A STEREOSELECTIVE PEPTIDE-BASED ARTIFICIAL RECEPTOR FOR SUGAR DERIVATIVES+

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Dedicated to Professor Otakar Červinka on the occasion of his 75th birthday, in appreciation of his contributions to organic stereochemistry.

A lipophilic sugar receptor containing two phenylalanine moieties shows in chloroform complexation free energies of ΔG = 13 kJ/mol for an alkyl glucoside, discriminating the corresponding galactoside by at least 8 kJ/mol. The observed ^{1}H NMR signal shifts at OH groups suggest the hydrogen bonds as the major driving force, in line with preliminary molecular mechanics simulations.

Key words: Carbohydrate receptors; Glycosides; Amides; Supramolecular complexes; Hydrogen bonds; Peptide–sugar interactions.

Carbohydrate receptors play a major role in biological systems[1], at the same time they they pose one of the most difficult problems of synthetic supramolecular chemistry, due to weak intramolecular forces involved in the complexations. In protein complexes with carbohydrates usually all sugar hydroxy protons except the anomeric ones, are involved in hydrogen bonds[1c]. Due to the effective competition of water, such interactions can materialize only inside lipophilic cavities; if one works with the nowadys achievable synthetic host compounds one is for the same reason essentially restricted to the use of lipophilic solvents such as chlorofom.

In synthetic host compounds anionic groups have been shown to be particular effective for sugar complexation[2,3] with a complexation free energy difference between *e.g.* α- and β-D-glucosides of $\Delta\Delta G_{\alpha,\beta}$ = 1.4 kJ/mol. Other

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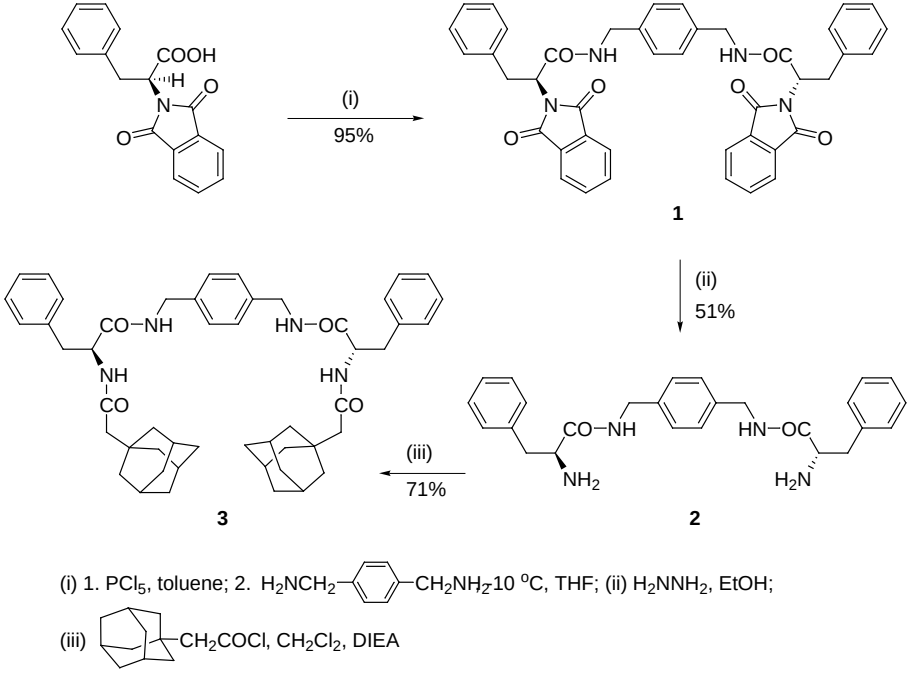
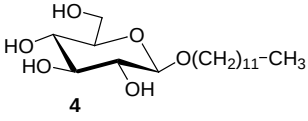
artificial receptors involve cyclotetramers obtained from resorcinaldehyde[4], a tetrahydroxycholaphane[5], polyaza-cleft compounds[6], aminocyclodextrins[7], steroid-bridged[8] and zinc[9] porphyrins, macrocycles containing cholic acid moeities[10] with $\Delta\Delta G_{\alpha,\beta}$ = 4 kJ/mol, glycophanes[11], polypyridine-macrocycles[12], spirobifluorene-containing clefts[13] ($\Delta\Delta G_{\alpha,\beta}$ = 1.25 kJ/mol)[13], and reversed micelles[14]. A particularly effective polycyclic host compound contains six amide functions and six phenyl rings; which in chloroform binds *e.g.* octyl α-D-mannopyranoside by $\Delta\Delta G \approx 8$ kJ/mol more strongly than corresponding glucose or galactose derivatives[15]. The well known boronic acid host compounds[16] do not interact non-covalently but by ester formation.

