **3**–**6** were then measured by UV-visible titrations in dichloromethane (Table 1), monitoring the red-shift and change in intensity of the porphyrin Soret band (Fig. 1).† Most of the *K* values are for the zinc derivatives **Zn2a**–**d** since these gave larger changes in UV-visible spectra. All titrations showed deviations from 1:1 porphyrin:sugar stoichiometry at higher sugar concentrations, ascribed to formation of 1:2 complexes.[9] Some of the *K* values were also checked by fluorescence titrations, with similar results.



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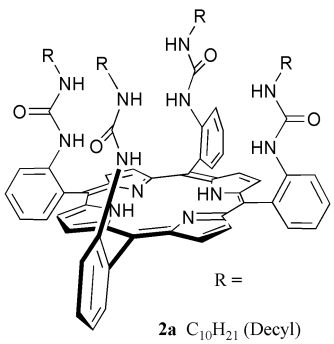


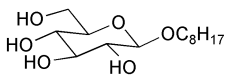
R =

2a $C_{10}H_{21}$ (Decyl)

2b L-Valine methyl ester

2c L-Threonine methyl ester

2d L-Tryptophan methyl ester



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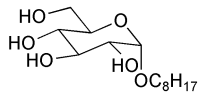

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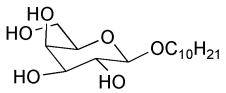

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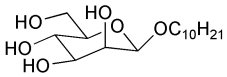

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Table 1 Equilibrium constants/10^4 measured by UV-visible titrations at 297.6 K in CH_2Cl_2 or by fluorescence in CH_2Cl_2 at RT (figures in brackets)

	R =	β-Glucoside **3**	α-Glucoside **4**	β-Galactoside **5**	β-Mannoside **6**
Zn2a	Decyl	30[a] (20[b])	15[a]	80[a]	20[a]
2a		15[b] (10[a])			
Zn2b	Valine	40[b]	7[a]	20[c]	7[a]
2b		20[b]			
Zn2c	Threonine	8[c] (10[a])	25[b]	40[c]	2.5[a]
2c		15[a] (20[b])			
Zn2d	Tryptophan	50[b]	3[c]	90[b]	10[a]
2d		50[a]	5[c]	60[c]	5[a]

[a] Estimated errors ±15%. [b] ±30%. [c] ±45%.

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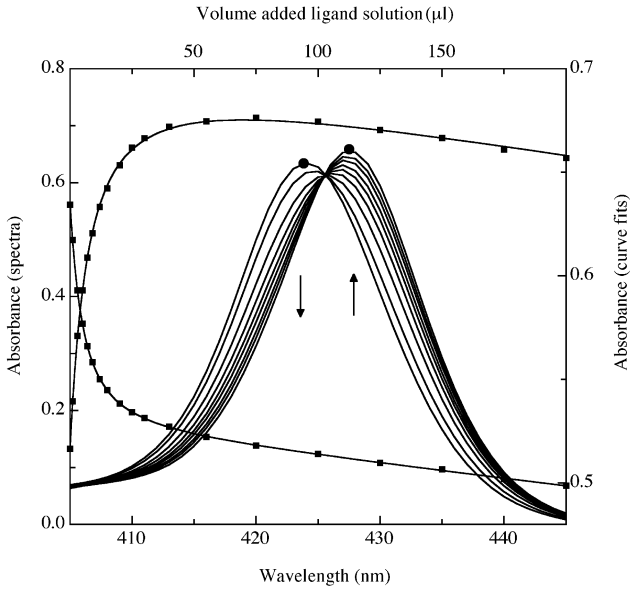

Fig. 1 Typical UV-visible titration; **Zn2a** + β-mannoside **6**, showing curve fits at two wavelengths (424 and 428 nm).

The urea-porphyrins proved to be quite effective receptors, with K values varying from 3×10^4 to 9×10^5. Several trends are evident from Table 1:

(i) Strong binding by the decyl substituted receptors **2a** and **Zn2a** suggests that most of the binding is due to the urea groups.

(ii) Amino acid substituents modulate the strength of association, with K values for a given sugar binding to different receptors varying by factors of between three and eight.

(iii) The urea-porphyrin design has some intrinsic selectivity, binding sugars in the order galactoside > glucoside > mannoside, as judged from average K values for **Zn2a**–**d**. This unusual preference is the reverse of the normal 'stickiness order' of mannoside > glucoside > galactoside found for unselective receptors.[1,10]

(iv) Anomeric selectivity follows the normal trend,[1,10] with the β anomer of glucoside **3** being bound more strongly than the α anomer **4** except for the threonine derivative **Zn2c**.[11]

(v) The zinc and free base porphyrins have similar K values, suggesting that the extra Lewis acid site provided by the central metal is not essential.

Addition of water or methanol to titrations in dichloromethane reduced K values, as is usually (but not always[10]) the case for hydrogen bonding in a non-polar solvent. Preliminary attempts to measure sugar binding in more biologically relevant polar solvents by UV-visible titration were thwarted by porphyrin aggregation. For example, the spectra of tetracarboxylic acid porphyrins, prepared by hydrolysis of the terminal ester groups of **2a**–**d**, slowly red-shifted on standing in aqueous solution.[12]

^{1}H NMR titrations with β-glucoside **3** in $CDCl_3$ confirmed strong binding, but were difficult to analyse quantitatively, again due to porphyrin aggregation.[13] Nevertheless the qualitative behaviour was consistent with hydrogen bonding as the main recognition process: the urea NH proton resonances moved downfield as the sugar/porphyrin ratio was increased, with limiting shifts of $\Delta\delta_{NH}$ = 0.7–1.0 ppm. The other protons on the porphyrin showed smaller changes (±0.1 ppm), and the β-pyrrolic protons for achiral porphyrin **2a** became non-equivalent as the chiral complex was formed. Broadened sugar resonances appeared above TMS in the early stages of some titrations *e.g.* with tryptophan derivative **2d** showing that the sugar is located over the porphyrin ring. Interestingly, weak binding ($K \sim 10$) between β-glucoside **3** and **2d** was observable by ^{1}H NMR in DMSO, a highly competitive solvent.[14]

In conclusion, these simple receptors have some of the highest recorded affinities for sugars in a non-polar solvent, showing that strong binding can be achieved without elaborate macrocylic architectures. Secondary association complicates the binding assay somewhat, but the acyclic design is notably easy to prepare. Detectable binding in DMSO suggests that further development could lead to genuinely biomimetic recognition.

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Notes and references

† In a typical titration porphyrin (1–5 μM) was titrated with sugar up to a final concentration of < 200 μM (below the concentration at which these pyranosides begin to aggregate[10]). Equilibrium constants were calculated using commercial software (pro Fit, www.quansoft.com), at 10–20 wavelengths simultaneously, simulating the UV-visible bands of free and bound species during least squares analysis with Voigt-type functions. Eight parameters per band gave a ratio of total data points to free parameters > 10 : 1. Dilution effects (downward slopes at larger added volumes in Fig. 1) were included during the fitting process – titrations at constant porphyrin concentration gave the same results.

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13 Dimerisation constants of K_d = 50–100 in $CDCl_3$ were measured for **Zn2a** and **2b**, treating aggregation as a simple monomer–dimer equilibrium.

14 $\Delta\delta_{NH} \approx 0.35$, 34% receptor saturation. Methyl β-glucoside or the α anomer **4** did not produce downfield shifts of the NH protons under the same conditions.