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An Acyclic Aminonaphthyridine-Based Receptor for Carbohydrate Recognition: Binding Studies in Competitive Solvents

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^{1}H NMR spectroscopic and microcalorimetric titrations revealed that receptor **3b**, consisting of three protonated 2-amino-1,8-naphthyridine units, binds *N*-acetylneuraminic acid (Neu5Ac), the most commonly occurring sialic acid, with high affinity in competitive solvents such as water/dimethyl sulfoxide. Receptor **3b** is able to form neutral/charge-reinforced hydrogen bonds and ion pairs with Neu5Ac, similar to sialic acid-binding proteins. Furthermore, indications for weak binding of neutral sugars, such as methyl β-D-glucopyranoside, D-maltose and D-cellobiose were provided by NMR spectroscopy. Molecular modelling calculations, synthesis and binding studies in aqueous media are described.

Introduction

The biological recognition processes involving neutral sugars use hydrogen bonding (both neutral and charge-reinforced hydrogen bonds), CH-π interactions, metal coordination and van der Waals forces for sugar binding.[1] Furthermore, ion pairing and ionic hydrogen bonding favour the binding of ionic sugars, such as sialic acids.[1a,2] The interactions observed in the crystal structures of protein–carbohydrate complexes inspire the development of different artificial receptor structures for the recognition of carbohydrates.[3–5] Our previous studies showed that acyclic receptors containing two to four recognition units interconnected by a phenyl or biphenyl spacer perform effective recognition of carbohydrates through multiple interactions.[4d–4g,4i,5] As in natural complexes, the combination of neutral and charge-reinforced hydrogen bonds, as well as hydrophobic interactions, provides impetus for the binding of neutral sugars in water.[4f] Both charge-reinforced hydrogen bonds and ion pairs seem to be the major driving force for the association of ionic sugars in competitive media.[4i]

In this study, we focused on the interactions of acyclic naphthyridine-based receptor **3b** with *N*-acetylneuraminic acid (for α- and β-anomers, see formulas **4α** and **4β**) in competitive media like H_2O/DMSO or D_2O/[D_6]DMSO (1:9, v/v). Additionally, comparative binding studies were carried out with methyl β-D-glucopyranoside (**6**), methyl β-D-galactopyranoside (**7**), D-maltose (**8**) and D-cellobiose (**9**) (See Figure 1). *N*-Acetylneuraminic acid (Neu5Ac) is the most commonly occurring sialic acid playing a key role in a wide range of biological processes, including different cellular recognition processes.[1a,6] Specificity for Neu5Ac-containing ligands is expressed by the hemagglutinins of numerous viruses, notably of influenza (including H5N1 influenza A viruses[6b]), as well as several others, such as Sendai, Newcastle disease and polyoma viruses.[1a] The design of artificial receptors for the recognition of Neu5Ac[7,8] may serve as a basis for the development of new therapeutics or sensors.

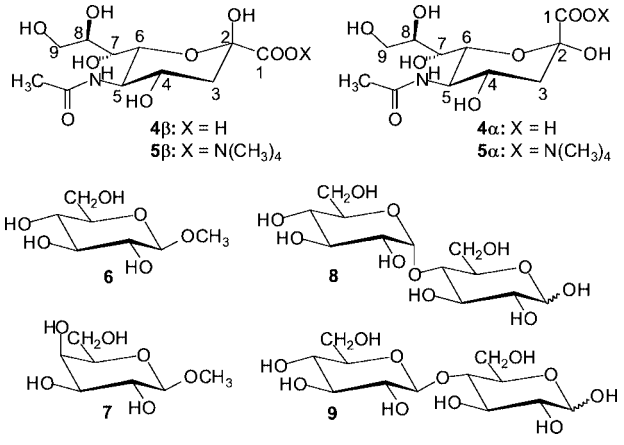

Figure 1. Structures of sugars investigated in this study.

