NMR (C_6D_6, 250 MHz, 25 °C, see ref. [9]): $\delta = 6.72$ (m, 2H), 5.67 (m, 4H), 1.39 (s, 18H), 0.19 (s, 6H).

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[1] J. P. Morken, A. H. Hoveyda, *Angew. Chem*. **1996**, *108*, 1378; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1263; R. B. Grossmann, R. A. Doyle, S. L. Buchwald, *Organometallics* **1991**, *10*, 3301; R. B. Grossmann, W. M. Davis, S. L. Buchwald, *J. Am. Chem. Soc*. **1991**, *113*, 2321; T. K. Hollis, W. Odenkirk, N. P. Robinson, J. Whelan, B. Bosnich, *Tetrahedron* **1993,** *49,* 5415.

[2] M. Bochmann, *J. Chem. Soc. Dalton Trans.* **1996**, 255; H. H. Brintzinger, D. Fischer, R. Mülhaupt, B. Rieger, R. M. Waymouth, *Angew. Chem.* **1995**, *107*, 1255; *Angew. Chem. Int. Ed. Engl.* **1995,** *34,* 1143.

[3] R. B. Grossmann, J. C. Tsai, W. M. Davis, A. Gutiérrez, S. L. Buchwald, *Organometallics* **1994,** *13,* 3892; R. L. Halterman, *Chem. Rev.* **1992**, 965; W. W. Ellis, T. K. Hollis, W. Odenkirk, J. Whelan, R. Ostrander, A. L. Rheingold, B. Bosnich, *Organometallics* **1993**, *12*, 4391; M. E. Huttenloch, J. Diebold, U. Rief, H. H. Brintzinger, A. M. Gilbert, T. J. Katz, *Organometallics* **1992**, *11,* 3600; G. M. Diamond, S. Rodewald, R. F. Jordan, *Organometallics* **1995,** *14*, 5; G. M. Diamond, R. F. Jordan, J. L. Petersen, *Organometallics* **1996**, *15,* 4045; S. T. Chacon, E. B. Coughlin, L. M. Henling, J. E. Bercaw, *J. Organomet. Chem*. **1995,** *497*, 171.

[4] I. E. Nifant'ev, P. V. Ivchenko, *Organometallics* **1997**, *16*, 713; I. E. Nifant'ev, M. V. Borzov, A. V. Churakov, *Organometallics* **1992**, *11*, 3942.

[5] L. Resconi, F. Piemontesi, I. Camurati, D. Balboni, A. Sironi, M. Moret, H. Rychlicki, R. Zeigler, *Organometallics* **1996**, *15*, 5046.

[6] a) M. Hüttenhofer, M. H. Prosenc, U. Rief, F. Schaper, H. H. Brintzinger, *Organometallics* **1996**, *15*, 4816; b) M. Hüttenhofer, Dissertation, Universität Konstanz, **1997**.

[7] L. A. Paquette, M. R. Sivik, *Organometallics* **1992**, *11*, 3503.

[8] K. Jones, M. F. Lappert, *J. Chem. Soc.* **1965,** 1944.

[9] H. Wiesenfeldt, A. Reinmuth, E. Barsties, K. Evertz, H. H. Brintzinger, *J. Organomet. Chem.* **1989**, *369,* 359.

[10] The ^1H and ^{13}C NMR spectra of **2** in $CDCl_3$ are in accord with the expected S_4 symmetry: The number of signals observed is only one fourth of that expected for an unsymmetrical molecule (see Experimental Section). The signal assigned to the H atom at C1 exhibits a large $^1H - ^{117/119}Sn$ coupling of 103 Hz (see ref. [6a]).

[11] Colorless monoclinic prisms of **2** ($C_4H_{60}Si_2Sn \cdot 0.5\,O(C_2H_5)_2$) were obtained by crystallization from diethyl ether at 4 °C. Further details on the crystal structure investigation of **2** may be obtained from the Fachinformtionszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-380134.

[12] The molecular geometry of **2** in the solid state is distorted from the idealized S_4 symmetry represented in Figure 1 in that the Si(1) – Sn axis deviates from the Sn – Si(2) axis by 18°. This distortion might be caused by packing effects related to the cocrystallization of a diethyl ether molecule.

[13] Compound **2** is thermally stable; even after several days in solution there were no indications of any rearrangement having occurred.

