3.57 – 3.66 (m; THF), 6.49 (t, 1H; Ph), 6.70 (d, 1H; Ph), 7.32 (t, 1H; Ph), 7.89 (d, 1H; Ph); IR (KBr disk): $\tilde{\nu} = 1599$ (s; C=C), 1540 (s; C–NO_2), 1502 (s), 1427 (s), 1324 (s), 1255 (s; C–O), 1135 (s), 1083 (s), 1018 (s), 799 (s), 746 (s) cm^{-1}; elemental analysis calcd. for $C_{112}H_{96}K_4Lu_4N_{16}O_{52}$ (3354.33): C 40.10, H 2.88, N 6.68; found: C 39.22, H 2.98, N 6.11.

2: In the presence of air hexane was layered on top of the recrystallization solution (THF/hexane, 1/4), and then the reaction vessel was closed. Orange crystals were obtained after 12 h. **2a**: Yield 110 mg (12%); IR (KBr disk): $\tilde{\nu} = 3526$ (w; OH), 3106 (w), 1604 (vs; C=C), 1541 (m; C–NO_2), 1503 (vs), 1463 (s), 1324 (vs), 1249 (vs; C–O), 1137 (vs), 1083 (s), 799 (s) 745 (s) cm^{-1}; elemental analysis calcd. for $C_{176}H_{178}Er_{14}N_{24}O_{98}$ (6539.06): C 32.72, H 2.39, N 5.24; found: C 32.85, H 2.99, N 5.98. **2b**: Yield 130 mg (14%); IR (KBr disk): 3520 (w; OH), 3100 (w),1604 (vs; C=C), 1557 (s; C–NO_2), 1541 (s), 1505 (vs), 1468 (s), 1324 (vs), 1258 (vs; C–O), 1136 (vs), 1086 (vs), 801 (s) 744 (s) cm^{-1}; elemental analysis calcd. for $C_{176}H_{178}N_{24}O_{98}Yb_{14}$ (6619.98): C 31.93, H 2.71, N 5.08; found: C 31.87, H 2.64, N 5.57.

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[11] Single-crystal X-ray diffraction data:[19] **1a** ($C_{112}H_{96}K_4N_{16}O_{52}Y_4$, $M_r = 3010.09$): space group $P\bar{1}$ (no. 2), $a = 1213.0(2)$, $b = 2063.2(4)$, $c = 2597.4(5)$ pm, $\alpha = 102.96(3)$, $\beta = 94.34(3)$, $\gamma = 94.77(3)^\circ$ at 203 K, $Z = 2$, $V = 6283(2)\ 10^6\,pm^3$, $\rho = 1.591\ g\,cm^{-3}$, $2\theta_{max} = 48^\circ$, 36557 reflections collected, 18671 independent reflections ($R_{int} = 0.1304$), 8511 refined reflections with $I > 2\sigma(I)$ to $R^1 = 0.0859$ and $wR^2 = 0.1853$. **1b** ($C_{112}H_{96}K_4Lu_4N_{16}O_{52}$, $M_r = 3354.33$): space group $P\bar{1}$ (no. 2), $a = 1210.6(2)$, $b = 2037.2(4)$, $c = 2591.9(5)$ pm, $\alpha = 103.00(3)$, $\beta = 93.91(3)$, $\gamma = 94.92(3)^\circ$ at 203 K, $Z = 2$, $V = 6180(2)\ 10^6\,pm^3$, $\rho = 1.802\ g\,cm^{-3}$, $2\theta_{max} = 50^\circ$, 42925 reflections collected, 20437 independent reflections ($R_{int} = 0.1010$), 16256 refined reflections with $I > 2\sigma(I)$ to $R_1 = 0.0774$ and $wR_2 = 0.2224$.

[12] We consider a K–O interaction to be a coordinating interaction if the K–O distance is significantly shorter than 300 pm.