Results and Discussion

Molecular modelling studies indicated that receptor **3b**, containing three protonated 2-amino-1,8-naphthyridine units,[9] should be able to form strong complexes with Neu5Ac through multiple interactions (see Figures 2 and 3a–c), including ion pairing, neutral and charge-reinforced

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hydrogen bonds and CH–π interactions (in line with the observations in the complexes formed between the Neu5Ac-containing ligands and sialic acid binding lectins[1a]). The above-mentioned noncovalent interactions should provide impetus for effective binding of Neu5Ac in aqueous media. Furthermore, the formation of charge-reinforced hydrogen bonds between the ionic groups of **3b** and the hydroxy groups of neutral sugar molecules (for examples of hydrogen bonding motifs, see Figure 2c,d; for examples of energy-minimised structures of the 1:1 complex between **3b** and β-D-maltose, see Figure 3d–f) should provide the major driving force for the complexation of neutral sugars in protic solvents (the binding of neutral sugars in aqueous media was expected to be much less effective than that of Neu5Ac). As in previously described artificial systems,[4d] the participation of the central phenyl ring of **3b** in CH–π interactions with sugar CHs was expected to provide additional stabilisation of the receptor–sugar complexes.

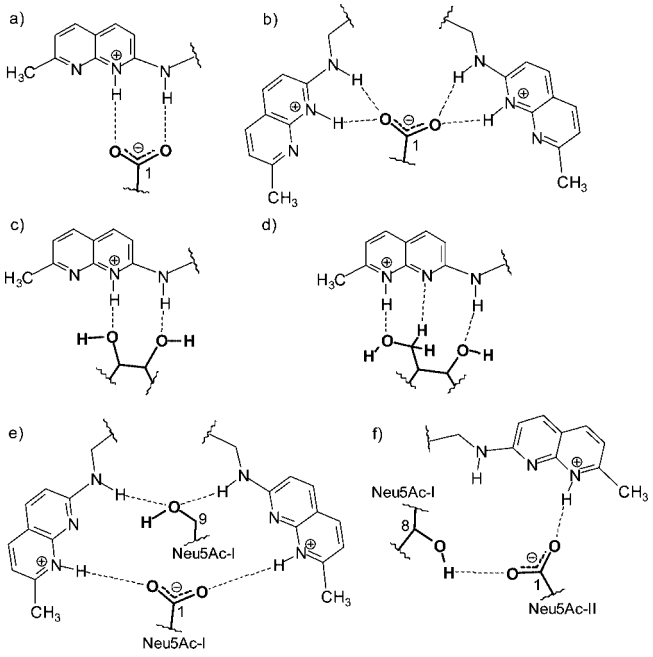


Figure 2. Examples of neutral/charge-reinforced hydrogen bonds and ion pairing found by molecular modelling studies in the complexes formed between receptor **3b** (N1- or N8-protonated) and (a,b,e,f) Neu5Ac **4β** (Neu5Ac-I/II: two Neu5Ac molecules involved in the formation of 1:2 receptor–sugar complexes), or (c,d) β-D-maltose (**8**) (1:1 receptor-sugar complexes). MacroModel V.8.5, OPLS-AA force field, MCMM, 50000 steps.

Protonation of 2-amino-1,8-naphthyridine is feasible at both the N-1 and N-8 positions (the protonation on N-1 would produce, for example, the hydrogen-bonding surface that is complementary to that of the carboxylate of Neu5Ac, as shown in Figure 2a). According to molecular modelling, both the carboxylate and the acetamido/hydroxy groups of Neu5Ac should be able to participate in the binding process. Examples of hydrogen bonding motifs indicated by molecular modelling are shown in Figure 2.