[14] K. Bernauer, H. Stoeckli-Evans, D. Hugi-Cleary, H. J. Hilgers, H. Abdul-el-Khalek, J. Porret, J. J. Sauvain, *Helv. Chim. Acta* **1992**, *75*, 2327; K.Bernauer, F.Gretillat, H. Stoeckli-Evans, R. Warmuth, *Helv. Chim. Acta* **1993**, *76*, 545.

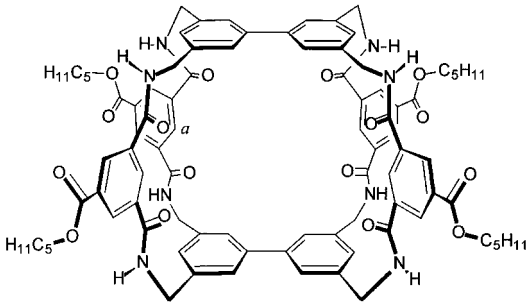
[15] J. Lorberth, *J. Organomet. Chem.* **1969**, *16*, 235.

A Tricyclic Polyamide Receptor for Carbohydrates in Organic Media**

Anthony P. Davis* and Richard S. Wareham

Carbohydrates are important[1] but especially challenging substrates for supramolecular chemistry. Their structures are complex, yet lack (in the general case) individual features, such as ionic or strongly hydrophobic units, able to partake in strong and specific noncovalent interactions.[2] The problem intensifies in hydroxylic solvents, where a receptor must distinguish its target from a large excess of similarly functionalized competitors. With the exception of boron-based systems which operate through covalent bond formation,[3] there are still no effective synthetic receptors for carbohydrates in aqueous solution.[4] Of the many published systems for operation in organic media,[5, 6] only a few can tolerate significant quantities of hydroxylic cosolvents.[6]

We now report a new carbohydrate receptor **1**, which shows unusual levels of affinity and selectivity in chloroform, and remains effective even in the presence of 8% CD_3OH. The design of **1** was inspired by carbohydrate-binding proteins,



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which commonly place aromatic surfaces against patches of carbohydrate CH groups while accepting the hydroxyl groups into networks of hydrogen bonds.[1d, 7] The intended target of **1**, the β-D-glucopyranosyl unit **2**, possesses axial CH groups and equatorially directed hydroxyl groups (Figure 1). The

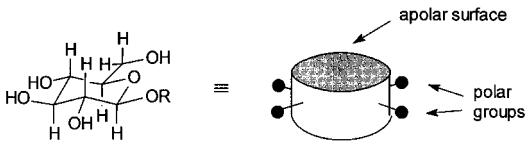

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Figure 1. Target molecule of the receptor **1** with axial hydrophobic and equatorial polar groups.

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complementary cavity should therefore have parallel arene rings, appropriately spaced, linked by moieties capable of hydrogen-bond donation and/or acceptance. Other perceived design requirements were sufficient rigidity that self-complemetary features in the receptor could not meet and satisfy each others' demands, and externally directed functionality which could be used to control solubility.

The tricyclic structure of **1** with two biphenyl and eight amide groups appeared to fit these criteria quite well. Molecular modeling[8] on the analogous tetramethyl ester indicated that the cavity defined by the biphenyl and benzene-1,3-dicarboxamide units was sufficiently large to accept a β-D-glucose molecule (Figure 2), forming up to six intermolecular hydrogen bonds and several CH-π interactions. Modeling in

