Diastereo- and Enantio-selective Binding of Octyl Glucosides by an Artificial Receptor

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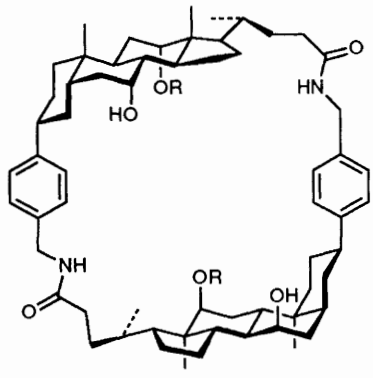
^{1}H NMR titration experiments have been used to measure the association constants between tetrahydroxycholaphane **1a** and the octyl glucosides **2–5**; the cholaphane has been shown to discriminate quite effectively between the stereoisomers, showing a diastereoselectivity of *ca.* 5.5 : 1 in respect of **2** and **3**, and an enantioselectivity of *ca.* 3 : 1 in respect of **3** and **5**.

The recognition of neutral, polar molecules by multiple H bonding in organic solvents has been subjected to intensive study in recent years.[1] However, despite the current interest in carbohydrate residues as recognition elements in biological systems,[2] there are still very few reports of synthetic receptors for carbohydrate nuclei.[3–5] A recent publication from this laboratory[4] described the complexation of dodecyl β-D-glucopyranoside in $CDCl_3$ by the tetrahydroxycholaphane **1a** and its dibenzylated analogue **1b**.[6] Given the nature of the proposed interaction, in which the cholaphane host surrounds

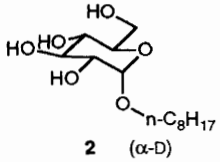
Table 1 ^{1}H NMR titration experiments involving tetrahydroxycholaphane **1a** and octyl glucopyranosides **2–5**[a]

Glucoside	Association constant[b]/ mol^{-1} dm^{-3}	Limiting NH chemical shift (δ)[c]
2	582 (±7%)	6.97
	545 (±4%)[d]	6.99
3	3100 (±14%)	6.68
4	1030 (±10%)	6.89
5	1000 (±14%)	6.92

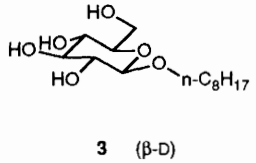
[a] Solutions of the glucosides in $CDCl_3$ were added to solutions of **1a** (*ca.* 2 mmol dm^{-3}) in the same solvent. ^{1}H NMR spectra (270 or 300 MHz) were run at 298 K. [b] Determined using an iterative least-squares curve-fitting program with weighting of data points according to the error analysis of Deranleau (D. A. Deranleau, *J. Am. Chem. Soc.*, 1969, **91**, 4044). The program takes account of the increasing volume of solvent as the titration progress. Figures in parentheses represent percentage standard deviations of the binding constant values calculated for each point on the curve. Typically 7–10 points were present in each data set, and the titration generally covered the range 0–90% binding of **1a**. [c] Estimated from the curve-fitting procedure. δ(N*H*) for pure **1a** 5.72 (±0.04). [d] Repeat experiment to check reproducibility; see text.



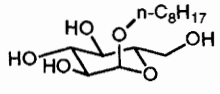
1a; R = H
1b; R = CH_2Ph



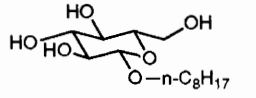
2 (α-D)



3 (β-D)



4 (α-L)



5 (β-L)

the carbohydrate guest, it seemed reasonable to suppose that the binding constant would be sensitive to fairly subtle changes in the structure of the guest. Moreover, the chirality of the hosts raised the possibility of the enantioselective recognition of carbohydrate derivatives. We have now studied the binding of tetrahydroxycholaphane **1a** to the four possible octyl glucopyranosides **2–5**, and report significant levels of diastereo- and enantio-selectivity.†