The synthesis of **3b** started from 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene (**1**),[10] which was converted into

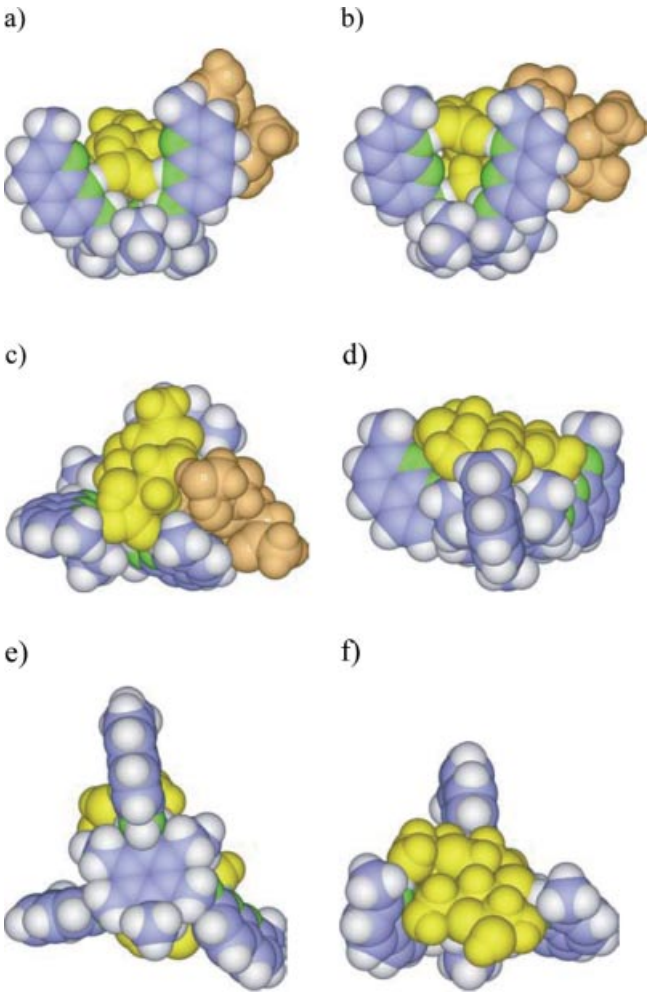
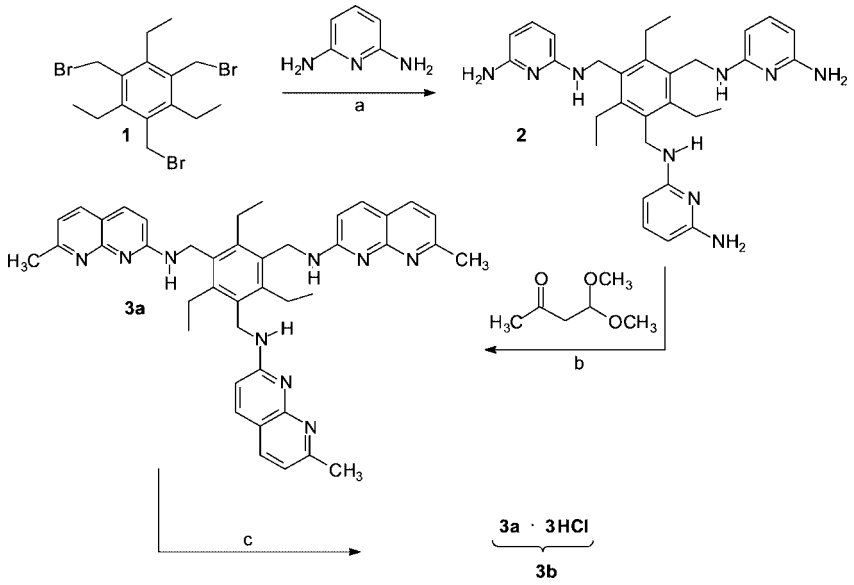


