Selective complexation of disaccharides by a novel D_2-symmetrical receptor in protic solvent mixtures

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The synthesis of an optically active, 1,1′-binaphthyl-derived cyclophane receptor with a preorganized central cavity lined with four anionic phosphodiester groups for ionic hydrogen bonding is described. In competitive protic solvent mixtures, this receptor forms stable 1:1 complexes with disaccharides whereas the smaller monosaccharides are not significantly bound.

Studies of carbohydrate complexation by artificial receptors[1] increasingly complement biological investigations[2] in the search for a molecular level understanding of the complex carbohydrate binding processes in nature.[3] We recently prepared the tetraanionic cyclophane (*R,R,R,R*)-(−)-**1** and observed 1:1 host–guest inclusion complexation with a suitably sized monosaccharide such as octyl β-D-glucoside in CD_3CN/CD_3OD 98:2 (*v/v*).[4] The formation of ionic hydrogen bonds[5] between the anionic phosphodiester groups lining the cavity in (*R,R,R,R*)-(−)-**1** and the hydroxy groups of the pyranoside was shown to provide the major driving force for this complexation process in the presence of a protic co-solvent which competes for the H-bonding sites of the two binding partners. Here we describe the synthesis of the new cyclophane receptor (*R,R,R,R*)-(−)-**2** and demonstrate that it discriminates in protic solvent mixtures between disaccharides, which are bound, and monosaccharides, which are not bound.

For the synthesis of (*R,R,R,R*)-(−)-**2** (Scheme 1), dialkynylated 1,1′-binaphthalene (*R*)-(+)-**3**[4] was mono-deprotected to give (*R*)-(−)-**4**, which was cross-coupled to 1,4-diiodobenzene under formation of (*R,R*)-(−)-**5**.[6] Alkyne-deprotection to (*R,R*)-(−)-**6** followed by Glaser–Hay coupling[7] afforded (*R,R,R,R*)-(−)-**7** which was transformed into the target compound (*R,R,R,R*)-(−)-**2** under the conditions previously applied to produce (*R,R,R,R*)-(−)-**1**.[4]

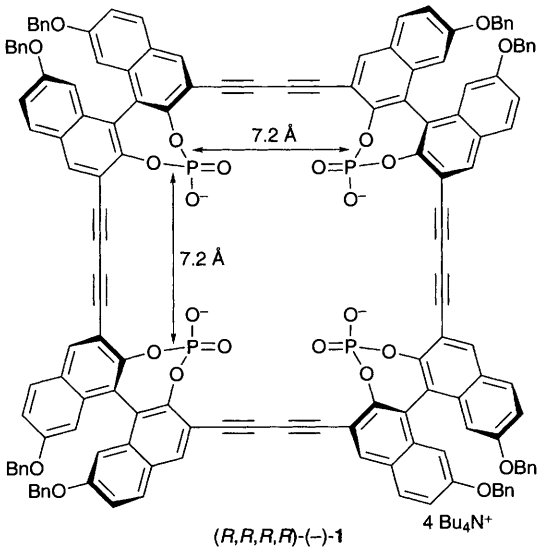
In the average D_2-geometry of (*R,R,R,R*)-(−)-**2**, the distances between the P-atoms in the highly preorganised rectangular cavity are 11.6 × 7.2 Å, which represents a significant enlargement of the binding site as compared to (*R,R,R,R*)-(−)-**1** with a squaric cavity of 7.2 × 7.2 Å.

Complexation of disaccharides **8–10** was investigated by ^1H NMR titrations at 300 K in CD_3CN/CD_3OD 88:12 (*v/v*) in which the upfield changes in chemical shifts of the anomeric proton H–C(1) upon addition of (*R,R,R,R*)-(−)-**2** were followed (Table 1). (*R,R,R,R*)-(−)-**2** exhibited a high binding affinity (K_a ≈ 10^4 dm^3 mol^{-1}, $-\Delta G^0$ ≈ 5.5 kcal mol^{-1}, 1 cal = 4.184 J) for all three disaccharides **8–10**. Whereas no selectivity among these substrates was observed, the selectivity over monosaccharides was very high. Upon addition of more than 2 equiv. of the receptor to a 0.25 mmol dm^{-3} solution of octyl β-D-glucoside **11**, no change in chemical shift of its anomeric proton H–C(1) was observed within the error range (Δδ ± 0.001 ppm), while disaccharides **8–10** produced 60–80% saturation binding

