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Novel macrocycles with 1,1′-binaphthyl substituents for the recognition of saccharides

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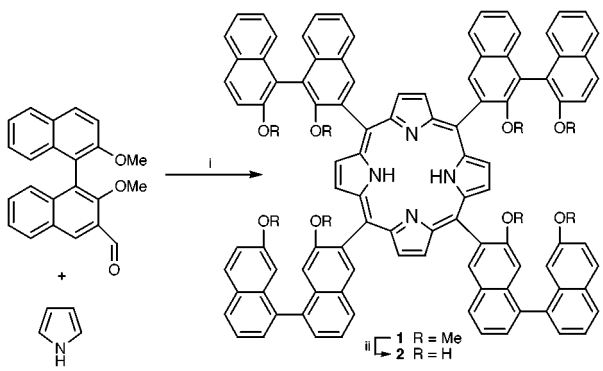
Novel saccharide-selective receptors 1 and 2 based on *a* porphyrin with 1,1′-binaphthyl substituents were synthesized and tested for binding of mono-, di- and tri-saccharides; *a* binding selectivity for di- and tri-saccharides was found.

Recent developments in the area of supramolecular chemistry have led to the study of carbohydrate complexation by artificial receptors.[1] The design of artificial receptors that bind selectively to sugars in aqueous or non-aqueous media is an important topic in bioorganic chemistry.[2] As a contribution to this effort we focused our attention on the preparation of a variety of macrocyclic derivatives with peripheral functionalities giving interesting recognition properties.[3–8]

Here we present the synthesis and basic properties of 1,1′-binaphthyl substituted porphyrins **1** and **2** designed as specific receptors for biologically important polyhydroxylic compounds. There are several host systems reported in the recent literature that utilized sterically organized receptors for recognition of biologically important substrates.[10–14] The design of receptors is based on multiple H-bonding, where receptor **1** is an H-bonding acceptor and receptor **2** is an H-bonding donor. The binding site of **2** contains eight acidic phenolic hydroxy groups that presumably can form hydrogen bonds with guests. The binding mode was proven by ^{1}H NMR, Raman and IR studies for methyl *O*-glucoside, where the 1,1′-binaphthyl subunit's interaction was clearly observed, indicating complex formation.[17] The synthesis of **1** (Scheme 1) was carried out according to the known methodology for the preparation of porphyrins (Rothemund protocol) by cyclotetramerization of protected 1,1′-binaphthyl-3-carbaldehyde with pyrrole.[1] TLC, HPLC and the photometric analysis of the reaction products was used to identify the major and minor porphyrinic components. The solvent was removed and the major product was isolated by column chromatography on silica gel with MeOH–CH_2Cl_2 (95 : 5) as eluent, characterized as the (*R,S*)-α,β,α,β-isomer and used for the complexation study. The structure was proved by ^{1}H NMR analysis, where characteristic signals for identical binaphthyls and singlet pyrrolic β-protons were observed, as described for the unsubstituted binaphthol–porphyrin derivative.[15] This product **1**, as a single atropoisomer, was collected in 4% yield. Product **2** was obtained by treatment of **1** with BBr_3 in dry CH_2Cl_2. The deprotected product was isolated in 80% yield.



Scheme 1 *Reagents and conditions*: i, propionic acid, reflux, 4 h, then silica gel, CH_2Cl_2–MeOH (95 : 5), 4%; ii, BBr_3 (10 equiv.), CH_2Cl, 1 day, room temp., wash with H_2O, dry, isolate on reverse phase column, MeOH, 80%.

The binaphthylic subunits of macrocycles **1** and **2** contain peripheral methoxy or hydroxy groups. These groups play an essential role in the formation of complexes with saccharides. The two host binding pockets formed by the bulky aryl substituents were specifically designed for binding of di- and tri-saccharides in a similar way as in lectins. The effect of solvent was also important. Thus the host **1** is insoluble in water whereas **2** is soluble in H_2O–MeOH (5–10% MeOH, v/v) allowing determination of binding constants for saccharides. The binding constants for both hosts were determined in DMSO at room temperature by UV–VIS titration experiments. The change in the absorbance at 427 nm was observed upon addition of the saccharide species to the hosts **1** and **2**. In this media the receptor **1** (R = OMe) displays low binding affinity for unmodified saccharides (for octyl glucopyranoside and *p*-nitrophenyl galactopyranoside strong binding was observed). The methoxy groups of the binaphthylic subunits form weak hydrogen bonds with the guests.[17] However substrates such as α- or β-D-methylglucopyranose are able to interact better with this host than unsubstituted glucose, with a remarkable selectivity for the β-anomer (Table 1). Saccharide derivatives with octyl and *p*-nitrophenyl substituents, namely octyl α-D- and octyl β-D-glucopyranoside and -galactopyranoside showed selectivity for the α-anomer and more pronounced interaction. The decisive role in these host–guest interactions apparently belongs to the hydrophobic interactions between the alkyl (or aryl) chain of the substrates and the naphthyl rings of the host **1**. A different tendency was observed for the host **2**. The receptor **2** (R = OH) easily interacts with unmodificated saccharides in