Figure 3. Energy-minimised structure of the (a) 1:2 complex between N1-protonated **3b** and Neu5Ac **4β,** (b,c) 1:2 complex between N8-protonated **3b** and Neu5Ac **4β** (two different representations), (d,e) 1:1 complex between N1-protonated **3b** and β-D-maltose (**8**) (two different representations), (f) 1:1 complex between N8-protonated **3b** and β-D-maltose (**8**) (MacroModel V.8.5, OPLS-AA force field, MCMM, 50000 steps). Colour code: receptor C, blue; receptor N, green; the sugar molecules are highlighted in yellow or orange.

compound **2** by treatment with 2,6-diaminopyridine.[5a] The reaction of **2** with 4,4-dimethoxy-2-butanone gave **3a** (the crystal structure of **3a** is shown in Figure 4), which was further converted into trihydrochloride **3b** (see Scheme 1 and Supporting Information).

Comparison of the ^{1}H and ^{13}C NMR chemical shifts of **3a** and **3b** with those of the pyridine derivatives (α-amino and methyl-substituted pyridines, before and after protonation, [D_6]DMSO) indicates that in the case of **3b** protonation occurs on N-8 rather than on N-1 (for comparison of the ^{1}H and ^{13}C NMR chemical shifts of **3a** with those of **3b**, see Figure S1, Supporting Information; for a discussion of the pH-dependence of the ^{13}C NMR chemical shifts in the pyridine ring, see ref.[11]).

The interactions of receptor **3b**[12,13] and the carbohydrates were investigated by ^{1}H NMR spectroscopy and



Scheme 1. Reaction conditions: a) CH_3CN/THF, K_2CO_3, 48 h (40%); b) H_3PO_4, 90 °C, 4 h (23%); c) CH_3OH, 10% HCl.

microcalorimetry. The titration experiments were carried out by adding increasing amounts of the tetramethylammonium salt of Neu5Ac (**5**)[14] to a solution of receptor **3b**.

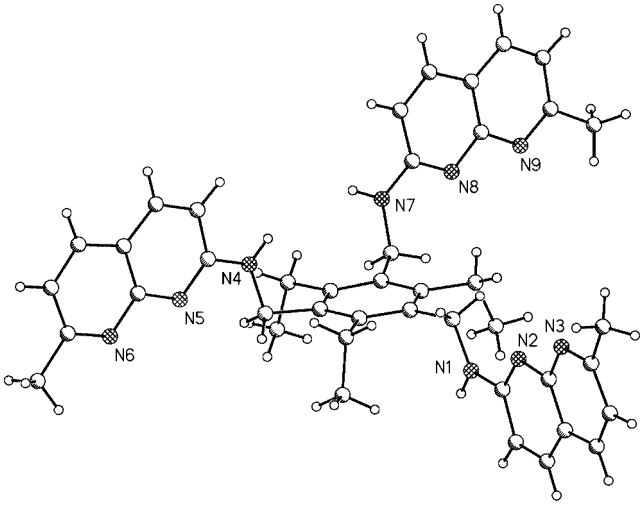


Figure 4. Crystal structure of **3a**.

^{1}H NMR Titrations

The complexation between receptor **3b** and sugar **5** (used as an anomeric mixture; for α- and β-anomer of the tetramethylammonium salt of Neu5Ac, see formulas **5α** and **5β**)[15] in D_2O/[D_6]DMSO (1:9) was evidenced by several changes in the NMR spectra (see Figure 5).[16a,16b] The upfield shifts of the CH_2, CH_3 and naphthyridine CH protons of **3b** were monitored as a function of sugar concentration (typical titration curves are shown in Figure 6 and Figure S2, Supporting Information). The signals for the naphthyridine CH protons moved in the range of 0.26–0.61 ppm, whereas those for the CH_2 and CH_3 protons shifted in the range of 0.11–0.20 ppm. The naphthyridine CHs broaden during the titration and became distinct near saturation, which occurred after the addition of approx. 2 equiv. of **5**.

