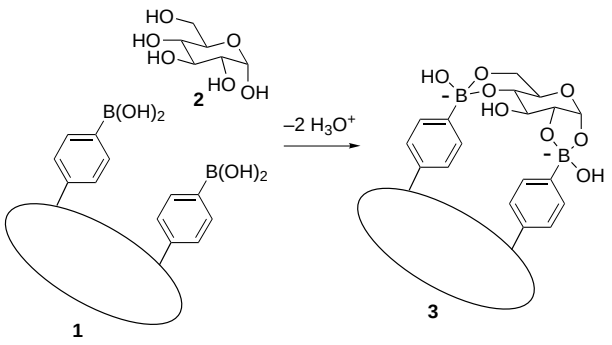
[6] a) K. Ichimura, S.-K. Oh, M. Nakagawa, *Science* **2000**, *288*, 1624; b) J. W. Weener, E. W. Meijer, *Adv. Mater.* **2000**, *12*, 741.
[7] A. P. H. J. Schenning, C. Elissen-Román, J. W. Weener, M. W. P. L. Baars, S. J. van der Gaast, E. W. Meijer, *J. Am. Chem. Soc.* **1998**, *120*, 8199.
[8] T. Gensch, J. Hofkens, J. van Stam, H. Feas, S. Creutz, K. Tsuda, R. Jerome, H. Masuhara, F. C. De Schryver, *J. Phys. Chem. B* **1998**, *102*, 8440.
[9] *Procedures in Scanning Probe Microscopies*, Wiley, Chichester, **2000**.
[10] B. M. Discher, Y.-Y. Won, D. S. Ege, J. C.-M. Lee, F. S. Bates, D. E. Discher, D. A. Hammer, *Science* **1999**, *284*, 1143.
[11] H. Hub, B. Hupfer, H. Koch, H. Ringsdorf, *Angew. Chem.* **1980**, *92*, 962; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 938.
[12] K. Tsuda, G. Dol, T. Gensch, J. Hofkens, L. Latterini, J. W. Weener, E. W. Meijer, F. C. De Schryver, *J. Am. Chem. Soc.* **2000**, *122*, 3445.
[13] M. Shimomura, R. Ando, T. Kunitake, *Ber. Bunsenges.Phys. Chem.* **1983**, *87*, 1134.
[14] M. Shimomura, T. Kunitake, *J. Am. Chem. Soc.* **1987**, *109*, 5175.
[15] S. R. McAlpine, S. L. Schreiber, *Chem. Eur. J.* **1999**, *5*, 3528.
[16] F. M. Menger, A. Archut, *Acc. Chem. Res.* **1998**, *31*, 789.
[17] F. M. Menger, J. S. Keiper, *Adv. Mater.* **1998**, 10, 888.
[18] A. Ashkin, *Phys. Rev. Lett.* **1970**, *24*, 156.
[19] A. Ashkin, J. M. Dziedzic, J. E. Bjorkholm, S. Chu, *Opt. Lett.* **1986**, *11*, 288.
[20] K. Svoboda, S. M. Block, *Annu. Rev. Biophys. Biomol. Struct.* **1994**, *23*, 247.
[21] L. I. McCann, M. Dykman, B. Golding, *Nature* **1999**, 785.
[22] C. D'Helon, E. W. Dearden, H. Rubinsztein-Dunlop, N. R. Heckenberg, *J. Mod. Opt.* **1994**, *41*, 595.
[23] M. E. J. Friese, H. Rubinsztein-Dunlop, N. R. Heckenberg, E. W. Dearden, *Appl. Opt.* **1996**, *35*, 7112.
[24] R. M. Simmons, J. T. Finer, S. Chu, J. A. Spudich, *Biophys. J.* **1996**, *70*, 1813.
[25] J. D. Moroz, P. Nelson, R. Bar-Ziv, E. Moses, *Phys. Rev. Lett.* **1997**, *78*, 386.
[26] P. Borowicz, J. Hotta, K. Sasaki, H. Masuhara, *J. Phys. Chem. B* **1998**, *102*, 1896.
[27] J. Hofkens, J. Hotta, K. Sasaki, H. Masuhara, T. Taniguchi, T. Miyashita, *J. Am. Chem. Soc.* **1997**, *119*, 2741.
[28] J. Hofkens, J. Hotta, K. Sasaki, H. Masuhara, K. Iwai, *Langmuir* **1997**, *13*, 414.

