imately 28% and 0.14%, respectively. c) The unsymmetrical binding shown was revealed by X-ray crystal structure analysis.
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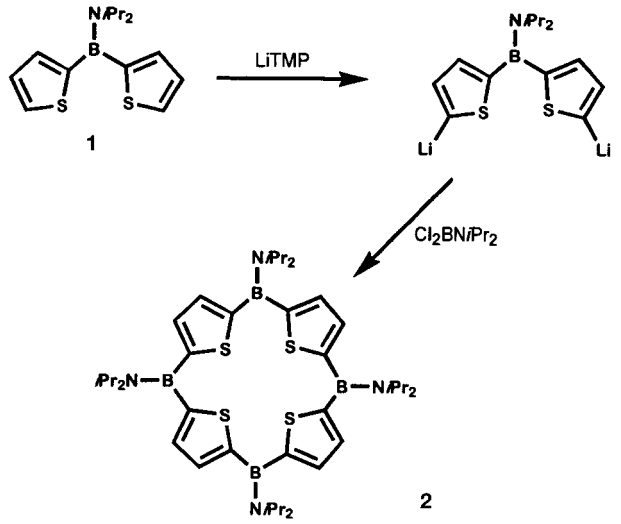
[19] Typical immunoassay calibration curves show hyperbolic behavior while sigmoidal behavior is common with semilogarithmic plots (J. Wyman, S. J. Gill, *Binding and Linkage*, University Science Books, Mill Valley, CA, USA, **1990**, pp. 55–57). We have sigmoidal behavior in linear plots because **1** is in large excess over **2**. As we add citrate it first binds to the free **1** before it competes significantly with **2**.
[20] We have further validated the method by HPLC analyses. A series of citric acid samples obtained from an industrial source were analyzed by our fluorescence method. The results were compared to those determined independently by the industrial donor using their in-house HPLC protocol. In all cases the results differed by at most 5%.

A Boron-Bridged Tetrathiaporphyrinogen**

Francis H. Carré, Robert J.-P. Corriu,* Thomas Deforth, William E. Douglas,* Walter S. Siebert,* and Wolfgang Weinmann

Few porphyrinoid macrocycles based on thiophene are known,[1] and to our knowledge none containing boron have been previously described, although various mono- and diborylthiophenes were isolated many years ago.[2] The first thiophene-containing porphyrinoids to be reported were a colorless carbon-bridged tetrathiaporphyrinogen and the violet tetrathiaporphyrin dication generated from it on oxidation.[3] Their more soluble ethyl-substituted analogues have also been described,[4] as has a carbon-bridged neutral aromatic porphyrinoid based on thiophene.[5] Recently silicon-bridged silatetrathiaporphyrinogens and a phosphorus-bridged phosphatetrathiaporphyrinogen have been reported.[6] Several such silicon-bridged macrocycles based on thiophene have also been prepared.[7]

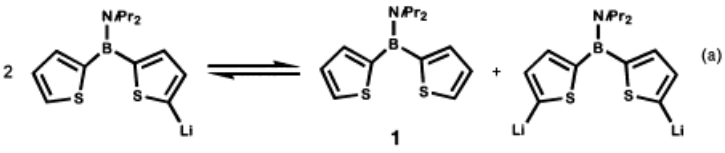
The novel boron-bridged tetrathiaporphyrinogen **2** reported here (see Scheme 1), which contains both Lewis base (sulfur) and Lewis acid (boron) sites, was isolated during an investigation into the synthesis of polymers containing boron and thiophene (or other aromatic) units in the backbone. Initial evidence for the formation of **2** was found in the mass spectrum of the product obtained from the reaction of Cl_2BNiPr_2 with 2,5-dilithiothiophene. The yield can be improved by starting from the *N*,*N*-diisopropyl derivative **1** of the previously reported *N*,*N*-dimethyl-1,1-di-2-thienylboranamine[2b] in which part of the porphyrinoid ring structure has been preformed. Thus, dimetalation of **1** followed by treatment with the stoichiometric quantity of Cl_2BNiPr_2 gave **2** in 62% yield (Scheme 1); no polymer formation was observed. To avoid any attack at boron, the sterically hindered



Scheme 1.

strong base lithium 2,2,6,6-tetramethylpiperidide (LiTMP) was used.

Remarkably, even monolithiation of **1** and treatment with the aminodichloroborane gives rise to **2**. As with the corresponding silicon system,[8] this can be explained in terms of the equilibrium between **1** and the mono- and dilithiated species [Eq. (a)].