Both the curve fitting of the titration data[17] and the mole ratio plots (see Figure S3, Supporting Information) suggested the existence of 1:1 and 1:2 receptor–sugar complexes in the D_2O/[D_6]DMSO mixture. The binding con-

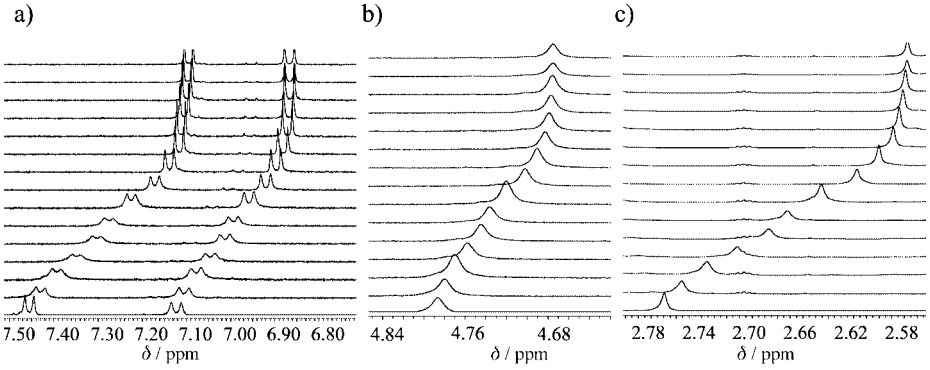


Figure 5. Partial ^{1}H NMR spectra (400 MHz; D_2O/[D_6]DMSO, 1:9) of receptor **3b** after the addition of (from bottom to top) 0.00, 0.25, 0.50, 0.76, 1.01, 1.35, 1.68, 2.11, 2.53, 2.95, 3.37, 3.80, 4.22, 4.64 and 5.06 equiv. of **5** ([**3b**] = 0.78 mM). Shown are chemical shifts of the (a) naphthyridine CH, (b) CH_2, and (c) CH_3 resonances.

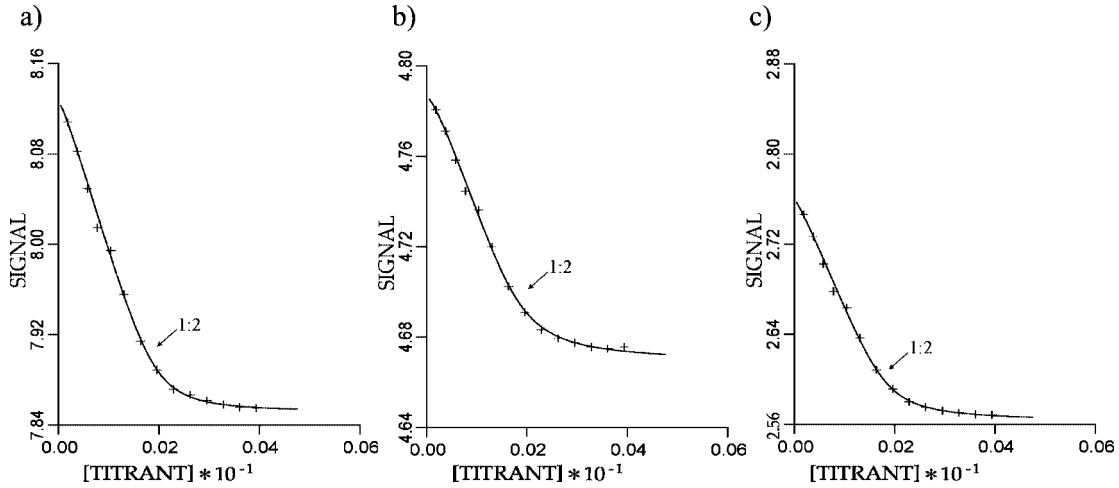


Figure 6. Plot of the chemical shifts of the naphthyridine CH (a), CH_2 (b), and CH_3 (c) resonances of **3b** as a function of added **5** in D_2O/[D_6]DMSO (1:9). The [receptor]:[sugar] ratio is marked.