Computer-Guided Design in Molecular Recognition: Design and Synthesis of a Glucopyranose Receptor**

Wei Yang, Huan He, and Dale G. Drueckhammer*

The design of compounds which are capable of specific recognition of molecules and ions is a long-standing challenge in organic chemistry. In addition to its fundamental interest, this work is of increasing practical value in the development of chemosensors for compounds of biological and environmental importance[1] and is a key element of biomimetic catalysis.[2] The specific binding of one compound from a complex mixture generally requires the interaction of multiple functional groups of the receptor with complementary functionality of the guest compound.[3, 4] Good affinity and selectivity requires the precise placement of the recognition elements of the receptor in the proper position and orientation for optimal complementarity to the guest. Nature uses proteins (enzymes, antibodies, and other protein-based receptors) as a basis for specific receptors. Efforts to achieve specificity and affinity in smaller synthetic molecules has relied primarily on intuition for the identification of molecular scaffolds that would permit proper orientation of the functionality for molecular recognition. We envisioned that the computer program CAVEAT, developed by Bartlett and co-workers and previously utilized for the design of enzyme inhibitors and conformationally constrained peptides, could serve as a valuable tool for the discovery of molecular backbones for the orientation of functional groups for molecular recognition.[5, 6] Described here is the demonstration of a CAVEAT-based design approach in the development of a glucopyranose receptor incorporating precisely positioned arylboronic acid groups as recognition elements.

Arylboronic acids have long been known to form stable complexes with sugars and other diols in aqueous solution.[7] Numerous arylboronic acids have been prepared and studied as sugar receptors, and those incorporating fluorescent aryl groups have been explored as fluorescence-based sugar sensors.[8–15] Of particular interest are glucose sensors for potential application in the maintenance of blood glucose levels in persons with diabetes.[16, 17] However, the simple arylboronic acids form stable complexes with a variety of sugars and thus are not useful as specific receptors or sensors for a single sugar. Compounds have been prepared that contain a pair of arylboronic acid groups in somewhat flexible structures which form two cyclic boronates with a single sugar molecule.[11–14] These bis-boronic acids, while not designed for complexation with a specific sugar, have demonstrated somewhat enhanced, though still modest, selectivity. A glucopyranose receptor **1** containing a pair of precisely positioned phenylboronic acid groups was chosen as an initial target for receptor design using CAVEAT (Scheme 1). The large oval structure in **1** represents a polycyclic organic framework to be identified using CAVEAT. Since glucopyranose **2** can form cyclic boronates between the α-1,2 and 4,6-hydroxy groups,[14, 18] the receptor was designed to incorporate arylboronic acid groups in the proper relative position to form a



Scheme 1. Complex formation between glucose and a bis-arylboronic acid.

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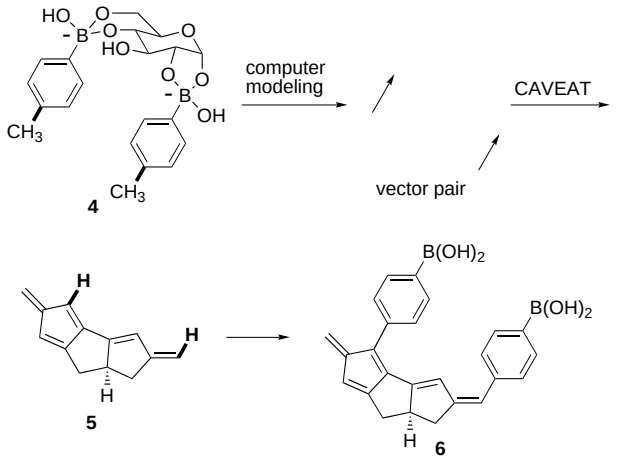
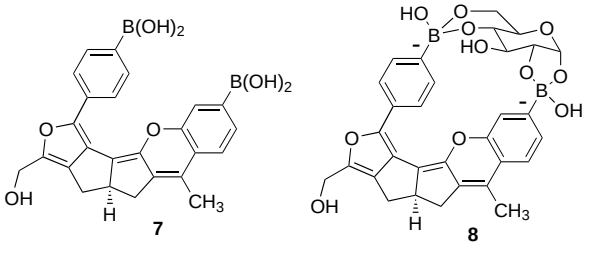
complex represented by structure **3**. This is in contrast to the simple arylboronic acids and the bis-arylboronic acids which form complexes in aqueous solution with the α-furanose form of glucose.[14, 15]