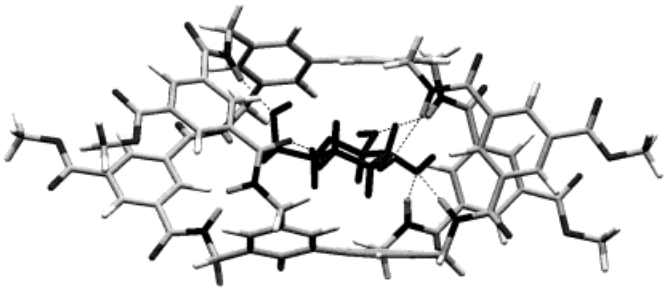
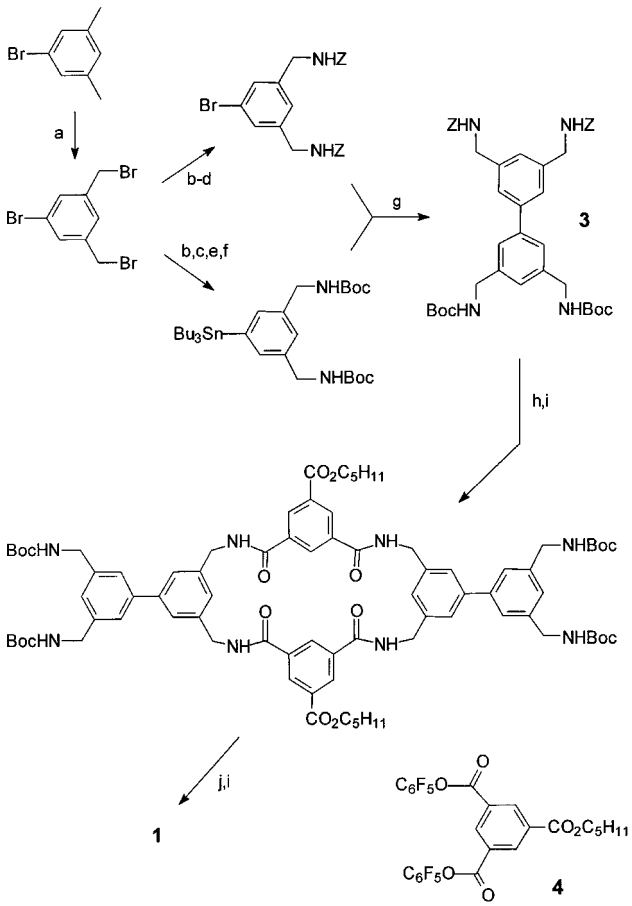


Figure 2. Baseline conformation resulting from a 1000 step Monte Carlo molecular mechanics study of **1**, modeled as the analogous tetramethyl ester, plus β-D-glucopyranose.[7] The six intermolecular hydrogen bonds are shown as broken lines. Hydrogen atoms on C1, C2, and C3 of the carbohydrate are positioned to form close CH-π interactions with the host.

the absence of substrate did reveal low-energy conformations possessing up to three intramolecular hydrogen bonds and no substantial cavities. However, these could only be accessed at the cost of two or three *syn*-amide linkages, representing strain energy available to open the cavity during the binding process. The peripheral pentyl ester groups seemed likely to confer solubility in organic solvents, and could in principle be hydrolyzed to allow studies in water.

The synthesis of **1** proceeded via the asymmetrically protected biphenyl intermediate **3** (Scheme 1).[9] Key steps were the [2+2] macrocyclizations involving bispentafluorophenyl ester **4**. Competition from [1+1] cyclizations was not observed, presumably due to steric/stereoelectronic effects.

Although quite soluble in $CDCl_3$, **1** could not be studied by NMR spectroscopy in this solvent because of strongly broadened spectra. However, spectra acquired in $CDCl_3$/CD_3OH (92:8) were well resolved and could be used for binding studies. Addition of octyl pyranosides **5**–**7** to **1** in this solvent system caused various changes in the ^{1}H NMR spectrum of the host. Interestingly, the signal due to amide NH moved upfield[10] by about 0.2 ppm and split into two multiplets of equal size. The creation of two NH environments is an expected consequence of the interaction of **1** (D_{2h} symmetry) with a chiral substrate.[11] The signals due to the benzylic methylene groups were also split into two broad multiplets, while that due to the inward-directed aromatic CH (position *a* in formula of **1**) moved downfield by about 0.3 ppm. The motions of the latter were consistent with 1:1



Scheme 1. Synthesis of **1**: a) NBS, AIBN, HCOOMe, $h\tilde{\nu}$; b) potassium phthalimide, DMF; c) $NH_2NH_2 \cdot H_2O$, CH_3OH/CH_2Cl_2, then HCl aq.; d) $PhCH_2O(CO)Cl$, THF, $i Pr_2NEt$; e) $(Boc)_2O$, THF, $i Pr_2NEt$; f) $(SnBu_3)_2$, $Pd(OAc)_2$, PPh_3, toluene, reflux; g) $[Pd_2(dba)_3]$, tri-(2-furyl)phosphane, NMP, 50 °C; h) H_2, 10% Pd/C, CH_3OH/CH_2Cl_2; i) **4**, $i Pr_2NEt$, THF-DMF, high dilution; j) TFA, CH_2Cl_2. AIBN = 2,2′-azobis(2-methylpropionitrile), Boc = *tert*-butoxycarbonyl, dba = dibenzylidenacetone, NBS = *N*-bromosuccinimide, NMP = *N*-methyl-2-pyrrolidinone, TFA = trifluoroacetic acid, Z = benzyloxycarbonyl.