stants for **3b·5** were found to be 3880 (K_{a1}) and 10930 M^{-1} (K_{a2}).[16c,16d]

The interactions between receptor **3b** and neutral sugars **6**–**9** in aqueous media are expectedly weaker than those observed with anionic sugar **5**. The complexation induced shifts observed after the addition of 10 equiv. of methyl β-D-glucopyranoside (**6**), methyl β-D-galactopyranoside (**7**), D-maltose (**8**) or D-cellobiose (**9**) into the solution of **3b** in D_2O/[D_6]DMSO (1:9) were small (in the range of 0.01–0.04 ppm), indicating weaker binding. It should be noted that the spectral changes observed after the addition of glucopyranoside **6** ($\Delta\delta \approx 0.04$ ppm), maltose **8** (see Figure 7) and cellobiose **9** were more substantial than those observed in the presence of galactopyranoside **7** ($\Delta\delta \approx 0.01$ ppm). In the case of neutral sugars, the formation of charge-reinforced hydrogen bonds between the charged groups of the receptor and the hydroxy groups of sugar molecules seems to be the major driving force for receptor–sugar association in highly competitive media (see also ref.[4f]). In the case of ionic sugars, both charge-reinforced hydrogen bonds and ion pairs provide the major driving force for the complexation in aqueous solutions.

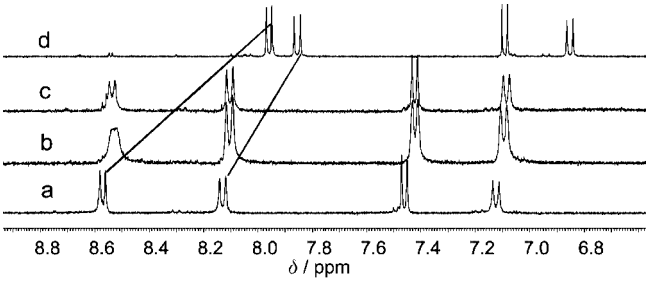


Figure 7. Partial ^{1}H NMR spectra (400 MHz; D_2O/[D_6]DMSO, 1:9) of receptor **3b** before addition of guest (a), and after addition of 10 equiv. of (b) methyl β-D-glucopyranoside (**6**), (c) D-maltose (**8**), and (d) Neu5Ac **5** ([**3b**] = 1.00 mM). Shown are chemical shifts of the naphthyridine CH resonances of **3b**.

Microcalorimetric Titrations

The microcalorimetric titrations (isothermal titration calorimetry, ITC) were carried out in H_2O/DMSO (1:9) at 298 K by use of a Thermometric titration calorimetric system(Thermometric, Sweden). The reproducibility of the calorimeter was checked with the complexation of Ba^{2+} by 18-crown-6. A solution of the tetramethylammonium salt of Neu5Ac (**5**) (6–7 mM) was titrated into a 0.66–0.90 mM solution of receptor **3b** (see, for example, the caption of Figure 8). The data obtained were analysed using the Digitam 4.1 software provided by Thermometric (heat of dilution was corrected).

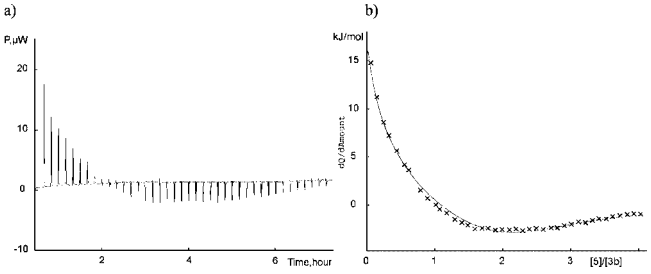


Figure 8. ITC Titration of receptor **3b** with **5** in H_2O/DMSO (1:9) at 25 °C. (a) Thermogram of the microcalorimetric titration (positive *P* values correspond to exothermic processes, negative *P* values correspond to endothermic processes). (b) Isotherm for titration of 0.66 mM **3b** with 10-μL aliquots of 6.12 mM **5** (40 injections). The molar ratio of the sugar to the receptor is given (for the thermodynamic parameters see Table 1).