The design approach for the receptor **1** is illustrated in Scheme 2. Initially a conformational search of the bis-*p*-tolylboronate derivative of glucose, namely **4**, was performed



Scheme 2. Computer-based design of a glucopyranose receptor.

using AM1-SM2, a semiemperical method incorporating an aqueous solvation model.[19] This search was followed by geometry optimization using HF//6-31G* to predict the lowest energy conformation of **4**. The resulting computer-generated structure was used to define a pair of vectors corresponding to the methyl – aryl bonds (in bold) of **4**. The program CAVEAT was then used to identify polycyclic organic structures having substituent bonds to the polycyclic framework matching the vector pair. TRIAD, a computer-generated collection of 4×10^5 tricylic hydrocarbons, was used as the database for the search.[5] This search identified about 300 structures having substituent bonds closely matching the vector pair defined by the computer-generated model of **4**. After elimination of most of the structures because of the presence of several chiral centers and/or highly strained and unusual ring systems, compound **5** was chosen as the lead structure, primarily because of its apparent ease of synthesis. The C–H bonds of **5** in bold correspond to the vectors defined by **4**. Simple replacement of these hydrogen atoms with phenylboronic acid groups leads to the prospective glucose receptor **6**. The structure was further modified to arrive at the structure **7**. One significant modification in arriving at structure **7** from **6** is the replacement of the fulvene ring with the more stable and synthetically accessible but isosteric furan ring. The other major modification is the introduction of a bridging oxygen atom to avoid the out of plane twisting caused by the interaction of the two hydrogen atoms for which the oxygen was substituted. More minor changes are the introduction of a hydroxymethylene group on the furan ring for increasing water solubility and for possible derivatization for further solubility enhancement, and the introduction of a methyl group on the pyran ring, a substitution which was dictated by the availability of the commercially available starting material **9** (see Scheme 3) bearing this extra methyl group. Geometry optimization of **7** using HF//6-31G* showed that its lowest energy conformation matched very well with the bis-phenylboronate glucose complex **4**. Likewise, geometry optimization of the glucose complex **8** by the same method indicated almost no change in the conformation of the receptor **7** and no accompanying increase in strain upon glucose binding. The superimposed structures of **7** and **8** (Figure 1) give a root mean square deviation (RMSD) of 0.279 Å for common atoms. On the basis of these positive results, the synthesis of the designed glucose receptor **7** was undertaken.



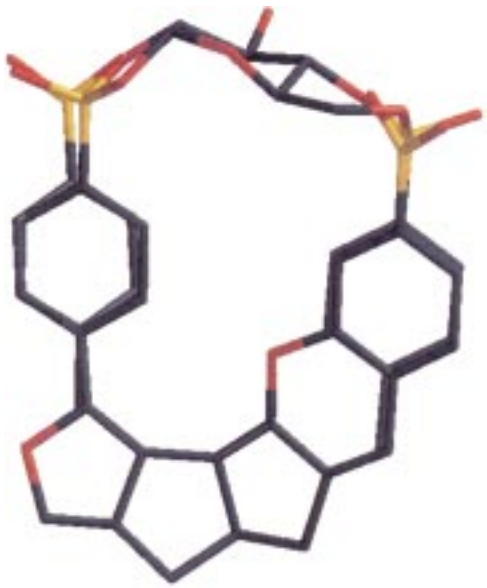
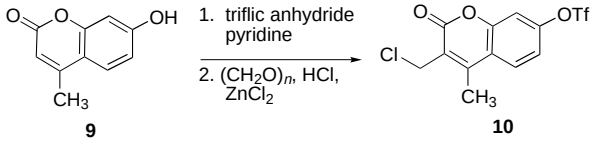


Figure 1. Superposition of the energy-minimized structures of the glucose receptor **7** and the glucose complex **8**.

The right side of **7** was derived from compound **10**, which was prepared as shown in Scheme 3. Commercially available 7-hydroxy-4-methylcoumarin (**9**) was converted into the triflate derivative followed by reaction with paraformaldehyde and HCl to introduce the chloromethylene group at C3 and give **10**.[20, 21] The synthesis of **7** is shown in Scheme 4.



