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Tuning selectivity in macrotricyclic carbohydrate receptors; CH → N mutations in aromatic spacers†

Trinidad Velasco,[a] Gregory Lecollinet,[a] Theo Ryan[b] and Anthony P. Davis*[a]

[a] *School of Chemistry, University of Bristol, Cantock's Close, UK BS8 1TS. E-mail: Anthony.Davis@bristol.ac.uk; Fax: (+44)117-929-8611*

[b] *Department of Chemistry, Trinity College, Dublin 2, Ireland*

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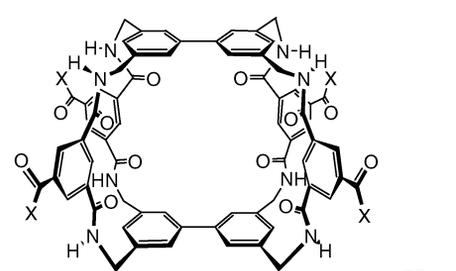
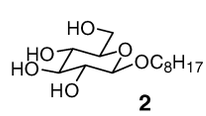
Dipicolinoyl spacer groups are used to control the conformational and H-bonding properties of tricyclic carbohydrate receptors 3 and 4. Binding selectivities are changed in relation to all-isophthaloyl system 1b.

Carbohydrate recognition is a central biological phenomenon, mediating carbohydrate metabolism, cell infection, cell–cell recognition and many aspects of the immune response.[1] This importance, coupled to poor understanding of the underlying principles, has fuelled research into saccharide binding by synthetic, potentially biomimetic receptors.[2] However, there are still few systems which show high affinities and selectivities towards closely related carbohydrate substrates. A recent example from this group is the tricyclic octa-amide **1**. The first version **1a** was shown to bind octyl glycosides in chloroform with unusual strength and discrimination.[3] Later variant **1b** proved capable of extracting the common hexoses from water into chloroform, a feat unprecedented for preorganised receptors operating through non-covalent bonding.[4] In both cases, particular selectivity was shown for equatorial substitution patterns. **1a** preferred β-glucoside **2** over the α anomer by a factor of 50, while **1b** extracted xylose in preference to ribose, and glucose in preference to galactose and mannose.



1a X = OC_5H_{11} **1b** X = NH



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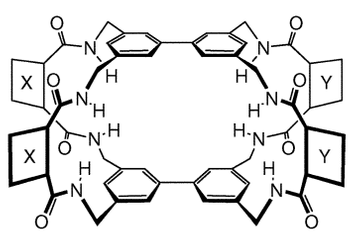
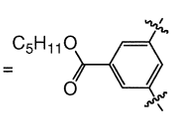
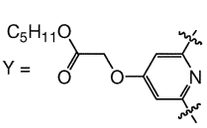
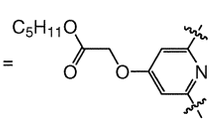
Given the diversity of carbohydrate structures, alternative selectivities are clearly of interest. Accordingly, we are investigating changes to **1** which might alter binding preferences while maintaining the same general architecture.[5] One possibility is the replacement of the isophthaloyl spacer groups with pyridine-based analogues. By participating in hydrogen bonding, the pyridine nitrogen is likely to affect both the geometry of the macrocycle and the array of H-bonding groups presented to the interior. We now report the synthesis and recognition properties of two macrotricycles **3** and **4** which feature this "mutation". The introduction of the pyridines is shown to invoke significant changes in binding selectivity.



3 X =  Y = 

4 X = Y = 

The synthesis of receptors **3** and **4** is summarised in Scheme 1. Biphenyl unit **5** and isophthaloyl derivative **6** were prepared as previously reported.[4] The novel pyridine-based spacer **11** was synthesised from chelidamic acid **7** *via* esterification to give **8**, *O*-alkylation to **9**, hydrogenolysis to **10**, and treatment with DCC/pentafluorophenol. Formation of the tricyclic "cages" was accomplished through sequential [2+2] macrolactamisations. Hydrogenolysis of the Cbz groups in **5** gave a diamine which was cyclised with **6** to give **12**, and **11** to give **13**. Acid-induced deprotection and cyclisation with **11** then gave **3** and **4**.

The affinities of receptors **3** and **4** for saccharide guests were investigated firstly by titration studies in organic media with octyl β-D-glucopyranoside **2**. Upon addition of the glucoside to **3** in $CDCl_3/CD_3OH$ (96 : 4), or **4** in $CDCl_3/CD_3OH$ (99 : 1), significant changes in the receptor ^{1}H-NMR spectra were observed.† However, signal broadening and the relatively small $\Delta\delta$ precluded quantitative analysis. Fluorescence titrations in $CHCl_3$ revealed ≥65% decreases in emission intensity from both receptors on addition of **2**, with saturation at close to 1 equivalent.† Analyses of the data at the emission maxima, assuming a 1 : 1 binding model, gave very high binding constants ($>10^7$ M^{-1} in each case). However, the fits were poor and changes in the emission profiles during the titrations suggested interference from other stoichiometries. Accurate and reliable K_a values were therefore unobtainable.