The best fit of titration data was obtained with the mixed 1:1 and 1:2 receptor–sugar binding model. The binding constants for **3b·5** were found to be K_{a1} = 5860 and K_{a2} = 10600 M^{-1} ($\beta_2 = 6.23 \times 10^7$ M^{-2})[16d] and are of the same magnitude as those determined by NMR spectroscopy in D_2O/[D_6]DMSO (1:9) (the β_2 values differ by a factor of about 1.4, such differences are typical for the results obtained by these two methods[18]).

Table 1. Results of microcalorimetric titrations of **3b** with **5** in H_2O/DMSO (1:9) at 25 °C.[a]

β_1	β_2	ΔH_1	ΔH_2	$T\Delta S_1$	$T\Delta S_2$	K_{a1}[b] (ΔG)	K_{a2}[b] (ΔG)	ΔH_{1s}	ΔH_{2s}	$T\Delta S_{1s}$	$T\Delta S_{2s}$
5.86×10^3	6.23×10^7	–12.3	1.3	9.2	45.8	5.86×10^3 (–21.5)	1.06×10^4 (–22.9)	–12.3	13.6	9.2	36.6

[a] In the ligand binding program of Digitam the equilibrium constants (β_i) and the reaction enthalpies (ΔH_i) for the overall reaction are determined. $\beta_1 = K_{a1}$ (M^{-1}); $\beta_2 = K_{a1}K_{a2}$ (M^{-2}). ΔH_{is}, reaction enthalpies for the stepwise reaction ($\Delta H_{1s} = \Delta H_1$; $\Delta H_{2s} = \Delta H_2 - \Delta H_1$). K_a (M^{-1}); ΔG, ΔH and $T\Delta S$ (kJ mol^{-1}). Errors in K_a are less than 10%. Errors in ΔH are less than 5%. [b] See ref.[16d]

The microcalorimetric data revealed that the first step is an exothermic and entropically driven process (see Table 1), whereas the second step was determined as an endothermic and entropically favoured binding event (for a discussion of the energetics of protein–carbohydrate interactions, see ref.[19]).

Our previous ITC studies with benzimidazolium- and aminopyrimidine/guanidinium based receptors, displaying very high affinity toward Neu5Ac, showed also that the binding processes based on neutral/ionic hydrogen bonds and ion pairing in aqueous media are entropically favoured.[4i] Our results are in agreement with ITC measurements carried out by Diederich and coworkers.[20a] These authors reported that the complexation of dicarboxylates by cleft-type diamidinium receptors in protic solvents is also entropically driven.[20a] They concluded that "associations between strongly solvated organic ions by ion pairing and ionic H-bonding in protic solvents such as MeOH or H_2O presumably are generally entropically driven". Furthermore, Berger and Schmidtchen reported that the complexation of the SO_4^{2-} ion by a bis(guanidinium) receptor in CD_3OD is also strongly entropically driven, with an unfavourable enthalpic change partially compensating the entropic driving force.[20b]

Conclusions

Receptor **3b**, including protonated 2-amino-1,8-naphthyridine subunits, was found to be an efficient receptor for the recognition of *N*-acetylneuraminic acid in competitive media. Furthermore, receptor **3b** seems to be able to form weak complexes with neutral sugar in aqueous media, as indicated by ^{1}H NMR spectroscopy. As in natural complexes, the charge-reinforced hydrogen bonds and ion pairs seem to be the major driving force for receptor–Neu5Ac association in competitive media. Both the ^{1}H NMR spectroscopic and the microcalorimetric titrations suggested the formation of complexes with 1:1 and 1:2 receptor–sugar binding stoichiometry. In D_2O/[D_6]DMSO (1:9) the binding constants K_{a1} and K_{a2} were found to be 3880 and 10930 M^{-1} ($\beta_2 = 4.24\times10^7$ M^{-2}), respectively. The binding constants determined on the basis of the ITC measurements in H_2O/DMSO (1:9) amounted to K_{a1} = 5860 and K_{a2} = 10600 M^{-1} ($\beta_2 = 6.23\times10^7$ M^{-2}). Thus, the β_2 values determined by the two methods are in the range of 10^7 M^{-2}. The microcalorimetric data revealed that the complexation of **5** by receptor **3b** in a H_2O/DMSO mixture is an entropically favoured binding event.