Scheme 3. Synthesis of the right side of the glucopyranose receptor. Tf = trifluoromethanesulfonyl.

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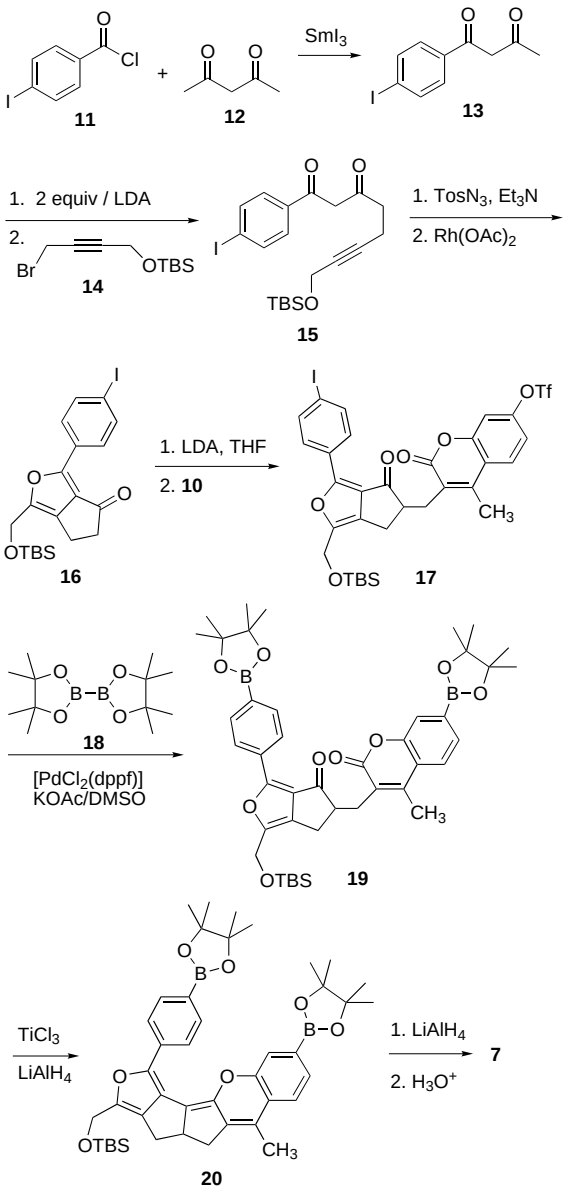

Scheme 4. Synthesis of the glucopyranose receptor **7**. LDA = lithium diisopropylamide; TBS = *tert*-butyldimethylsilyl; Tos = toluene-4-sulfonyl; Ac = acetyl; dppf = 1,1′-bis(diphenylphosphanyl)ferrocene; DMSO = dimethyl sulfoxide.

Reaction of *p*-iodobenzoyl chloride (**11**) with 2,4-pentanedione (**12**) and samarium iodide gave the diketone **13**.[22] Formation of the dienolate of **13** followed by reaction with the bromide **14**, which was prepared in two steps from 2-butyn-1,4-diol,[23] gave **15**. Conversion of **15** into the diazo compound by reaction with tosyl azide followed by a rhodium-catalyzed cyclization gave **16**.[24] Deprotonation of **16** adjacent to the carbonyl group followed by alkylation of the resulting enolate with **10** resulted in the formation of **17**. Reaction of **17** with the diboron diester **18** using a palladium catalyst gave the protected bis-boronic acid **19**.[25, 26] An intramolecular McMurry reaction between the ketone and lactone carbonyl groups produced **20**.[27, 28] Deprotection of the boronic acids and the primary alcohol gave the glucose receptor **7** in racemic form.[29]