† Electronic supplementary information (ESI) available: experimental details for the synthesis of receptors **3** and **4**, binding studies of receptors **3** and **4** with monosaccharide **2**, and extraction experiments. See http://www.rsc.org/suppdata/ob/b3/b315447e/

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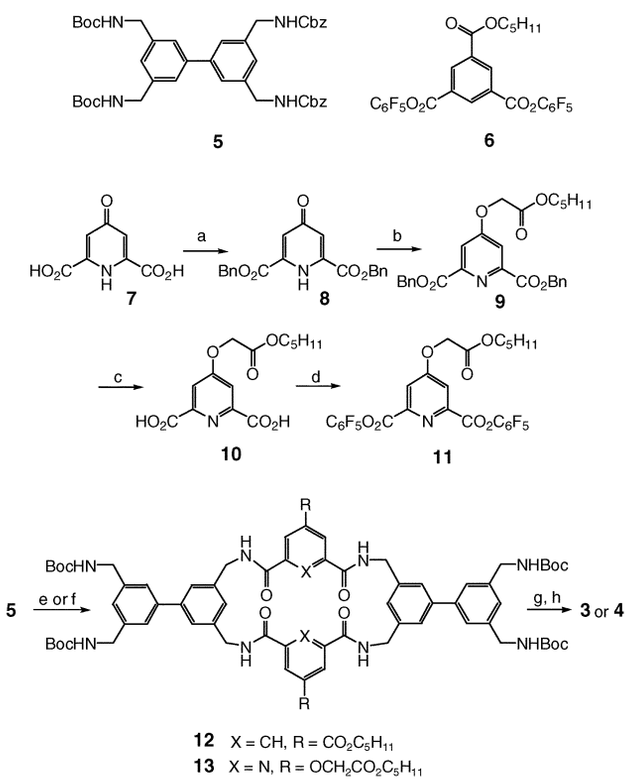
Table 1 Extractabilities of aldohexoses **14**–**16** from aqueous solutions into $CHCl_3$ by receptors **1b**, **3** and **4**[a]

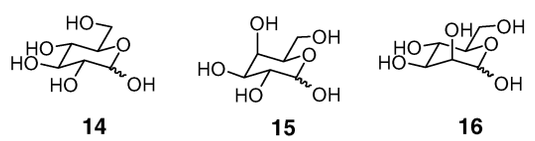
	D-Glucose **14**			D-Galactose **15**			D-Mannose **16**
	1 M[b]	0.5 M[b]	0.1 M[b]	1 M[b]	0.5 M[b]	0.1 M[b]	1 M[b]
1b	1	0.5	<0.1[c]	0.2	<0.1[c]	n.d.[d]	<0.1[c]
3	0.55	0.2	n.d.[d]	0.6	0.17	n.d.[d]	0.3
4	0.15			<0.1[c]			n.d.[d]

[a] Values in mole equivalents with respect to receptor, as determined by ^{1}H-NMR (integration of anomeric CH *vs*. receptor protons). Estimated error +20%. Results for **1b** from ref. 4. [b] Concentration of substrate in aqueous phase. [c] Carbohydrate detectable, but amount too small for quantification by NMR integration. [d] None detectable.



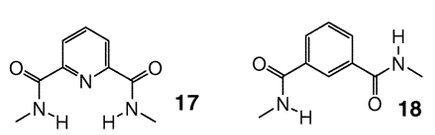
Scheme 1 Synthesis of receptors **3** and **4**. *Reagents, conditions and yields*: a) i) $(COCl)_2$, DMF, THF, ii) BnOH, *i*Pr_2NEt, 72%; b) K_2CO_3, pentyl bromoacetate, $(CH_3)_2CO$, 97%; c) H_2, Pd/C, EtOAc, 97%; d) DCC, DMAP, C_6F_5OH, *i*Pr_2NEt, THF, 56%; e) H_2, Pd/C, DCM/CH_3OH, 72%; f) **6**, *i*Pr_2NEt, THF, high dilution, 80%, *or* **11**, *i*Pr_2NEt, THF, high dilution, 62%, g) CF_3CO_2H, DCM; h) **11**, *i*Pr_2NEt, THF, high dilution, 23% (**3**) or 11% (**4**).

The extraction of substrates from water into non-polar solvents provides an alternative means of studying carbohydrate recognition. Such experiments allow straightforward comparisons between receptors under conditions which mimic, to some extent, the cytosol–membrane interface in biology. Receptors **3** and **4** were tested using the procedure previously applied to **1b**.[4] Solutions of receptor in chloroform (0.35 mM) were warmed to 30 °C then shaken vigorously with aqueous carbohydrate. The phases were separated, and the organic phase was passed through hydrophobic filter paper to remove residual aqueous solution. The chloroform was evaporated and the residue analysed by ^{1}H NMR in $(CD_3)_2SO$. D-Glucose **14**, D-galactose **15** and D-mannose **16** were used as substrates. The results are shown in Table 1, along with the data obtained earlier for **1b**. Both **3** and **4** succeeded as monosaccharide extractors. The symmetrical cage **4** proved relatively weak, while the asymmetrical receptor **3** was found to be roughly similar in affinity to **1b**. Significantly, however, the selectivities observed for **3** were quite different to those of the earlier system. Compared to **1b**, receptor **3** showed increased affinity to galactose and D-mannose, but decreased affinity to glucose. As a result, galactose and glucose are extracted to similar extents, in contrast to the strong preference of **1b** for glucose. While it might appear that **3** is simply less selective than **1b**, it should be noted that the monosaccharides are not equally hydrophilic. Indeed, physical chemical measurements have suggested that galactose is more strongly hydrated than glucose,[6] implying that **3** may be intrinsically galactose-selective.



Control experiments with tetra *N*-Boc protected macrocyclic intermediates **12** and **13** were carried out with D-glucose **14** (1 M aqueous solution). No sugar was detected in the organic phase, confirming that the macrotricyclic frameworks of **3** and **4** are necessary for efficient extraction.

The selectivity differences between **1b** and **3** are probably due to the conformational properties of the spacers. It is established that the dipicolinamide unit prefers the *syn–syn* conformation **17** because of electrostatic interactions between the NH groups and the pyridine N. In contrast, the isophthalamide unit prefers the *syn–anti* arrangement **18**.[7] The two spacers will thus tend to present different arrays of H-bonding groups to a bound substrate, and will also promote different cavity dimensions.



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