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1,1′-Binaphthyl substituted calixresorcinols–methyl red complexes: receptors for optical saccharide sensing

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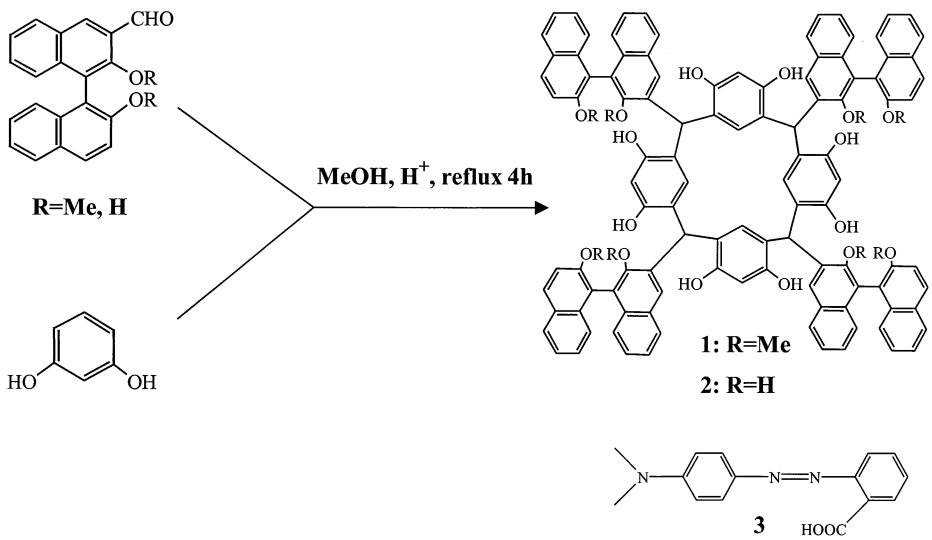
Abstract—Novel 1,1′-binaphthyl substituted calixresorcinols (**1** and **2**) were synthesized. Macrocycles **1** and **2** form water-soluble complexes with methyl red **3**, which are, in turn, able to bind saccharides by a competition process in aqueous media and which exhibit color transitions during titration. Preferential binding of oligosaccharides compared to monosaccharides was found. The association constants of effectively bound oligosaccharides in aqueous media varied around 10^3 M^{-1}.

The interaction of saccharides with synthetic receptors in aqueous media remains an intriguing question of modern chemistry.[1,2] We have recently described chromophore–containing macrocyclic systems which allow direct monitoring of the saccharide–receptor interaction.[3,4] In this paper, we demonstrate another model where the chromophore which is not covalently bound to the macrocyclic receptor plays the role of reporter group (color label). With such a system, saccharides can be quantified by measuring changes of absorbance employing a competition assay of macrocycle **1** or **2** with the indicator methyl red **3**. The principal idea of this approach consists of the simple preparation of the primary complex: the macrocycle–indicator, followed by its application in aqueous media with monitoring of expressive color transitions.

The utilization of indicators as non-covalent bound chromophores has recently been described in several papers,[5–12] specifically for anion recognition, including biologically important anions (e.g. citrates, tartrates, phosphates, and halides) with the application of car-



Scheme 1. Synthesis of macrocycles **1** and **2** (see Ref. 20).

Keywords: calixresorcinols; methyl red; receptors; saccharide binding.

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boxyfluorescein and other indicators. Boronic acid based color sensors for saccharides have also been described.[13,14] Our receptors **1** and **2** show only a slight absorption in the visible spectral range, but their complexes (1:1) with methyl red **3**, exhibit expressive absorbances in that spectral range. Cyclic tetramers of resorcinol have been studied intensively for their interaction with saccharides.[15–17] An investigation of the interaction mechanism clearly showed strong interactions of the saccharides with the resorcinol rings.

Here we propose the application of sterically organized polycyclic structures **1** and **2** with 1,1′-binaphthyl subunits designed for the recognition of biologically important polyhydroxylic compounds in aqueous media (Scheme 1).[18–20] Binaphthyl recognition groups have recently been employed for saccharide recognition systems.[3] The 1,1′-binaphthyl-substituted resorcinol molecule is a cup-shaped structure with a smaller polyhydroxylic lower rim and bulky binaphthyls on the upper part providing a deep cavity. These groups play, together with the other aromatic moieties, an essential role in complexation with saccharides.