The glucopyranosides were obtained commercially (in the case of the D-isomers **2** and **3**) or synthesized using literature procedures (in the case of **4**[7] and **5**,[8] L-glucose being used as starting material‡). The complexation of these molecules by **1a** in $CDCl_3$ was investigated using the ^{1}H NMR titration method, essentially as described in our previous report.[4] In each case addition of the glucoside to the cholaphane caused substantial changes to the spectrum of the latter. In most respect these changes were qualitatively similar for all the glucosides, *i.e.* a downfield shift of the N–H signal (probably due to its participation in intermolecular H bonding), an increase in the separation of the signals due to the CH_2–N protons, and changes in the CH–NH vicinal couplings (*cf.* ref. 4). However, there were significant quantitative differences, and differences in the binding constants which could be derived by analysis of the movement of the N*H* signal.

The results of these analyses are shown in Table 1. For each run there was an acceptable fit between the experimental points and the calculated curve, suggesting that simple 1 : 1 complexation was occurring. Variable concentration ^{1}H NMR studies of glucosides **2** and **3** supported our assumption that there was no significant self-association over the concentration ranges used for the experiments. We were mindful of the possibility that variation of the conditions used for the experiment, and in particular the amount of water present,[10] could invalidate the results. We thus used the same bottle of solvent for the sequence of experiments on all four glucosides, starting with **2**, and then repeated the experiment with **2**. As shown in Table 1, this last result was sufficiently close to the first to suggest that the differences between the isomers are indeed genuine. The experiment with **3** was also repeated, using a fresh sample of **1a** and a new bottle of solvent. The measured binding constant of 3280 mol^{-1} dm^3 (*cf.* the entry for **3** in Table 1) gave us further confidence in our results.

The figures in Table 1 confirm our expectation that the cholaphane **1a** should be able to discriminate between the stereoisomeric glucopyranosides. Thus there are factors of *ca.* 3 between the association constants for enantiomers **3** and **5**, and *ca.* 0.55 between those for enantiomers **2** and **4**, while there is a ratio of *ca.* 5.5 between the association constants for diastereoisomers **3** and **2**. There must be some question as to whether the latter figure is entirely due to differing interactions between **1a** and the two diastereoisomers, as it is impossible to be absolutely sure that self-association of the carbohydrates is not affecting the results (presumably to differing extents). However, the enantioselectivities are quite secure, as any self-association would have identical effects for the two enantiomers.

Further evidence for enantiodifferentiation was provided by the movement of the signals due to the anomeric C*H*s on the glycosides. Thus, on incremental addition of the β-L-isomer **5** to **1a**, the anomeric signal first appeared 0.27 ppm upfield of its final position. As the fraction of the carbohydrate which is bound to the host is at its greatest early in the experiment, this result implies that the anomeric proton is quite strongly shielded in the complex (presumably by an aromatic ring **1a**). In contrast, while a corresponding shift was observed for the β-D-isomer **3** (which is more strongly bound), it was only to a degree of 0.05 ppm.

In conclusion, we have demonstrated that receptor **1a** can exhibit significant stereoselectivity in its interactions with carbohydrate nuclei. These results encourage us to hope that molecules related to **1a** might be suitable for a range of applications, *e.g.* in the analysis and separation of carbohydrate derivatives.

† The receptor described by Aoyama and coworkers was also found to be diastereoselective.[3a] As far as we are aware, there is no precedent for the enantioselective recognition of carbohydrate nuclei by an artificial receptor operating in organic solution. For the resolution of carbohydrates on template-imprinted polymers, see; G. Wulff and S. Schauhoff, *J. Org. Chem.*, 1991, **56**, 395.

‡ Compounds **4** and **5** were identical with their enantiomers by high field NMR and TLC: $[\alpha]_D^{18}$ for **4** −118 (*c* 1.07, MeOH) (*cf.* 117.9 for **2**[7]); $[\alpha]_D^{18}$ for **5** 29.1 (*c* 1, MeOH) (*cf.* −30 for **3**[9]).

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