[13] Single crystal X-ray diffraction data:[19] **2a** × 8THF ($C_{176}H_{178}Er_{14}N_{24}O_{98}$, $M_r = 6539.06$): space group $P4/nnc$ (no. 126), $a = 1927.0(9)$, $c = 3381.0(7)$ pm at 203 K, $Z = 2$, $V = 12555(4)\ 10^6\,pm^3$, $\rho = 1.730\ g\,cm^{-3}$, $2\theta_{max} = 45^\circ$, 19412 reflections collected, 4059 independent reflections ($R_{int} = 0.0744$), 2940 refined reflections with $I > 2\sigma(I)$ to $R_1 = 0.0481$ and $wR_2 = 0.1477$. **2b** × 8THF ($C_{176}H_{178}N_{24}O_{98}Yb_{14}$, $M_r = 6619.98$): space group $P4/nnc$ (no. 126), $a = 1919.7(3)$, $c = 3465.6(7)$ pm at 203 K, $Z = 2$, $V = 12403(4)\ 10^6\,pm^3$, $\rho = 1.773\ g\,cm^{-3}$, $2\theta_{max} = 45^\circ$, 34864 reflections collected, 4040 independent reflections ($R_{int} = 0.0680$), 3239 refined reflections with $I > 2\sigma(I)$ to $R_1 = 0.0506$ and $wR_2 = 0.1524$. In both structures the H atoms could not be refined.

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[18] Compound **2a** was made four times and **2b** twice. The lattice constants of the obtained crystals were determined by single-crystal X-ray diffraction each time and found to be the same.

[19] X-ray structure analyses: General: All data sets were collected by STOE-IPDS. The structure was solved by Patterson methods (SHELXS-86 and SHELXL-93) and refined by full-matrix least-square techniques. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-134394 (**1a**), -134395 (**1b**), -136363 (**2a**), and -134397 (**2b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+(44) 1223-336-033; email: deposit@ccdc.cam.ac.uk).

Molecular Recognition of Carbohydrates by Artificial Polypyridine and Polypyrimidine Receptors**

Monika Mazik,* Heinz Bandmann, and Willi Sicking

The molecular recognition of carbohydrates is one of the challenging goals of supramolecular chemistry.[1a] This is due to the three-dimensional complexity of sugar structures and to the key roles which carbohydrates play in a wide range of biological processes.[1b] The analysis of the X-ray crystallographic structures of sugar – protein complexes reveals that hydrogen bonds between hydroxy groups as well as between ring oxygens of the sugar molecule and polar residues of the protein are the main factors in conferring specificity and affinity to protein – carbohydrate interactions.[2] Furthermore, stacking of sugar CH moieties with aromatic amino acid side chains, such as the indole and phenol rings of Trp and Tyr, respectively, modulates the stability of protein – carbohydrate complexes.

Mimicking these binding strategies may lead to effective, artificial systems as a key for developing new types of biorelevant materials. Systematic biomimetic studies with synthetic receptors should lead to better understanding of carbohydrate recognition in biological processes. Despite intense current interest in the development of artificial carbohydrate receptors,[3–5] only a few effective hydrogen-bonding host molecules can be found in the literature for sugars in organic solvents. The described carbohydrate receptors mostly possess macrocyclic structures, are accessible only by multistep syntheses, and, although multidentate, are often essentially two-dimensional.[6]

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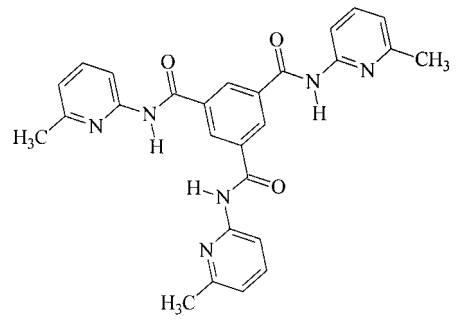

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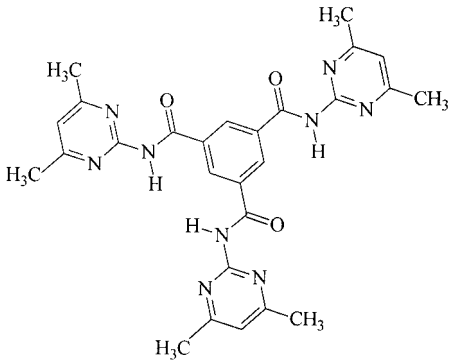