The formation of a complex with glucose was initially analyzed by ^{1}H NMR spectroscopy and mass spectrometry. The receptor **7** was combined with 1.8 equivalents of NaOD and 0.5 equivalents of D-glucose in CD_3OD. Only 0.5 equivalents of glucose were used in an effort to observe complex formation with only the preferred enantiomer of **7** and thus avoid the spectral complexity of diasteromeric complexes. The resulting sample was used for both mass spectral and ^{1}H NMR analysis. The electrospray ionization (ESI) mass spectrum showed large peaks at m/z 301.12 for the dianionic tetradeuterated complex **8** ($C_{31}H_{24}B_2O_{11}D_4$, $M_r = 602$) and at m/z 603.25 for the corresponding protonated monoanion. Smaller peaks were observed at m/z 249.01 for the dianionic heptadeuterated boronate form of **7** ($C_{25}H_{17}B_2O_9D_7$, $M_r = 497$) and at m/z: 498.72 for the corresponding protonated monoanion. Importantly, no peaks were observed at m/z 321 or 643, which correspond to the dianionic and protonated monoanionic forms, respectively, of a complex of glucose with only one of the boronic acid groups of **7**. Such a complex would be 40 mass units (two equivalents of D_2O) larger than **8**. Interestingly, no peaks were observed that corresponded to complete or partial exchange of the boronic acid OH groups in complex **8** or the free receptor **7** with OCD_3 from the solvent.

The 300 MHz ^{1}H NMR spectra obtained within a few minutes of mixing **7** and glucose showed complete disappearance of the peaks corresponding to free glucose, with substantial shifts of these protons mostly downfield, which is indicative of complex formation. No further changes were observed in the spectra taken 4 and 16 h after mixing, which indicated that complex formation was complete within a few minutes and that no isomerization of the initially formed complex occurred.[14] The protons of the glucose moiety in the complex were assigned using chemical shift predictions generated using ACDLabs software. Coupling constants were measured and compared to the coupling constants for 1,2;4,6-di-*O*-benzylidine glucopyranose and 1,2;5,6-di-*O*-isopropylidine glucofuranose (Table 1). The coupling constants between H5 and the protons on C6 are not included, as they are dependent upon the conformation of the C5–C6 bond and not necessarily indicative of the ring form. A similar comparison of coupling constants has been used in the assignment of the structures of other boronate complexes of glucose.[14] The coupling constants, most notably $J_{2,3}$ and $J_{3,4}$, are clearly consistent with complex formation with the pyranose form of glucose, as expected on the basis of the receptor design and computer modeling studies.[30] The NMR and mass spectral results confirm the formation of complex **8** as predicted by computer modeling studies.

Table 1. ^{1}H-^{1}H Coupling constants for the glucose moiety of complex **8** and related reference compounds.

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
8	6.3	7.8	8.0	8.8
pyranose[a]	4.9	6.4	9.4	9.2
furanose[b]	3.6	0	2.8	6.8

[a] 1,2;4,6-Di-*O*-benzylidine-α-D-glucopyranose. [b] 1,2;5,6-Di-*O*-isoproylidine-α-D-glucofuranose.

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Fluorescence experiments were conducted to evaluate the affinity of **7** for glucose and its selectivity for glucose versus other common sugars. Profiles of the changes in fluorescence versus concentrations of glucose, galactose, mannose, and fructose at pH 7.5 are shown in Figure 2.[31] Glucose exhibited

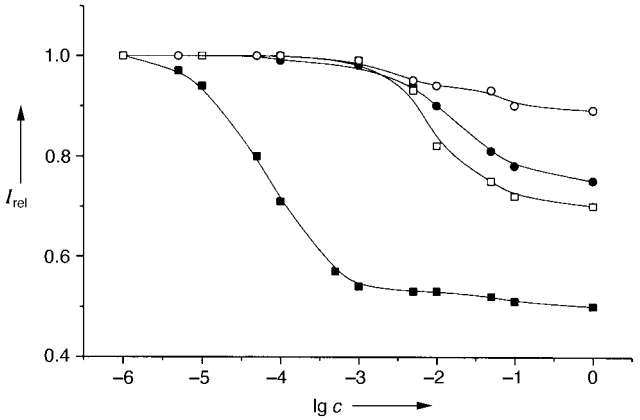

Figure 2. Relative fluorescence intensity I_{rel} of **7** as a function of the saccharide concentrations lg c at 25 °C with 1.0×10^{-5} M of **7** in 30 % MeOH/aqueous phosphate buffer at pH 7.5. $\lambda_{ex} = 375$ nm, $\lambda_{em} = 447$ nm. ■ D-glucose, □ D-galactose, ● D-mannose, ○ D-fructose.