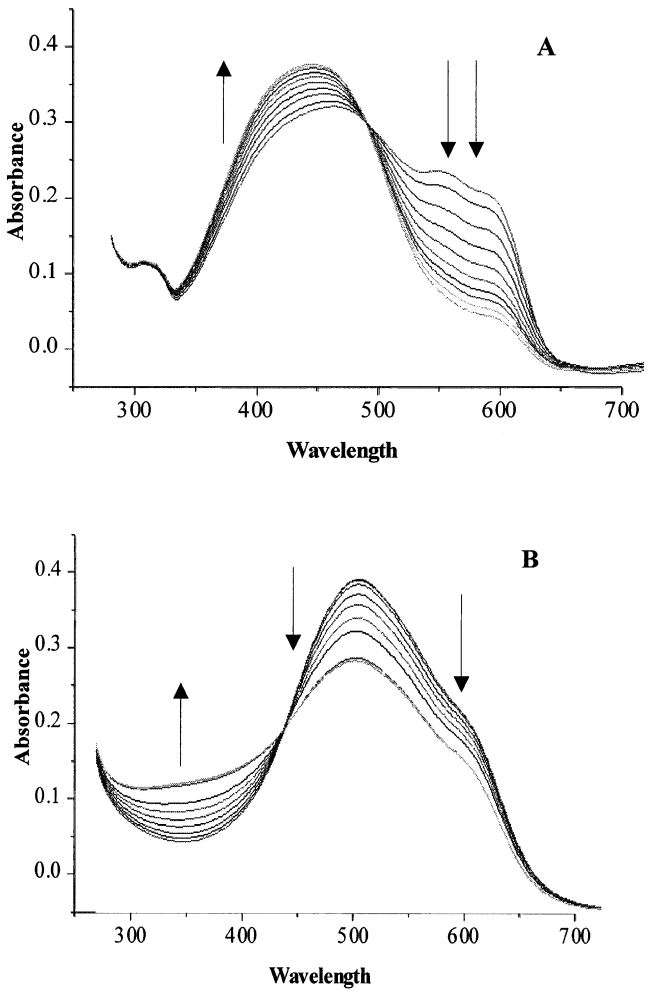

Fig. 1. Interaction of complexes (**1**–**3**) (**A**) and (**2** and **3**) (**B**) with α-D-glucose in aqueous media, followed by UV–vis titration: for **A** at λ_{max} 436, 519 and 547 nm; for **B** at λ_{max} 513 nm.

We found out that the colorimetric indicator methyl red (**3**) binds to the receptors **1** and **2**. This conclusion is based on an ^{1}H NMR study, which revealed shifts of aromatic protons for both components (**1**, **2** and **3**) and also shifts of the protons of the dimethylamino group of **3**. We also observed by ^{1}H NMR spectroscopy in acetonitrile-d_3 a broadening of the signals of the resorcinol OH protons (for the receptor **1**) and signals from the CH_3-protons of **3** that suggested complex formation with the lower rim of the receptor in organic solvents. For the receptor **2**, the aromatic OH groups of the 1,1′-binaphthylic moieties were involved in complexation with methyl red, when shifts of their aromatic protons were observed ($\sim$0.5 ppm). These data indicate that the receptor **1** might form mainly sandwich-type complexes in acetonitrile and methanol solution.

The complex **2**–**3**, formed originally in acetonitrile, are easily soluble in water and NMR data (the shift of the aromatic protons of **2** and **3**, by $\sim$0.2 ppm) indicate that the receptor **2** prefers an inclusion-type complex with **3** in water.

The study of the interaction of these receptors **1** and **2** with methyl red **3** showed the formation of weak complexes ($K_a = 0.6\times10^2$ and 0.8×10^2 M^{-1}, respectively, in acetonitrile). In the next step, we applied, not the receptor **1** or **2**, but their complexes with **3** for selective saccharide binding, resulting in a color change. The Job's plot obtained from UV–vis and ^{1}H NMR spectroscopic measurements in acetonitrile and/or methanol indicates 1:1 stoichiometry for both complexes **1**–**3** and **2**–**3**. Due to the poor solubility of methyl red **3** and both receptors **1** and **2** in pure water, methanol-containing solutions (up to 1% v/v) were used for the initial complex formation (the receptor **1** or **2** with **3**). The starting solutions were prepared by the addition of water to an equimolar mixture of **1** or **2** with methyl red in methanol (the final methanol concentration in water was 1%). Under these conditions, orange (for **1**–**3**) and violet (for **2**–**3**) complexes in water were obtained. All measurements were run at pH 6.0. No pH changes during titration were observed. Both hosts have intensive absorbance in the UV range of the spectrum and only **2** has low absorbance at 513 and 422 nm. The complex **1**–**3** has three intensive absorption maxima in aqueous media at 436, 519, 547 nm and complex **2**–**3**, only one at 513 nm that is suitable for visual detection of analytes.

A serious problem in studies of the complexation between an apolar host and guest in aqueous solution is caused by aggregation. The formation of stoichiometric complexes should be studied in a concentration range in which the complexation equilibrium is unaffected by additional aggregation equilibria. In our case, the linear dependence of the absorption on the concentration of the aqueous complex macrocycle–methyl red (**2**–**3**) was observed over the concentration range 0–2.5×10^{-4} mol L^{-1}. For this reason all measurements were carried out at 1.19×10^{-4} mol L^{-1} where no aggregation was observed. The gradual increase of the saccharide concentration in the solution of the non-covalent receptors

1–**3** and **2**–**3** was accompanied by color changes from orange to yellow (for **1**–**3**), violet to yellow (for **2**–**3**) and changes of the maxima intensity at the above mentioned wavelength. Fig. 1 shows the results of titration experiments with α-D-glucose. Isosbestic points at 470 nm (for the receptor **1**–**3**) and 467 nm (for the receptor **2** and **3**) were observed in both cases. This suggests formation of the macrocycle (**1** or **2**) saccharide complexes with a ratio of 1:1. Parallel experiments were carried out with octyl-α-D-glucopyranoside and the above mentioned receptor–indicator complexes by ^{1}H NMR spectroscopy in acetonitrile-d_3. In both cases we observed strong shifts of resorcinol and the saccharide OH signals indicating a competition of the saccharide guest with the indicator for binding sites in complexes **1**–**3** and **2** and **3**.