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We describe here the recognition and binding of monosaccharides to simple, acyclic saccharide receptors, **1** and **2**, which incorporate three pyridine–amide or pyrimidine–amide moieties interconnected by a phenyl spacer. Although these host molecules possess an acyclic structure, they are able to bind effectively to monosaccharides. These types of host molecules provide both hydrogen bonding sites and π-bonds for facilitating stacking interactions and should thus be able to participate in three-dimensional recognition of sugars.

As a starting point for the design of monosaccharide receptors, we examined the adaptability of the polypyridine **1** and polypyrimidine **2** receptors for the recognition of glucopyranosides. Additionally, comparative complexation studies with hosts **3** and **4** were carried out. To evaluate the recognition capabilities of the receptors for glucopyranoside in aprotic solvents such as chloroform, the octyl derivatives **5** and **6** were selected.

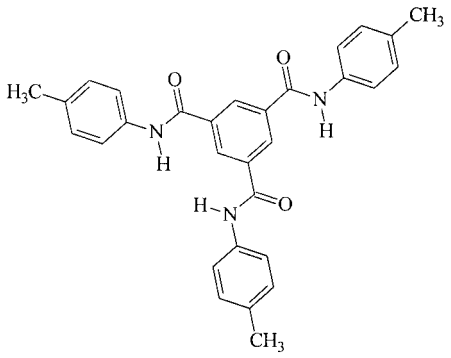
Compounds **1**–**3** were synthesized from benzene-1,3,5-tricarbonyl chloride (trimesic chloride) and 2-amino-6-methyl-pyridine,[7] 2-amino-4,6-dimethyl-pyrimidine or *p*-toluidine, respectively. Compound **4** was prepared by reaction of isophthaloyl dichloride with 2-amino-6-methylpyridine.[8,9]

The interactions between hosts **1**–**4** and glucopyranosides were investigated by ^{1}H NMR spectroscopy. The complexation of glucopyranosides through receptors **1** and **2** (selected data is shown in Table 1) was shown in the NMR spectrum of the complex by the significant downfield shifts of the signals for the receptor amide protons ($\Delta\delta = 0.7$) and the upfield shifted resonance signals for the aromatic protons of the receptor. The former downfield shift of signals reflects the formation of a hydrogen-bonded complex, and the latter may be attributed to the stacking interactions between aromatic groups of the receptors and the glucopyranoside ring.

The formation of a complex between **5** and **1** is also visible during the addition of powdered *n*-octyl-β-D-glucopyranoside to a suspension of receptor **1** in $CDCl_3$, which leads to facile dissolution and formation of a clear solution. The binding constants were determined in chloroform at 25 °C by NMR titration experiments; the titration data were analysed by nonlinear regression analysis using the Hostest 5.6 program.[10] For all binding experiments the ratio method indicates a 1:1 stoichiometry.[11] In contrast to β-glucopyranoside **5**, the α-anomer **6** showed lower affinity for **1**.

Molecular modeling revealed a possible structure for the complex of **1** and **5**, which suggests the formation of six hydrogen bonds (three amide-NH···OH and three pyr-N···HO bonds) and stacking interactions of the pyranoside ring with the central phenyl ring. All the OH groups of **5** participate in hydrogen bonding; the CH_2OH group participates in cooperative hydrogen bonds (Figure 1).

The existence of these hydrogen-bonding and stacking interactions is also indicated by the NMR data (downfield



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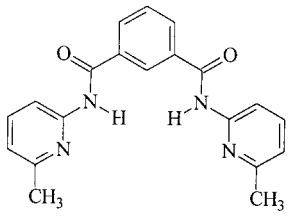

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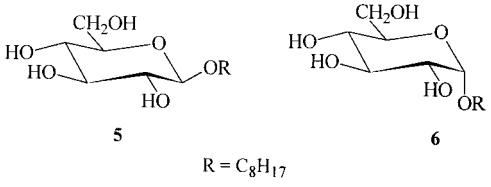

5 6

R = C_8H_{17}

Table 1. Selected physical and spectroscopic data of compounds **1** and **2**.