binding, and could be analyzed to yield the data shown in Table 1. We were pleased to record quite substantial binding

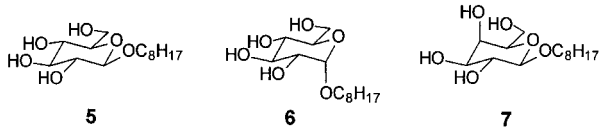


Table 1. Results from ^{1}H NMR titrations of **1** with octyl pyranosides **5**–**7**.[a]

Pyranoside	K_a [M^{-1}]	$-\Delta G^\circ$ [kJ mol^{-1}]	$\Delta\delta$ [ppm][b]
5	980 (±2%)	17.4	0.32
6	20 (±23%)	7.8	0.30
7	220 (±5%)	13.6	0.27

[a] In $CDCl_3/CD_3OH$ (92:8). [**1**] = in the range 0.66 to about 0.52 mM for titrations with **5** and **7**, and between 2.2 and 1.53 mM for titrations with **6**. ^{1}H NMR spectrum of **1** was independent of concentration within this range. Guest concentrations 0.066–2.75 mM (**5**), 0.86–15.0 mM (**6**), 0.066–3.61 mM (**7**). T = 303 K. Association constants K_a were calculated from movements of the signal due to ArH^a using HOSTEST version 5.0.[13a] Uncertainties are standard deviations calculated by using the Monte Carlo error analysis incorporated in the program. [b] Limiting change in chemical shift of ArH^a.

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constants (K_a) for **5** and **7**, considering the presence of competing methanol, and a remarkable selectivity of about 45 between anomers **5** and **6**.

This success in a hydroxylic medium prompted a return to chloroform, the solvent which would best allow comparison of **1** with other systems. With no recourse to NMR spectroscopy, we investigated fluorescence spectroscopy as an indicator of complexation. On excitation at 285 nm **1** emits fluorescence between 350 and 450 nm (maximum at 387 nm). Addition of **5**–**7** appears to reduce intensity by two mechanisms, one which exhibits saturation and one which is linear with concentration. As illustrated in Figure 3, titration data could

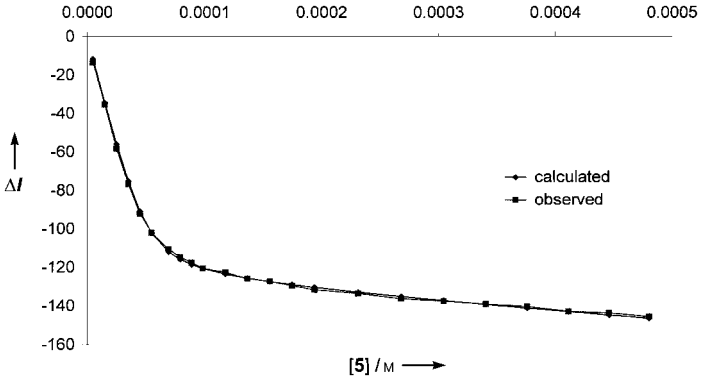


Figure 3. Experimental and calculated values for the fluorescence binding study of **1**+**5**.

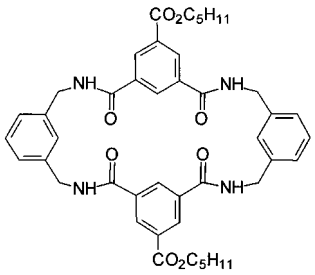
be reproduced to good accuracy by assuming that the first of these processes corresponded to 1:1 complex formation. The binding constants implied by the analyses are listed in Table 2. The selectivity between **5** and **6** is maintained, while the K_a for **5** is raised to 300000 M^{-1}.