a 400-fold greater affinity than any of the other sugars for **7**, with an apparent dissociation constant for the complex of 2.5×10^{-5} M.[32] The dissociation constants for the galactose and mannose complexes were 1.0×10^{-2} and 1.6×10^{-2} M, respectively. The dissociation constant for the fructose complex appears similar to the latter two, although the change in fluorescence intensity was too small for an accurate determination. The selectivity is attributed to the fact that only glucose is believed to form a bidentate complex involving both of the boronic acid groups of the receptor. The degree of selectivity observed is unprecedented in receptors based on boronic acid; the apparent previously most selective glucose sensor exhibits a 12-fold and 25-fold selectivity versus fructose and mannose, respectively.[12] The maximum change in the fluorescence intensity was also much greater with glucose, with a 50 % decrease in the intensity observed at saturating glucose concentrations, while a change of less than a 30 % was observed for the other sugars.

Apparently both enantiomers of **7** form glucose complexes with similar binding constants: the fluorescence curve of Figure 2 shows no evidence for two discernable binding constants and the 50 % decrease in fluorescence is too large to be attributed to complex formation with only half of the racemic **7**. This proposal is supported by computational evaluation of the glucose complexes with both enantiomers of **7** and the fact that the two phenyl boronic acids and their point of attachment to the rigid structure are almost coplanar and parallel.

Work is underway to further explore the potential application of **7** and derivatives thereof as fluorescence-based glucose sensors. In addition to the practical application of **7**, this work demonstrates a novel computer-based design approach for molecular recognition that uses the computer program CAVEAT. It is anticipated that this general approach may find use in the design of receptors for the recognition of a wide range of molecules and ions.

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[1] A. W. Czarnik, *Chem. Biol.* **1995**, *2*, 423 – 428.
[2] R. Breslow, *Acc. Chem. Res.* **1995**, *28*, 146 – 153; P. Tecilla, V. Jubian, A. D. Hamilton, *Tetrahedron* **1995**, *51*, 435 – 438.
[3] E. V. Anslyn, A. Metzger, *Angew. Chem.* **1998**, *110*, 682 – 684; *Angew. Chem. Int. Ed.* **1998**, *37*, 649 – 652; C.-Y. Huang, L. A. Cabell, E. V. Anslyn, *J. Am. Chem. Soc.* **1994**, *116*, 2778 – 2792.
[4] G. Das, A. D. Hamilton, *J. Am. Chem. Soc.* **1994**, *116*, 11 139 – 11 140; T. W. Bell, Z. Hou, Y. Luo, M. G. B. Drew, E. Chapoteau, B. P. Czech, A. Kumar, *Science* **1995**, *269*, 671.
[5] G. Lauri, P. A. Bartlett, *J. Comput. Aided Mol. Des.* **1994**, *8*, 51 – 66.
[6] P. A. Bartlett, G. T. Shea, S. J. Telfer, S. Waterman in *Molecular Recognition: Chemical and Biological Problems* (Ed.: S. M. Roberts), Royal Society of Chemistry, London, **1989**, pp. 182 – 196; P. A. Bartlett, F. A. Etzkorn, T. Guo, G. Lauri, K. Liu, M. Lipton, B. P. Morgan, G. T. Shea in *Chemistry at the Frontiers of Medicine*, *Proceedings of the Robert A. Welch Foundation Conference on Chemical Research XXXV* (Houston TX), **1992**, pp. 45 – 68.
[7] J. P. Lorand, J. O. Edwards, *J. Org. Chem.* **1959**, *24*, 769 – 774.
[8] J. Yoon, A. W. Czarnik, *J. Am. Chem. Soc.* **1992**, *114*, 5874 – 5875; T. D. James, K. R. A. S. Sandanayake, S. Shinkai, *J. Chem. Soc. Chem. Commun.* **1994**, 477 – 478.
[9] H. Suenaga, M. Mikami, K. R. A. S. Sandanayake, S. Shinkai, *Tetrahedron Lett.* **1995**, *36*, 4825 – 4828.
[10] P. Linnane, T. D. James, S. Imazu, S. Shinkai, *Tetrahedron Lett.* **1995**, *36*, 8833 – 8834; K. R. A. S. Sandanayake, T. D. James, S. Shinkai, *Chem. Lett.* **1995**, 503 – 504; T. D. James, P. Linnane, S. Shinkai, *Chem. Commun.* **1996**, 281 – 288. T. D. James, K. R. A. S. Sandanayake, S. Shinkai, *Nature* **1995**, *374*, 345 – 347.
[11] T. D. James, K. R. A. S. Sandanayake, S. Shinkai, *Angew. Chem.* **1996**, *108*, 2038 – 2050; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1910 – 1922.
[12] T. D. James, K. R. A. S. Sandanayake, S. Shinkai, *Angew. Chem.* **1994**, *106*, 2287 – 2289; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2207 – 2209; T. D. James, K. R. A. S. Sandanayake, R. Iguchi, S. Shinkai, *J. Am. Chem. Soc.* **1995**, *117*, 8982 – 8987.
[13] K. Tsukagoshi, S. Shinkai, *J. Org. Chem.* **1991**, *56*, 4089 – 4091.
[14] M. Bielecki, H. Eggert, J. C. Norrild, *J. Chem. Soc. P2* **1999**, 449 – 455.
[15] H. Eggert, J. Frederiksen, C. Morin, J. C. Norrild, *J. Org. Chem.* **1999**, *64*, 3846 – 3852.
[16] C. R. Cooper, T. D. James, *Chem. Lett.* **1998**, 883 – 884.
[17] D. A. Gough, J. C. Armour, *Diabetes* **1995**, *44*, 1005 – 1009. R. J. McNichols, G. L. Cote, *J. Biomed. Opt.* **2000**, *5*, 15 – 16.
[18] G. T. Morin, M.-F. Paugam, M. P. Hughes, B. D. Smith, *J. Org. Chem.* **1994**, *59*, 2724 – 2728.
[19] C. J. Cramer, D. G. Truhlar, *Science* **1992**, *26*, 213 – 217; all calculations were carried out using the Gaussian 98 suite of programs: Gaussian 98 (Revision A.7), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1998**.
[20] S. S. Lele, N. G. Savant, S. Sethna, *J. Org. Chem.* **1960**, *25*, 1713 – 1716.
[21] D. I. Ivanova, S. V. Eremin, V. I. Shvets, *Tetrahedron* **1996**, *52*, 9581 – 9588.
[22] W. Hao, Y. Zhang, T. Ying, P. Lu, *Synth. Commun.* **1996**, *26*, 2421 – 2427.