1: M.p. 253 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.48$ (s, 9H; $3 \times CH_3$), 6.95 (d, $J = 7.5$ Hz; $3H_{arom}$), 7.66 (m; $3H_{arom}$), 8.17 (d, $J = 7.9$ Hz; $3H_{arom}$), 8.73 (s; $3H_{arom}$), 8.91 (s, 3H; $3 \times$ NH); ^{13}C NMR (125 MHz): 163.36 (C=O), 157.07, 150.39, 138.87, 135.69, 129.24, 119.84, 111.09, 23.97 (CH_3); HR-MS, calcd for $C_{27}H_{24}N_6O_3$: 480.1910; found: 480.1903

2: M.p. 188 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.40$ (s, 18H; $6 \times CH_3$), 6.76 (s; $3H_{arom}$), 8.75 (s; $3H_{arom}$), 9.34 (s 3H; $3 \times$ NH); ^{13}C NMR (125 MHz): 168.41 (C=O), 163.72, 157.10, 135.55, 130.22, 116.37, 23.87 (CH_3); HR-MS, calcd for $C_{27}H_{27}N_9O_3$: 525.2237; found: 525.2229

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shifts of NH signals, upfield shifts of the signals for aromatic protons of the receptor). The binding constant of *n*-octyl-β-glucopyranoside (**5**) and receptor **1** was found to be 8700 ($-\Delta G_{298} = 22.47$ kJ mol^{-1}), and for *n*-octyl-α-glucopyranoside (**6**) and **1**, the binding constant amounts to 4000 M^{-1} ($-\Delta G_{298} = 22.47$ kJ mol^{-1}), and for *n*-octyl-α-glucopyranoside (**6**) and **1**, the binding constant amounts to 4000 M^{-1} ($-\Delta G_{298} = 20.54$ kJ mol^{-1}). Replacement of the pyridine groups by pyrimidine groups in the receptor structure leads to larger binding constants for both the β- and the α-anomer and also a similar affinity of host **2** to both anomers. The receptor **2** revealed K_a values of 13700 M^{-1} ($-\Delta G_{298} = 23.60$ kJ mol^{-1}) and 12500 M^{-1} ($-\Delta G_{298} = 23.37$ kJ mol^{-1}) for **5** and **6**, respectively.