Table 2. Results from fluorescence titrations of **1** with octyl pyranosides **5**–**7**.[a]

Pyranoside	K_a [M^{-1}][b]	$-\Delta G^\circ$ [kJ mol^{-1}]	$-\Delta I$ [%][c]
5	300000 (±6%)	30.7	36.4
6	13000 (±8%)	23.1	18.8
7	110000 (±12%)	28.3	22.8

[a] In $CHCl_3$. [**1**] ≈ 0.05 mM, guest concentrations 0.005–0.48 mM (**5** and **7**), 0.005–0.23 mM (**6**). [b] Calculated using specially written nonlinear least-squares curve-fitting programs implemented within Excel version 5.0 and Systat version 5.2. The programs made allowance for bimolecular (Stern–Vollmer) quenching of both **1** and complex by free pyranoside at a common rate, and gave the same results to a high level of accuracy. Uncertainties are asymptotic standard errors delivered by the Systat program. [c] Potential limiting change in fluorescence on complex formation (excluding Stern–Vollmer effect).

The geometries of the complexes between **1** and **5**–**7** remain uncertain. Although the exceptional binding constants and selectivities may imply that the strongly bound carbohydrates (**5** and **7**) enter the cavity of **1** as anticipated, we have as yet no direct indication that this is the case.[12] However, control experiments on macrocycle **8** suggest that the complete structure of **1** is required for full effect. The behavior of **8** with **5** in $CDCl_3$ is complicated by dimerization



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(K_{dim} = 600 M^{-1}) and multiple stoichiometries, but appears to be compatible with K_a for 1:1 binding of just 850 M^{-1}.[13]

Finally, a useful and important test for the recognition of carbohydrates is their extraction into nonpolar organic media. This may be said to mimic transport across biological membranes, and has practical implications for carbohydrate separation[3c] and detection,[3a,b] and for the moderation of carbohydrate reactivities.[14] Although boron-based receptors[3] and certain "unstructured" organic systems[15] appear to be broadly effective, preorganized organic receptors have been restricted to less challenging substrates such as ribose,[5e,i] fucose,[5e] or methyl glucoside.[5d,f] All reported attempts to extract hexoses with such receptors have been unsuccessful.[5e,i] When **1** was stirred with an excess of glucose in $CDCl_3$, significant quantities of the carbohydrate could be detected by TLC after filtration of the solution (0.45 μm microfil). No glucose was detected in a control run in the absence of **1**. Complex formation was confirmed by fluorescence spectroscopy ($\Delta I = -25\%$) and by ^{1}H NMR spectroscopy after evaporation and re-solution in $(CD_3)_2SO$. Integration of the latter spectrum indicated that 0.8–0.9 equivalents of glucose had been solubilized in the $CDCl_3$. The ratio of β- to α-anomers was approximately 7:1, substantially different to the equilibrium ratios in $(CD_3)_2SO$ (55:45) and D_2O (65:35),[16] and presumably reflecting the preference of **1** for the β-pyranosyl unit.

The success of **1** gives reason to hope that tricyclic polyamide receptors with related structures may prove effective even under aqueous conditions.

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Keywords: carbohydrates · hydrogen bonds · molecular recognition · receptors · supramolecular chemistry

[1] For leading references to the biological significance of carbohydrate recognition, see: a) S. D. Rosen, C. R. Bertozzi, *Curr. Opin. Cell Biol.* **1994**, *6*, 663; b) N. Sharon, H. Lis, *Essays Biochem.* **1995**, *30*, 59; c) Y. C. Lee, R. T. Lee, *Acc. Chem. Res.* **1995**, *28*, 321; d) W. I. Weis, K. Drickhamer, *Annu. Rev. Biochem.* **1996**, *65*, 441; e) R. U. Lemieux, *Acc. Chem. Res.* **1996**, *29*, 373.

[2] The alkanol hydroxyl group, characteristic of carbohydrates, is of course capable of hydrogen-bond donation and acceptance, and can also ligate to metal ions. However, it is considerably less basic or acidic than many other groups involved in biochemical recognition, and forms correspondingly weaker interactions. See for example; D. H. Williams, *Aldrichimica Acta* **1991**, *24*, 71.

[3] a) T. D. James, P. Linnane, S. Shinkai, *Chem. Commun.* **1996**, 281; b) T. D. James, K. R. A. S. Sandanayake, S. Shinkai, *Angew. Chem.* **1996**, *108*, 2038; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1911; c) B. D. Smith, *Supramol. Chem.* **1996**, *7*, 55.