We describe here a new cleft-like host **1** with four amide functions and two chiral centers, derived from L-phenylalanine. The receptor was easily prepared *via* the precursors **2** and **3** (Scheme 1); all compounds showed satisfactory analytical data including ^{1}H and ^{13}C NMR spectra. The observation of single NMR signal sets, of sharp melting points and of sizeable optical rotations indicate the absence of racemization. Adamantyl groups were introduced in order to make the host soluble in chloroform.



SCHEME 1

Dilution experiments with **1** in chloroform showed that self-association starts only at concentrations above 1 mmol/l, which was above the concentration used in NMR titrations. These were carried out with the lipophilic glycosides **4** and **5**, using protocols as described before[17]. Only with the glucoside **4** the non-linear least square fit NMR shift changes of OH group showed a satisfactory agreement with a 1 : 1 association model (Fig. 1; only the 4-OH signal was used, the others were partially overlapping during titration). The fitting yielded an association constant $K = 185 \pm 20$ M^{-1}; and complexation induced shifts (CIS, at 100% complexation) of CIS = 0.72 ppm. In contrast to the glucose guest derivative **4**, the shifts observed with the galactose derivative **5** varied only in a nearly linear way with the host concentration (see Fig. 1), indicating a much weaker complex far from saturation. With the reasonable assumption[3] of a similar CIS (0.7 ppm) for **5** an upper limit of $K < 7$ M^{-1} can be calculated from the observed shifts. The corresponding difference in complexation free energy between the diasteromeric glycosides of $\Delta\Delta G \geq 8$ kJ/mol compares favourably with literature values discussed above.



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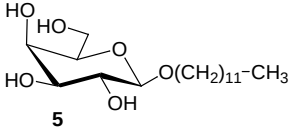

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The observed NMR shifts of the other OH signals in **4** are also substantially shifted downfield as expected; they indicate that hydrogen bonds between the sugar OH groups and the amide oxygen atoms are the major

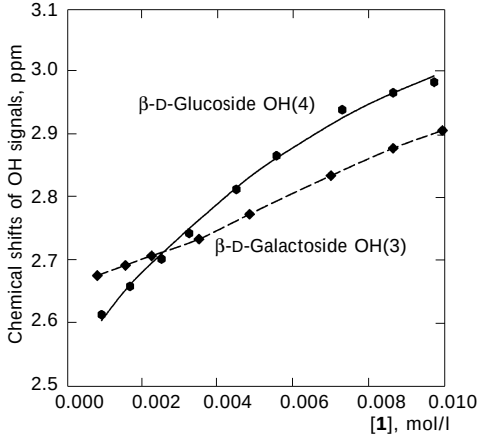

FIG. 1
NMR titration of receptor **1** with the glucoside **4** (circles with curve form non-linear least square) and with the galactoside **5** (dashed line, see text)

driving force for complexation, in line with observations with natural receptors. Preliminary simulations of the complex **1**–**4** with the CHARMm force field[18] show, that at least three hydrogen bonds can be formed with the host structure, which does not need to build up any significant torsional strain for such a complexation (Fig. 2). The observed complexation energy of ΔG = 13 kJ/mol is in line with free energy binding increments found earlier for related complexes in chloroform, which showed about 5 kJ/mol for each hydrogen bond[19]. Computer-aided molecular modelling indicates, that a similar complex with the galactoside **5** is indeed less favourable.