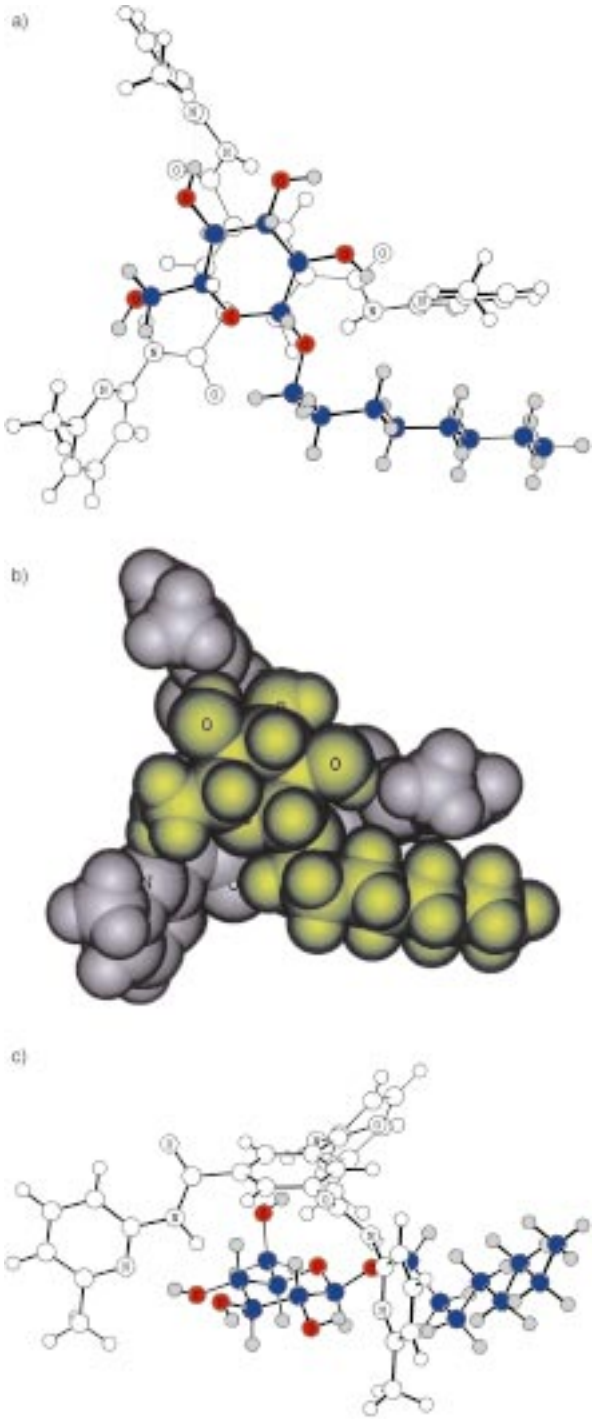

Figure 1. The energy-minimized structure of the complex formed between receptor **1** and octyl β-D-glucopyranoside (**5**) (Molecular modeling with MacroModel 5.0, Amber* force field). The intermolecular amide-NH$\cdots$OH and pyr-N$\cdots$HO hydrogen bonds (1.87–1.94 Å) and the stacking interactions in the complex are shown. a) top view, b) CPK model (top view), c) side view.

In order to test the importance of the presence of the pyridine nitrogen atoms in the receptor structure, compound **3** was synthesized. Contrary to **1**, compound **3** is poorly soluble in chloroform and could not be solubilized in this solvent even at high concentrations of octyl glucopyranoside, which indicates a weak binding between **5** and **3**. These results indicate that the nitrogen atoms in the structure of **1** are of great importance for the binding affinity and hydrogen bonding between amide-NH/pyridine-N or pyrimidine-N of the receptors and the OH groups of **5** or **6** is primarily responsible for the complexation in chloroform. As the positions of the ^{1}H NMR signals for the methyl protons of **1** and **2** and the octyl protons of **5** and **6** are virtually unaffected, it is highly unlikely that these subunits contribute significantly to the stabilisation of the resulting complex.

In order to prove how important the presence of the three pyridine-amide subunits in the receptor structure is, compound **4** was prepared and its complexation affinity was determined. In $CDCl_3$ receptor **4** forms 1:1 complexes with octyl glucopyranosides, as determined by the ratio method. The complexation of **4** with **5** or **6** can also be followed by ^{1}H NMR spectroscopy. The signals for the amide-NH protons undergo downfield shifts upon binding of guests **5** or **6**. The binding constants amount to 1100 and 460 M^{-1} ($-\Delta G_{298} = 17.35$ kJ mol^{-1} and $-\Delta G_{298} = 15.19$ kJ mol^{-1}) for **5** and **6**, respectively. This shows that the hydrogen-bonding interactions with host **4**, which has a multiple but essentially two-dimensional binding site, are less favorable than with host **1**. Receptor **1** being a superior receptor to the bipyridyl receptor **4** for glucopyranoside in chloroform is also supported by the pronounced downfield shift of the signals for the key amide protons in **1** on complexation with pyranoside ($\Delta\delta = 0.7$ compared to 0.2 in the complex with **4**). The smaller binding constants and the shifts of the ^{1}H NMR signals for **4** reflect the importance of three-dimensional recognition.