Crystals of **2** suitable for an X-ray structure determination[9] were obtained from a solution of the crude reaction product in

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CH_2Cl_2/*n*-hexane (2/1). The four boron atoms of the macrocycle are not in the same plane (Figure 1), unlike the planar arrangement of the bridging groups in the corresponding carbo-[3a] and silatetrathiaporphyrinogens.[6a] Macrocycle **2** has a $\bar{4}$ symmetry axis, whereas the latter two compounds are centrosymmetric. The distance between neighboring sulfur

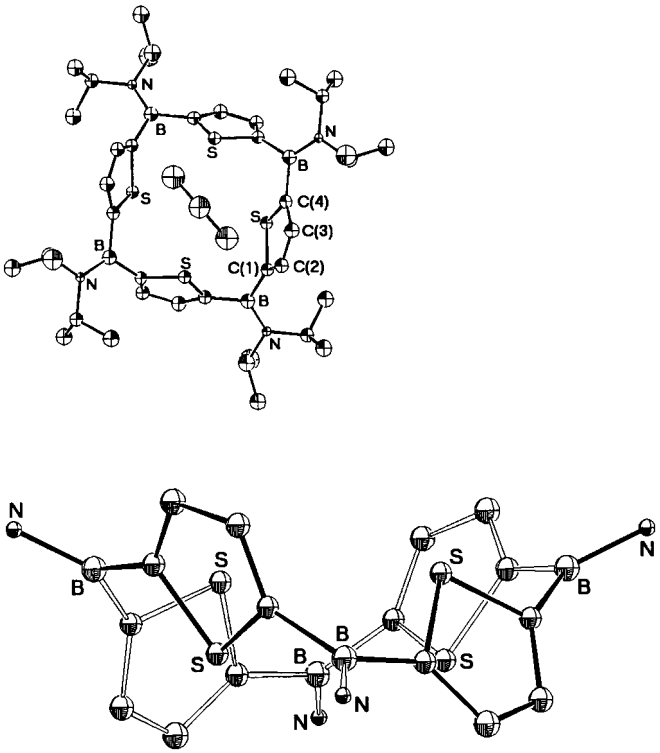

Figure. 1. Structure of **2** (ORTEP drawing). Top: Viewed along the $\bar{4}$ axis (only the CH_2Cl_2 molecule situated below the ring is shown; the position of the other CH_2Cl_2 molecule can be found by performing the $\bar{4}$ symmetry operation); bottom: perspective view of the central ring of **2** (*i*Pr groups omitted for clarity). The ellipsoids are drawn at the 30% probability level. Selected distances [Å] with standard deviations in parentheses: C(4)–B 1.569(6), B–N 1.408(6), C(1)–C(2) 1.343(6), C(2)–C(3) 1.408(6), S–C(1) 1.726(4), S–C(4) 1.728(4), C(3)–C(4) 1.368(6), B–C(1) 1.579(6).

atoms (3.74 Å) is greater than twice the van der Waals radius of sulfur (3.60 Å).[10] The distance between opposite sulfur atoms is 5.01 Å. The two molecules of CH_2Cl_2 contained in the unit cell (situated above and below the ring) are too remote to interact with the porphyrinogen.

Since **2** is colorless and nonplanar, the electrons are probably not delocalized in the macrocycle. Moreover, the B–C distance (1.57 Å) is that expected for a single bond (1.56 Å),[11] and the chemical shift of the signal for the boron atoms in **2** ($\delta = 40$) lies close to that for **1** ($\delta = 37$) in the region expected for such thienylboranamine derivatives.[2b, 12] The thiophene units show the bond-length relation C(1)–C(2) < C(2)–C(3) (Figure 1), whereas for electron-delocalized systems such as porphyrins the reverse is generally so.[3a] Any appreciable ring current or communication between the thiophene aromatic systems through the boron atoms can therefore be ruled out.

Further studies on **2** are in progress in the Heidelberg laboratory, concerning in particular its oxidation and complexation chemistry. It is expected that these properties should be interesting in view of the electron-donor/electron-acceptor nature of **2**.