EXPERIMENTAL

Methods

NMR measurements (δ, ppm; *J*, Hz) were done at 400 MHz at ambient temperature with a Bruker AM400 system; measuring conditions see below. Titrations were carried out as decribed earlier[17], by adding the receptor **1** (stock solution in $CDCl_3$) in 9 steps to the glycosides (1 mM in $CDCl_3$) with resulting concentrations as shown in Fig. 1. Least square line fitting was performed with SIGMAPLOT to the equation describing a 1 : 1 complex formation[17]. CHN analyses were carried out with a Carlo Erba Elemental Analyzer 1106. Melting points (Gallenkamp apparatus) are uncorrected. Optical rotations were measured with a Perkin–Elmer polarimeter 241 ($[\alpha]_D$ are given in 10^{-1} deg cm^2 g^{-1}).

N^2,$N^{2'}$-Diphthaloyl-N^1,$N^{1'}$-(1,4-phenylenedimethylene)di(L-phenylalaninamide) (**3**)

N-Phthaloyl-L-phenylalanine[20] (9 g, 29.7 mmol) and PCl_5 (6.8 g, 32.6 mmol) were dissolved in dry toluene (100 ml) and kept for 2 h at 60 °C. After evaporation under reduced pressure, the reaction mixture was flashed twice with 100 ml of dry toluene. The resulting acyl chloride was used without further purification for the following aminolysis: DIEA (6.2 ml,

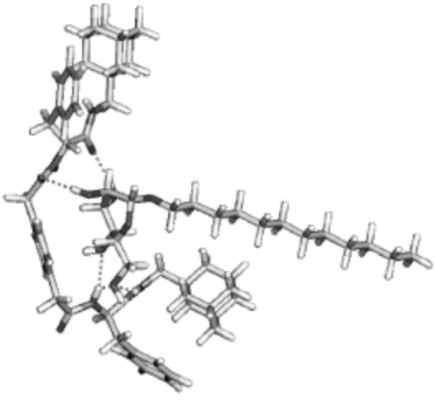

FIG. 2
Binding mode of the complex with receptor **1** and the glucoside **4**

1.2 equivalent) was added at –10 °C to a solution of the acid chloride in 100 ml of dry THF. A solution of *p*-xylylendiamine (1.975 g, 14.5 mmol) in absolute THF (20 ml) was added during 1/2 h to the chilled solution of the acyl chloride. After stirring for 12 h at room temperature, CH_2Cl_2 (100 ml) and 5% HCl (100 ml) were added. The mixture was stirred vigorously for 1 h and most of the organic solvent was evaporated. The crude product was filtered off, refluxed with ethanol, filtered, chilled and recrystallized from ethanol–ether to yield 9.5 g (95%) of the desired product as colourless crystals, m.p. 229–232 °C, $[\alpha]_D^{20}$ –38.6 (*c* 0.4 in $CHCl_3$). ^{1}H NMR (DMSO-d_6, TMS): 8.65 (s, 2 H, NH); 7.75–7.72 (m, 8 H, Phth-H); 7.12–7.07 (m, 10 H, Phe-H); 5.05–5.01 (dd, *J* = 4.8, *J* = 11.9, 2 H, CH); 4.36 (d, *J* = 4.9, 4 H, Xylyl-CH_2); 3.62–3.58 (dd, *J* = 4.8, *J* = 9.5, CH_{2a}); 3.5–3.42 (overlapped by H_2O, CH_{2b}).^{13}C NMR (DMSO-d_6/$CDCl_3$, TMS): 167.9, 167.4, 137.4, 133.7, 131.5, 128.5, 128.0, 127.1, 126.2, 122.7, 54.6, 42.8, 42.5, 33.9. For $C_{42}H_{34}N_4O_6$ (690.7) calculated: 73.02% C, 4.96% H, 8.11% N; found: 72.58% C, 5.15% H, 8.07% N.