Table 1 Association constants for binding of saccharide derivates with porphyrins **1** and **2** in DMSO (UV–VIS titration)[a]

	$K_a/10^2$ M^{-1}	
Saccharide	**1**	**2**
Octyl α-D-glucopyranoside	5.42	6.41
Octyl β-D-glucopyranoside	0.08	1.96
Methyl α-D-glucopyranose	< 0.08	0.72
Methyl β-D-glucopyranose	1.89	2.01
p-Nitrophenyl galacto-β-pyranoside	3.61	2.58

[a] The formation and UV–VIS estimation constants of sugar–receptor complexes. In a 1 cm square quartz cuvette was placed a 6.15×10^{-6} M solution of macrocycle **1** or **2** in DMSO or H_2O contained 5% of MeOH (v/v). A known amount of saccharide was added in increments (0–1000 equiv.). The absorbance changes were measured in maxima (room temperature), and data were then evaluated with the aid of the Benesi–Hildebrand equation. From the linear plot of $-1/A$ *vs.* 1/[saccharide], the intercept was estimated as K_a. Linear fits had a correlation coefficient of 0.95. The K_a was calculated for 1 : 1 complexes. The reproducibility of the K_a values was ±10% in triplicate runs.

Table 2 Association constants for complexation of host **2** with saccharides in DMSO and H_2O

	$K_a/10^2$ M^{-1}		
	Fluorescence	UV–VIS	
Saccharide	DMSO	DMSO	H_2O
D-glucose	0.42	1.16	0.60
D-Fructose	0.72	1.22	2.00
D-Galactose	0.32	1.14	0.92
D-Ribose	1.42	1.53	1.50
D-α-Lactose	27.60	28.00	2.55
D-β-Lactose	23.50	32.60	7.30
D-Trehalose	11.56	20.00	4.86
Maltotriose	6.28	9.50	8.77

water (with 5–10% MeOH) and DMSO and displays a significant preference for the di- and tri-saccharides over the monosaccharides. The results of the UV–VIS titration of **2** with different sugars are presented in Table 2. The tendency for preferable interaction of host **2** with di- and tri-saccharides was confirmed also by fluorescence spectroscopy (Table 2). Moreover, for monosaccharides, differences between pyranoses and furanoses were observed in both media (K_a see Table 2). Cooperation of several H-bonds in binding to particular saccharides led to higher values of binding constants. Introduction of the hydroxy groups into the porphyrin core often drastically changed their binding abilities for neutral guests.[16] The Job's plots for different series of the macrocycle–sugar interactions showed the initial formation of 1 : 1 host–guest type complexes, although in our observations, ditopic hosts **1** and **2** also formed other complexes at higher saccharide concentration. The sensitivity of **1** and **2** to the saccharides could be changed by incorporation of metal into the porphyrin core;[12] this work is now underway.

In conclusion, we have found that 1,1′-binaphthyl receptor **2** displayed effective complexation abilities for unmodificated saccharides, while **1** formed complexes with alkyl- or aryl-glycosides. The receptor **2** can serve as a successful model for efficient and selective di- and tri-saccharide binding in highly competitive media such as DMSO and H_2O, where sugar binding is easy monitored in the visible wavelength region. Due to the size of the host binaphthylic cavity above and below the porphyrin plane, trends towards stronger binding of oligosaccharides in comparison with monosaccharides were observed.

The study of the binding of saccharides with receptors based on phosphorylated analogues of compound **2** under physiological conditions is in progress.

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17 *Selected data* for **1**: δ_H(300 MHz, $CDCl_3$) 9.15–8.61 (H, m, Ar), 8.18–7.26 (H, m, Ar), 4.01 (H, m, OCH_3), 2.65 (H, m, OCH_3), −2.41 (s, 2H, NH); *m/z* (FAB) 1560.5 (MH_2^+, 100%, calc. for $C_{108}H_{78}N_4O_8$: 1559.8). For **2**: *m/z* (FAB) 1448.5 (MH_2^+, 100%, calc. for $C_{108}H_{72}O_{16}$: 1447.5). All compounds gave satisfactory elemental analyses. Complexation studies revealed that receptor **1** forms weak H-bonded complexes, while receptor **2** on the other hand showed strong H-bonding donor ability. The complex of **2** with β-D-methylglucopyranose showed a downfield shift of 0.6 ppm with respect to free **2** in CD_3CN; IR showed the strong complexation of the phenolic OH (shift from 3060 to 3100 cm^{-1} and from 3300 to 3400 cm^{-1}) and Raman spectra also indicated the strong complexation (broadening and merging of the multiple peaks in the area of 1460–666 cm^{-1}).

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