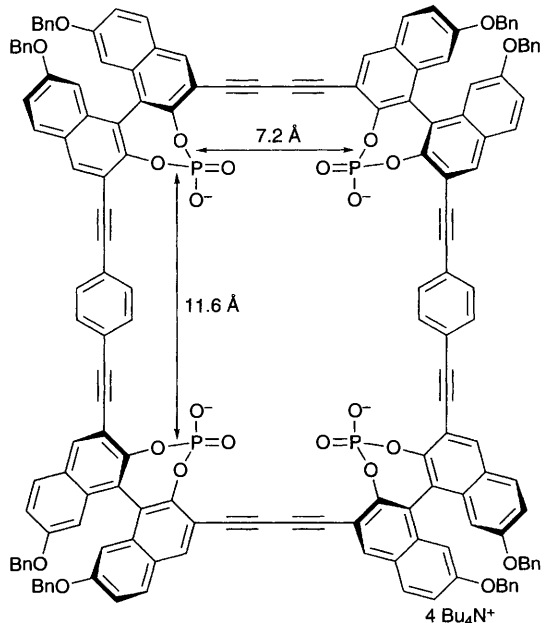
Table 1 Association constants K_a and binding free enthalpies $-\Delta G^0$ from ^1H NMR binding titrations for 1:1 complexes of mono- and di-saccharides with (*R,R,R,R*)-(−)-**2** in CD_3CN/CD_3OD 88:12 (*v/v*) at 300 K

Substrate[a]	K_a[b] / dm^3 mol^{-1}	$-\Delta G^0$ / kcal mol^{-1}	$\Delta\delta_{max\ obs}$[c] / ppm	$\Delta\delta_{sat}$[c] / ppm
8	11000	5.5	0.077	0.11
9	12500	5.6	0.085	0.11
10	10750	5.5	0.127	0.18
11	no binding			

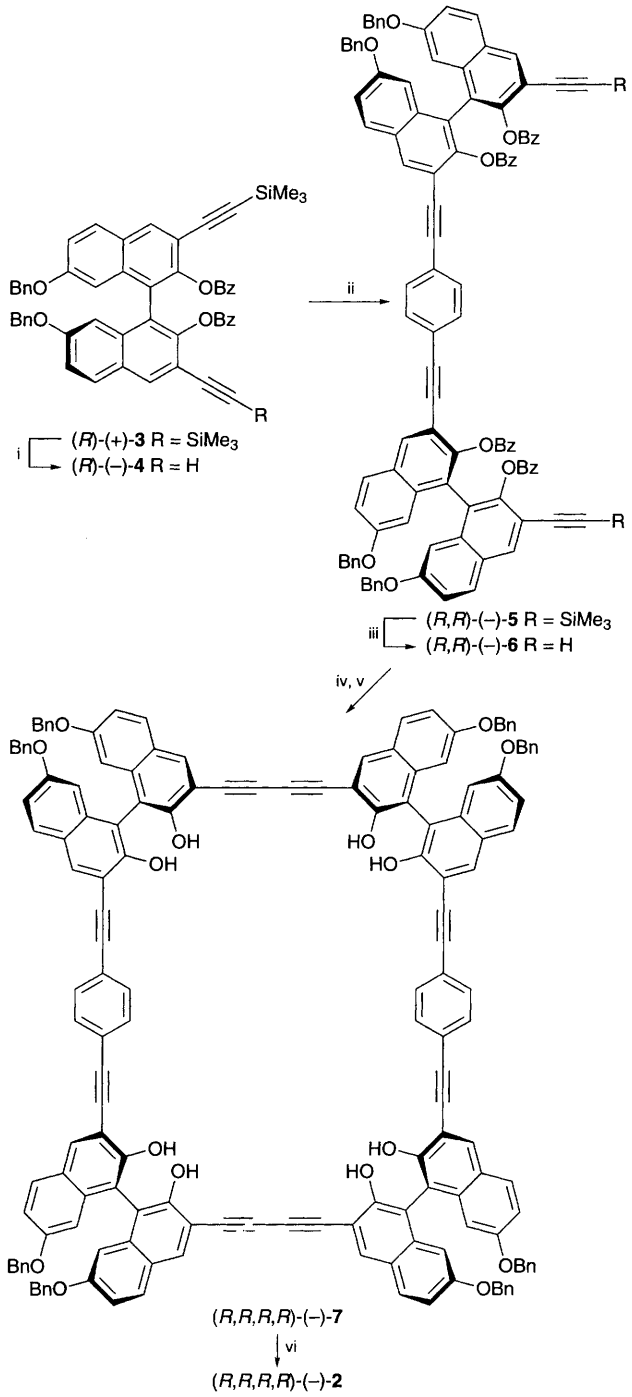
[a] The substrate concentration was held constant at *ca.* 2.5 × 10^{-4} mol dm^{-3} and the receptor concentration varied between 0.3 and 4.5 × 10^{-4} mol dm^{-3}. [b] The reproducibility of the K_a values was ±20% in duplicate and triplicate runs. [c] Also shown are the complexation-induced changes in chemical shift at saturation binding ($\Delta\delta_{sat}$), and the maximum shifts ($\Delta\delta_{max\ obs}$) observed for the anomeric protons H–C(1).