(N^1,$N^{1'}$-(1,4-Phenylenedimethylene)di(L-phenylalaninamide) (**2**)

Compound **3** (3 g, 4.3 mmol) and hydrazine hydrate (20 ml) in ethanol (100 ml) were refluxed overnight. After cooling, the solution was filtered from precipitated phthaloylhydrazide and evaporated. The crude product was purified by column chromatography (SiO_2, EtOH–Et_2O 2 : 1, R_F 0.21) to yield 940 mg (51%) of the free diamine as a colourless oil, $[\alpha]_D^{20}$ –19.4 (*c* 0.1 in ethanol). ^{1}H NMR (DMSO-d_6, TMS): 10.98 (s, 2 H, NH); 8.61 (s, 4 H, NH_2); 7.56–7.18 (m, 18 H, Ar-H); 4.36, (m, 2 H, CH); 3.88 (s, 2 H, CH_2), 3.21–3.18 (m, 4 H, 2 × CH_2). ^{13}C NMR (DMSO-d_6, TMS): 166.2 (C=O), 136.7, 135.9, 134.8, 129.4, 128.7, 128.2, 126.9, 119.7, 64.7, 48.4, 36.7.

N^2,$N^{2'}$-Bis(adamantane-1-acetyl)-N^1,$N^{1'}$-(1,4-phenylenedimethylene)di(L-phenylalaninamide) (**1**)

Compound **2** (300 mg, 0.697 mmol) and DIEA (290 μl) were dissolved in dry CH_2Cl_2 (30 ml) and cooled to –20 °C. Crude adamantane-1-acetyl chloride (prepared from adamantane-1-acetic acid (271 mg, 1.933 mmol) and 1.1 equivalent PCl_5 in 50 ml of toluene at 60 °C) was dissolved without prior purification in dry CH_2Cl_2 (10 ml) and added slowly to the solution of the diamine. After adding 50 ml of CH_2Cl_2 the organic layer was washed with saturated $KHCO_3$ and 5% $KHSO_4$ solution (2 × 50 ml), respectively, and finally with water (100 ml). The organic layer was dried over $MgSO_4$ and evaporated. The obtained yellow crude product was purified by column chromatography (SiO_2, EtOH–$CHCl_3$ 1 : 3, R_F 0.42) to yield 387 mg (71%) of the product **1** as colourless crystals, m.p. 237–239 °C, $[\alpha]_D^{20}$ –53.2 (*c* 0.4 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, TMS): 7.25–7.22 (10 H, m, 2 × Phe-H), 7.20 (2 H, s, 2 × NH (xylylene)); 6.99 (4 H, s, xylylene-Ar-H); 6.58 (2 H, d, *J* = 6.6, 2 × NH (Phe)); 4.93 (2 H, m, 2 × CH); 4.26–4.1 (4 H, m, 2 × CH_2); 3.15–3.00 (4 H, m, 1.85–1.78 (6 H, m, 2 × γ-Ad-CH); 1.66–1.61 (12 H, m, 2 × δ-Ad-CH_2); 1.51–1.45 (12 H, m, β-Ad-CH_2); 1.34 (4 H, s, Ad-CH_2). ^{13}C NMR($CDCl_3$, TMS): 171.19, 171.24 (2 × C=O), 136.85, 136.83 (2 × quart. Ar-C); 129.37, 128.53, 128.03, 126.8 (3 × Phe-C (*o*,*m*,*p*), 1 × *o*-Xylyl-C); 54.29, 51.41 (Phe-CH, Xylyl-CH_2); 43.26 (quart. Ad-C), 42.5 (β-Ad-CH_2), 38.46 (Phe-CH_2), 36.68 (γ-Ad-CH), 32.74 (CH_2-Ad), 28.6 (δ-Ad-CH_2). For $C_{50}H_{62}N_4O_4$ (783.1) calculated: 76.69% C, 7.98% H, 7.15% N; found: 76.15% C, 8.23% H, 7.02% N.

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