The association constants calculated for different saccharide species are summarized in Table 1. Both receptors (**1** and **2**) bind oligosaccharides more strongly than monosaccharides, showing interesting selectivity. Control experiments of binding of saccharides to methyl red gave very low association constants (below 0.2×10^2 M^{-1}). Association constants of methyl-α-D-glucopyranoside with the receptors **1**–**3** and **2**–**3** were higher than for unmodified monosaccharide analogues. Two saccharide-like guests, namely L-sorbitol and L-gulonic acid γ-lactone were also tested. Despite their similarity to saccharides, both receptors were able to distinguish these guests from other saccharides (association constants were lower than for monosaccharides). The macrocycles **1** and **2** exhibit a great potential for further investigation. The sensitivity of both receptors (**1** and **2**) to saccharides could be further modified by chemical transformation (e.g. phosphorylation or sulfonation) and covalent attachment of indicator type reporter units. This work is in progress.

Table 1. Association constants for binding of saccharides and other selected compounds with receptors [(**1** or **2**)-methyl red] complexes in water followed by UV–vis titration[a]

Test compound	Association constant (K_a), 10^2 [M^{-1}]	
	1	**2**
Methyl-α-D-glucopyranoside	11.9	15.0
D(+) Galactose	9.0	9.5
D(−) Fructose	7.7	7.5
D(−) Ribose	8.1	7.3
L-Sorbitol	1.4	1.9
L-Gulonic acid γ-lactone	1.0	1.6
α-D-Glucose	9.9	11.0
D(+) Maltose	45.2	45.5
Maltotriose	39.9	40.2
Maltotetraose	28.4	40.0
α-D-Lactose	18.7	35.3
β-D-Lactose	16.4	33.0

[a] 1.19×10^{-4} M/L solution of receptor (**1** or **2**)-methyl red (1:1) in a methanol/water mixture (0.5% methanol, v/v) was placed in a 1 cm square quartz cuvette. A known amount of a given saccharide was added in increments (0–50 equivalents; concentration of the receptor in cuvette hold constant). The absorbance changes at 436 nm (for **1**) and at 513 nm (for **2**) were measured at room temperature and the data evaluated with the aid of the least squares curve fitting. The K_a are calculated for 1:1 complexes. The reproducibility of the K_a values was ±10% in triplicate runs.

In conclusion, we found that water-soluble complexes of 1,1′-binaphthyl calixresorcinols **1** and **2** with the indicator methyl red **3** (color label) can be employed as effective systems for chemical sensing of neutral guests, namely saccharides. The interactions with saccharides are based on a competition mechanism with the weakly bound color label, which allows sugar binding to be monitored visually.

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18. Selected data: Receptor **1**: ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ): 8.67 (s, 4H, OH); 7.99–6.78 (m, 44H, Ar); 6.34 (s, 4H, Ar); 6.2 (d, 4H, Ar); 5.62 (s, 4H, OH); 5.30 (s, 4H, CH); 3.81 (d, 12H, OCH_3); 3.05 (d, 12H, OCH_3); 2.06 (d, 12H, CH_3); 1.7 (s, 12H, CH_3). Mass spectrum (FAB positive) m/z: 1738.5 (for $C_{111}H_{88}O_{16}$ calcd: 1737.6). UV–vis spectrum (CH_3OH): λ_{max}: 335; 325; 282; 235.
    Receptor **2**: ^{1}H NMR spectrum (300 MHz, CD_3CN–$CDCl_3$, 1:1, δ): 7.77–5.87 (m, 44H, Ar; 8H, OH); 5.45 (s, 8H, OH); 5.2 (s, 4H, CH). Mass spectrum (FAB positive)

m/z: 1626 (for $C_{108}H_{72}O_{16}$ calcd: 1625.5). UV–vis spectrum (CH_3OH): λ_{max}: 513; 422; 282; 235.

19. We observed racemization of optically pure starting 1,1′-binaphthyl aldehydes during acid-catalyzed macrocyclization, therefore we have used only racemic 1,1′-binaphthyl aldehydes for synthesis.
20. Synthesis: A mixture of 0.2 g of (*R*,*S*)-2,2′-dimethoxy-3-formyl-1,1′-binaphthol (or (*R*,*S*)-2,2′-dihydroxy-3-formyl-1,1′-binaphthol) and 0.07 g of resorcinol in 100 mL MeOH (HCl as catalyst) was refluxed for 4 h. The reaction mixture was washed with water, filtered, the solid product dissolved in MeOH, dried and separated by column chromatography with MeOH–CH_2Cl_2 (10:90, v/v). The yields for **1** and **2** were 55 and 85%, respectively.