The results obtained with **3b** serve as a basis for the construction of new effective and selective artificial receptors for the recognition of neutral and ionic sugars in aqueous media. Syntheses of new aminonaphthyridine-based receptors including additional recognition units and different spacers are in progress.

Experimental Section

1,3,5-Tris[(7-methylnaphthyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (3a): 1,3,5-Tris[(6-aminopyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (**2**)[5a] (4.7 g, 8.9 mmol), 4,4-dimethoxy-2-butanone (26.3 mmol) and H_3PO_4 (50 mL) were held at 90 °C for 4 h and then stirred at room temperature for 2 h. The reaction mixture was poured into water (300 mL), neutralised and extracted several times with chloroform. The collected organic layer was dried with $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified several times by column chromatography (silica gel, $CHCl_3$/CH_3OH, 7:1 to 2:1). Yield: 1.3 g (23%). R_f = 0.89 (silica gel 60 F_{254} plates, $CHCl_3$/CH_3OH, 2:1). M.p. 207–208 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.5 Hz, 9 H), 2.69 (s, 9 H), 2.82 (q, J = 7.5 Hz, 6 H), 4.74 (br. s, 3 H), 4.82 (d, J = 3.0 Hz, 3 H), 6.58 (d, J = 8.6 Hz, 3 H), 7.04 (d, J = 8.1 Hz, 3 H), 7.72 (d, J = 8.6 Hz, 3 H), 7.79 (d, J = 8.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.9, 23.1, 25.3, 40.6, 112.1, 115.2, 118.3, 132.9, 136.2, 136.9, 144.5, 156.7, 158.4, 161.3 ppm. HRMS: calcd. for $C_{42}H_{44}N_9$ 674.3719; found 674.3714.

Trihydrochloride 3b: Compound **3a** (0.1 g, 0.148 mmol) was dissolved in MeOH (3 mL) and HCl (1 mL, 10%) was added. The resulting solution was stirred at room temperature for 30 min and evaporated in vacuo. This procedure was repeated twice to obtain trihydrochloride **3b**. M.p. 237–238 °C. ^{1}H NMR (400 MHz, [D_6]-DMSO): δ = 1.16 (t, J = 9.9 Hz, 9 H), 2.78–2.82 (s + q, 9 H + 6 H), 4.80 (d, J = 3.5 Hz, 3 H), 7.33 (d, J = 12.1 Hz, 3 H), 7.48 (d, J = 10.6 Hz, 3 H), 8.15 (d, J = 12.1 Hz, 3 H), 8.61 (d, J = 10.6 Hz, 3 H), 9.08 (br. s, 3 H), 15.29 (br. s, 3 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 15.9, 19.5, 22.8, 39.5, 116.1, 116.8, 117.8, 130.7, 136.2, 143.7, 149.5, 154.8, 159.5 ppm. ESI-MS: m/z = 676 $[M - 2H]^+$, 338.6 $[M - H]^{2+}$, 226.1 $[M]^{3+}$ ($C_{42}H_{48}N_9^{3+}$).

CCDC-641444 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Synthesis of **2**, ^{1}H und ^{13}C NMR spectra of **3a** and **3b**, further examples of titration curves, representative mole ratio plots and X-ray data for compound **3a**.

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