(*R,R,R,R*)-(−)-**1**

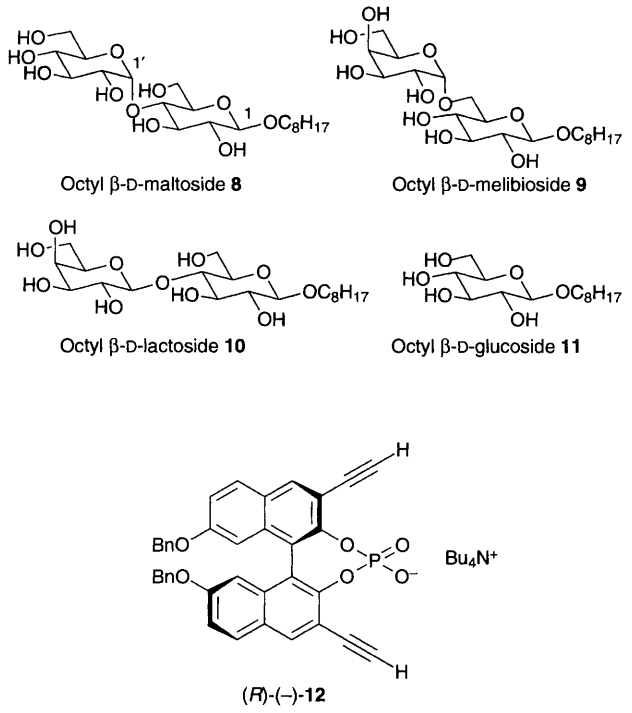


(*R,R,R,R*)-(−)-**2**



Scheme 1 Synthesis of (*R,R,R,R*)-(−)-**2**. *Reagents and conditions*: i, $Na_2B_4O_7 \cdot 10\,H_2O$, THF/$H_2O$ 1 : 1, 37%; ii, $[Pd_2(dba)_3]$, PPh_3, Et_3N, $C_6H_4I_2$, toluene, 50%; iii, K_2CO_3, MeOH, THF, 91%; iv, CuCl, *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), CH_2Cl_2, air, 20%; v, KOH, MeOH–THF, 89%; vi, $POCl_3$, Et_3N, CH_2Cl_2; then THF, H_2O, 40 °C; then Dowex (Bu_4N^+), $CHCl_3$/MeCN 1 : 1, 63%.

under these conditions. This high selectivity [$\Delta(\Delta G^0) > 3$ kcal mol^{-1}] is readily explained by the size of the cavity of (*R,R,R,R*)-(−)-**2**, which fits disaccharides well but, unlike the cavity in (*R,R,R,R*)-(−)-**1**, is much too spacious for incorporating a monosaccharide under formation of ionic H-bonds to all four convergent phosphates. Apparently, ionic hydrogen bonding of **11** to only the two phosphate groups in (*R,R,R,R*) = (−)-**2**,



which are separated by 7.2 Å, is not sufficient to establish stable complexation in the competitive protic solvent mixture used. In pure CD_3CN, (*R,R,R,R*)-(−)-**2** was found to bind monosaccharide **11**, but with a host–guest stoichiometry higher than 1 : 1 and presumably 2 : 1 as suggested by *Job* plot analysis. Octyl β-D-maltoside **8** displayed no binding to monophosphate (*R*)-(−)-**12** in CD_3CN/CD_3OD 88 : 12 (*v/v*) in concentration ranges below 10 mmol dm^{-3}. Simultaneous ionic hydrogen bonding between the substrate and the four encircling phosphodiesters of (*R,R,R,R*)-(−)-**2** is necessary for stable complexation to occur in the competitive solvent mixture.

Support by the Chiral 2 program of the Swiss National Science Foundation is gratefully acknowledged.

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Received, 10th April 1996; Com. 6/02484J