In summary, the hydrogen-bonding receptors presented here were found to be effective for the recognition of pyranosides. The results demonstrate the adjustability of the amido–pyridine and amido–pyrimidine arrangement as hydrogen-bonding motifs for monosaccharides. The advantages of these systems are a) a simple and quick synthesis of small subunits (uneffective macrocyclisations are not necessary), b) the possible variation of the structure (variation of the spacer and the heteroaromatic moieties in order to modulate the selectivity of the receptors), c) the easy construction of water soluble host molecules (suitable substituents in spacer or in aromatic subunits), and d) the capability for three-dimensional recognition of guest molecules.

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Sequential Nucleophilic Substitution: A Powerful Strategy for the Solid-Phase Production of Diverse Compound Libraries

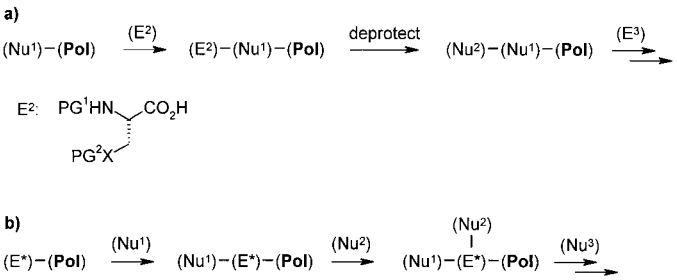
Florencio Zaragoza* and Henrik Stephensen

Solid-phase synthesis enables automated multistep syntheses to be performed in parallel and, therefore, plays an outstanding role in the quest for new candidates for development in the pharmaceutical industry.[1] We report here a new synthetic strategy which is rapid, because a new element of diversity is introduced in each step, and which enables the direct use of unprotected, polyfunctional reagents.

Solid-phase synthetic sequences suitable for library production must be based on reagents available in large number and with a broad variety of additional structural elements. For drug discovery it is important to include structural elements relevant for protein binding (e.g. hydrogen-bond donors and acceptors, cationic, anionic, aromatic, or lipophilic groups).[2] The efficient development of synthetic sequences must be initiated by an evaluation of commercially available reagents and of reactions which can be conducted on insoluble supports. Such an analysis reveals that only a few types of reagent are available in a wide variety for the preparation of diverse compound libraries. The most suitable of these are amines, alcohols, carboxylic acids, and thiols. Reagents with two required reactive groups (amino acids, amino alcohols, haloketones, anthranilic acids, 2-iodophenols, etc.), on the other hand, are not available in large numbers and are, therefore, less suitable for library production.

The evaluation of reactions shows that acylations and other electrophilic transformations of support-bound intermediates will severely limit the choice of additional functional groups present in the final product. Hydrogen-bond donors, for instance, must generally be protected to prevent them from being acylated as well (Scheme 1), but monoprotected bifunctional reagents are expensive and not readily available. On the other hand, nucleophilic transformations of support-bound intermediates do not usually require protection of the additional functional groups, which enables the direct use of unprotected, polyfunctional reagents. Moreover, most of our preferred reagents (see above) are nucleophiles, and we conclude that, for the production of large and diverse arrays of potential drug candidates, nucleophilic substitutions must play a central role. Syntheses which enable repetitive nucleophilic substitutions to be carried out with a support-bound polyelectrophile (Scheme 1) will be most useful.[3]

As an illustrative example of sequential nucleophilic subsitution, we present here a solid-phase synthesis of substituted 2-thio-3-aminopropionic acid derivatives (Scheme 2). We used 2,3-dichloropropionic acid as a polyelectrophile, either esterified with Wang resin (**1a**) or linked to a support-bound amine (**1b**).[4] Treatment of **1** with excess thiol R^1SH in the presence of DIPEA led to a clean, double nucleophilic substitution, yielding the resin-bound 2,3-dithio-



Scheme 1. a) Traditional oligomer (e.g. peptide) synthesis by sequential acylations/deprotections. Side-chain protection is required; few building blocks are available. b) Sequential nucleophilic substitutions on a support-bound polyelectrophile. No side-chain protection is required; many building blocks are available. Nu: nucleophile, E: electrophile, E*: polyelectrophile, Pol: polymeric support, PG: protective group.

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