  1433-7851/98/3716-2272 $ 17.50+.50/0

[4] Studies in aqueous media have either registered very low binding constants, or have employed carbohydrate substrates with hydrophobic appendages. For examples, see: Y. Aoyama, Y. Nagai, J. Otsuki, K. Kobayashi, H. Toi, *Angew. Chem.* **1992**, *104*, 785; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 745; A. V. Eliseev, H.-J. Schneider, *J. Am. Chem. Soc.* **1994**, *116*, 6081; K. Kobayashi, Y. Asakawa, Y. Kato, Y. Aoyama, *J. Am. Chem. Soc.* **1992**, *114*, 10307; B.-L. Poh, C. M. Tan, *Tetrahedron* **1993**, *49*, 9581; J. Jimenez-Barbero, E. Junquera, M. Martinpastor, S. Sharma, C. Vicent, S. Penades, *J. Am. Chem. Soc.* **1995**, *117*, 11198; S. A. Staley, B. D. Smith, *Tetrahedron Lett.* **1996**, *37*, 283.

[5] Reports from this laboratory: a) R. P. Bonar-Law, A. P. Davis, B. A. Murray, *Angew. Chem.* **1990**, *102*, 1497; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1407; b) K. M. Bhattarai, R. P. Bonar-Law, A. P. Davis, B. A. Murray, *J. Chem. Soc. Chem. Commun.* **1992**, 752; c) A. P. Davis, S. Menzer, J. J. Walsh, D. J. Williams, *Chem. Commun.* **1996**, 453; d) K. M. Bhattarai, A. P. Davis, J. J. Perry, C. J. Walter, S. Menzer, D. J. Williams, *J. Org. Chem.* **1997**, *62*, 8463. Representative examples from other laboratories: e) Y. Aoyama, Y. Tanaka, S. Sugahara, *J. Am. Chem. Soc.* **1989**, *111*, 5397; f) Y. Kikuchi, Y. Tanaka, S. Sutaro, K. Kobayashi, H. Toi, Y. Aoyama, *J. Am. Chem. Soc.* **1992**, *114*, 10302; g) R. Liu, W. C. Still, *Tetrahedron Lett.* **1993**, *34*, 2573; h) C.-Y. Huang, L. A. Cabell, E. V. Anslyn, *J. Am. Chem. Soc.* **1994**, *116*, 2778. i) M. Inouye, T. Miyake, M. Furusyo, H. Nakazumi, *J. Am. Chem. Soc.* **1995**, *117*, 12416; j) G. Das, A. D. Hamilton, *J. Am. Chem. Soc.* **1994**, *116*, 11139.

[6] a) S. Anderson, U. Neidlein, V. Gramlich, F. Diederich, *Angew. Chem.* **1995**, *107*, 1722; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1596; b) U. Neidlein, F. Diederich, *Chem. Commun.* **1996**, 1493; c) P. B. Savage, S. H. Gellman, *J. Am. Chem. Soc.* **1993**, *115*, 10448; d) R. P. Bonar-Law, J. K. M. Sanders, *J. Am. Chem. Soc.* **1995**, *117*, 259; e) T. Mizutani, T. Murakami, N. Matsumi, T. Kurahashi, H. Ogoshi, *J. Chem. Soc. Chem. Commun.* **1995**, 1257. The receptors in references [6a–c] exploit strong hydrogen bonds to ionic centers, while those in references [6d,e] employ Zn–O interactions.

[7] F. A. Quiocho, *Pure Appl. Chem.* **1989**, *61*, 1293.

[8] MacroModel V5.5; F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440. Calculations employed the MM2* force field and $CHCl_3$ GB/SA solvation.

[9] **1**: ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 0.91$ (t, J = 7.0 Hz, 12H, CH_3), 1.38 (m, 16H, $CH_2CH_2CH_3$), 1.76 (quintet, J = 7.0 Hz, 8H, $CH_2CH_2CH_2CH_2$), 4.33, (t, J = 6.5 Hz, 8H, CO_2CH_2), 4.43 (dq, J = 18.0, 5.0 Hz, 16H, CH_2NH), 7.26 (s, 4H, biaryl Ar*H*), 7.81 (s, 8H, biaryl Ar*H*), 8.15 (s, 4H, spacer Ar*H*), 8.46 (s, 8H, spacer Ar*H*), 9.09 (t, J = 5.0 Hz, 4H, NH); ^{13}C NMR (100.6 MHz, DMSO-d$_6$): $\delta = 13.83$ (CH_3), 21.77 (CH_2), 27.60 (CH_2), 27.84 (CH_2), 43.73 (NHCH_2), 65.26 (CO_2CH_2), 124.87 (Ar CH), 129.11 (Ar CH), 130.27 (2 × Ar CH), 130.38 (Ar C), 135.26 (Ar C), 136.70 (Ar C), 139.76 (Ar C), 164.77 (*C*O), 164.80 (*C*O); LSI-MS: *m*/*z*: 1517.7 [*M*H$^+$] (100), 534.9 (20), 460.9 (68).