  1433-7851/01/4009-1717 $ 17.50+.50/0

[23] **14** was prepared by reaction of 2-butyn-1,4-diol with 1.0 equiv *tert*-butyldimethylsilyl chloride and imidazole to form the mono-TBS protected derivative followed by reaction with triphenylphosphane and carbon tetrabromide.
[24] A. Padwa, F. R. Kinder, *J. Org. Chem.* **1993**, *58*, 21–28; T. R. Hoye, C. J. Dinsmore, D. S. Johnson, P. F. Korkowski, *J. Org. Chem.* **1990**, *55*, 4518–4520.
[25] T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.* **1995**, *60*, 7508–7510.
[26] A. Giroux, Y. Han, P. Prasit, *Tetrahedron Lett.* **1997**, *38*, 3841–3844; T. Ishiyama, Y. Itoh, T. Kitano, N. Miyaura, *Tetrahedron Lett.* **1997**, *38*, 3447–3450.
[27] J. E. McMurry, D. D. Miller, *J. Am. Chem. Soc.* **1983**, *105*, 1660–1661.
[28] J. E. McMurry, T. Lectka, J. G. Rico, *J. Org. Chem.* **1989**, *54*, 3748–3749.
[29] Compounds **20** and **7** were characterized by high- and low-resolution mass spectra, respectively, in addition to ^{1}H NMR analysis.
[30] Computer-based modeling also predicts that glucofuranose should not form a stable complex with both boronic acid groups of **7**.
[31] Values of I_{rel} versus c were fitted to the equation $c = [(I_{rel}-1)/\Delta\varepsilon]/K\{[7]_{init.} - (I_{rel}-1)/\Delta\varepsilon\} + (I_{rel}-1)/\Delta\varepsilon$ using Origin 5.0. The curves of Figure 2 were generated using B-spline fitting.
[32] The reported values are apparent dissociation constants as the reactions involve uptake or release of hydroxide ions on complex formation and dissociation, respectively, and the apparent equilibrium constants are thus pH dependent.[8]

A Porphyrin Prism: Structural Switching Triggered by Guest Inclusion**

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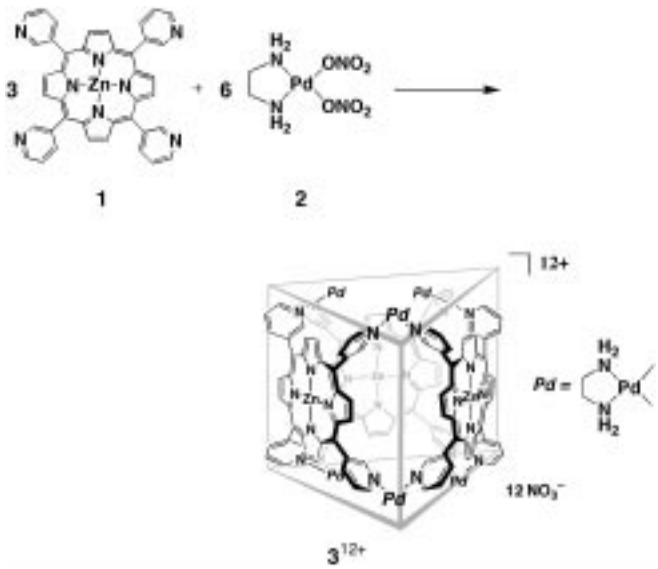
Porphyrin assemblies play an essential role in biological systems for oxygen transport,[1] electron transfer, and energy migration and conversion.[2] In this regard, designing molecular assemblies with porphyrin units is a promising approach for constructing artificial functional systems. Both covalent[3] and noncovalent[4] syntheses of polyporphyrins have offered some novel classes of compounds with respect to their structures and functions. Here, we report a porphyrin-based hollow framework which is expected to open up a new area of porphyrin chemistry based on host–guest interactions. Our strategy employed here is the molecular paneling[5] of a pyridine-functionalized porphyrin by metal coordination. A prismlike hollow structure is quantitatively assembled from three porphyrin ligands and six $[Pd^{II}(en)]^{2+}$ (en = ethylenediamine) building blocks (Scheme 1). The spatially fixed



Scheme 1. Self-assembly of porphyrin prism $\mathbf{3}^{12+}$.

porphyrin ligands surround a large hydrophobic cavity which can accommodate neutral organic molecules, such as pyrene and perylene, in an aqueous solution. Though metal-linked porphyrinic square arrays have been reported by several groups,[6] the porphyrin cores in the arrays seem to adopt cofacial rather than perpendicular conformations and provide no distinct hollow structures capable of guest inclusion. Quite recently, a Pd^{II}-linked porphyrin cage which bound diamines was reported by Shinkai and co-workers.[7]

The ligand designed here is the (3-pyridyl)-functionalized porphyrin **1**. This square panel-like ligand can be hinged by $[Pd^{II}(en)]$ units at two opposite ridges of the square, and hence is anticipated to give a discrete porphyrin box structure.[8] Thus, the treatment of porphyrin ligand **1** with **2** (2 mol equiv) in H_2O/CH_3CN at 80 °C gave a purple homogeneous solution after one day. ^{1}H NMR spectroscopic analysis showed the formation of a single product, which was isolated as a violet precipitate in 96% yield by adding acetone to the solution. After exchange of NO_3^- with PF_6^- ions, the structure of the product was assigned as $\mathbf{3}^{12+}$ by coldspray-ionization mass spectrometry (CSI-MS)[9] and NMR analyses. The CSI mass spectrum displayed prominent peaks corresponding to $[M - n(PF_6^-) + m(CH_3CN)]^{n+}$, $(n = 3-9,\ m = 0-16)$[10] (see Supporting Information). Interestingly, one NO_3^- ion was not exchanged by an PF_6^- ion even when the complex was treated with a large excess of NH_4PF_6. The unexchanged NO_3^- ion was strongly trapped by the prism $\mathbf{3}^{12+}$. This was clearly evidenced by exact mass measurement.[11] For example, the highest peak at m/z 567.7613 (7^+ charge) corresponds to $[M - 6PF_6^- - NO_3^- + 7CH_3CN]^{7+}$ (calcd 567.7561) and not

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