[10] This unexpected direction of shift may be due to displacement of methanol by the carbohydrate, giving a structure in which not all NH groups are maximally hydrogen-bonded. Alternatively, a conformational change may take place, altering the position of the NH protons in relation to the arene rings.

[11] At first sight it might be thought that, at fast exchange, all eight NH protons would be equivalent. However, the carbohydrate substrate lacks any element of symmetry, and therefore creates eight different NH environments on interaction with the receptor. Coalescence of these eight signals would require fast exchange between eight equivalent binding orientations. The symmetry of **1** allows only four such orientations, and the NH protons are therefore split into two groups of four.

[12] Data from the ^{1}H NMR studies in $CDCl_3/CD_3OH$ (92:8) suggest that the carbohydrate protons experience upfeld shifts of about 0.2–0.3 ppm on complexation. These modest shifts might imply attachment to the exterior of **1**, or might reflect competing shielding/deshielding effects from the arene rings defining the cavity.

[13] ^{1}H NMR titrations analyzed by HOSTEST 5.0. See: a) C. S. Wilcox in *Frontiers in Supramolecular Chemistry and Photochemistry* (Eds.: H.-J. Schneider, H. Dürr), VCH, Weinheim, **1990**, p. 123.

[14] Y. Tanaka, C. Khare, M. Yonezawa, Y. Aoyama, *Tetrahedron Lett.* **1990**, *31*, 6193.

[15] Inverse micelles: N. Greenspoon, E. Wachtel, *J. Am. Chem. Soc.* **1991**, *113*, 7233; T. Kida, D. Furue, A. Masuyama, Y. Nakatsuji, I. Ikeda, *Chem. Lett.* **1996**, 733. "Unimolecular inverse micelles": K. Kobayashi, F. Ikeuchi, S. Inaba, Y. Aoyama, *J. Am. Chem. Soc.* **1992**, *114*, 1105.

[16] F. Franks, P. J. Lillford, G. Robinson, *J. Chem. Soc. Faraday Trans. 1* **1989**, *85*, 2417.

Oligomers with Intercalating Cytosine–Cytosine$^+$ Base Pairs and Peptide Backbone: DNA i-Motif Analogues**

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The ends of chromosomes are built up of telomeric DNA with an up to 1000-fold repeating guanine-rich DNA and complementary cytosine-rich sequence.[1] The organization of guanine strands in tetrads based on a guanine donor/acceptor pattern that allows for simultaneous pairing by the Watson–Crick and Hoogsteen sides is a familiar structural motif.[2] Surprisingly, however, the cytosine-rich oligomers are also able to form tetramers since pyrimidine molecules lack a Hoogsteen side they contribute less to the complex stability through stacking interactions. Nevertheless, at pH 4.5–6.5 the semiprotonated C–C$^+$ base pairs are formed in the reverse Watson–Crick mode with three hydrogen bonds building up a parallel double strand; two C–C$^+$ pairing double strands intercalate and stabilize the structure in a four-stranded complex.[3–5] The interaction of consecutive base pairs is provided only by the stacking of the exocyclic carbonyl and amino groups that are oriented with opposed dipoles (Scheme 1). This base-pair arrangement makes a considerable contribution to the stabilization of the pairing complex as indicated by a base-pair distance of only 3.1 Å. DNA tetramers containing C–C$^+$ pairing were called i-motif in reference to intercalating double strands, and were described by Gehring et al. in an NMR structural analysis of the DNA oligomer d(TCCCCC) that forms an i-motif[3] and by Chen et al. with an X-ray structure of d(C_4).[4] In the meantime, the intercalating C–C$^+$ double strands that form C tetrads were established as a structural motif.[5] Unwinding of the double helix is required to facilitate intercalation and leads to a helical twist of only 12.4–16° in the DNA i-motif. As part of

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