Experimental Section

1: Thiophene (10.5 g, 125 mmol) was added drop by drop from a syringe to a solution of *n*BuLi (125 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA; 20 mL, 133 mmol) in *n*-hexane (100 mL) at 0°C. After the reaction mixture had been allowed to warm to room temperature, it was stirred for 1 h, then cooled to −60°C, and treated drop by drop with Cl_2BNiPr_2[13] (11.5 g, 63 mmol) in *n*-hexane (50 mL). The stirred mixture was allowed to warm to room temperature overnight, and the LiCl precipitate was removed by filtration through a glass frit (porosity 3). The solvent and TMEDA were removed under vacuum. Distillation (92°C, 10^{-2} mbar) of the residue yielded 13.93 g (80.5%) of **1**. M.p. 37°C; ^{1}H NMR ($CDCl_3$): $\delta = 7.52$-7.49 (m, 2H; H_{Ar}), 7.14-7.08 (m, 4H; H_{Ar}), 4.11 (sept, $J =$ 6.8 Hz, 2H; $CH(CH_3)_2$), 1.30 (d, $J = 6.8$ Hz, 12H; $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$): $\delta = 145$ (br, C_{Ar}), 133.2/129.2/127.4 (C_{Ar}), 49.8 ($CH(CH_3)_2$), 24.7 ($CH(CH_3)_2$); ^{11}B NMR ($CDCl_3$): $\delta = 37$; MS (70 eV, EI): *m*/*z* (%) 277 (6) [M^+], 262 (84) [$M^+ - CH_3$], 177 (20) [$M^+ - NiPr_2$], 111 (100) [$BNiPr_2^+$].

2: A solution of **1** (2.50 g, 9 mmol) in *n*-hexane (10 mL) was added drop by drop to a solution of LiTMP, freshly prepared by treating TMP (2.54 g, 18 mmol) with *n*BuLi (18 mmol) in *n*-hexane. After some seconds a suspension of the dilithiated product was formed. The reaction mixture was stirred for 1 h at room temperature, and then a solution of Cl_2BNiPr_2[13] (0.82 g, 4.5 mmol) in *n*-hexane (10 mL) was added drop by drop at room temperature. The reaction mixture was stirred at 50°C for 3 h. Volatile material was pumped off, and the crude product was taken up in toluene (10 mL). The resulting solution was filtered through a glass frit (porosity 3), and the toluene was removed under vacuum. Crystallization from CH_2Cl_2/*n*-hexane (2/1) afforded **2** in 62% yield. M.p. 182°C (decomp); ^{1}H NMR ($CDCl_3$): $\delta = 7.19$ (s, 8H; H_{Ar}), 4.08 (sept, $J = 6.8$ Hz, 8H; $CH(CH_3)_2$), 1.24 (d, $J = 6.8$ Hz, 48H; $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$): $\delta = 151$ (br, C_{Ar}), 131.1 (C_{Ar}), 49.4 ($CH(CH_3)_2$), 24.7 ($CH(CH_3)_2$); ^{11}B NMR ($CDCl_3$): $\delta = 40$; MS (FAB^+): *m*/*z* (%): 773 (61) [$M^+ + H$], 758 (17) [$M^+ + H - CH_3$], 673 (9) [$M^+ + H - NiPr_2$] , 102 (100) [$HNiPr_2$+H].

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reflections 982 assumed as observed with $I > 2\sigma(I)$. Refinement of 134 parameters with anisotropic thermal parameters for non-hydrogen atoms gave $R = 0.037$, $wR = 0.103$ (on F^2), and $S = 0.913$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Centre as supplementary publication no. 100475. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@chemcrys.cam.ac.uk).

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Carbohydrate – Arene Interactions Direct Conformational Equilibrium of a Flexible Glycophane in Water**

Juan Carlos Morales and Soledad Penadés*

The confluence of many weak intermolecular forces is crucial for carbohydrate recognition processes. Knowledge about these forces derives mainly from the crystal structure analyses and NMR spectroscopy of complexes between oligosaccharides and lectins, antibodies, or periplasmic binding proteins.[1] These studies show that beyond the expected intermolecular forces always found in biological associations (hydrogen bonding, van der Waals forces, hydrophobic effects), stacking interactions between aromatic side chains and saccharides play an important role in stabilizing the complexes.[1,2] Besides the interactions at atomic level, change in oligosaccharide conformation on binding[3] and desolvation effects[4] are essential in determining the structural and energetic properties associated with carbohydrate recognition. Oligosaccharides observed in solution exist as an ensemble average of all possible conformations, and proteins may select oligosaccharide conformations that pre-exist in solution, or induce changes in the oligosaccharide upon binding. This selection has consequences in the thermodynamics of binding;[5] therefore it is important to assess which factors determine the conformation to be bound. However, the inherent oligosaccharide flexibility and the lack of strong intermolecular interactions places extreme demands on these studies.[3]

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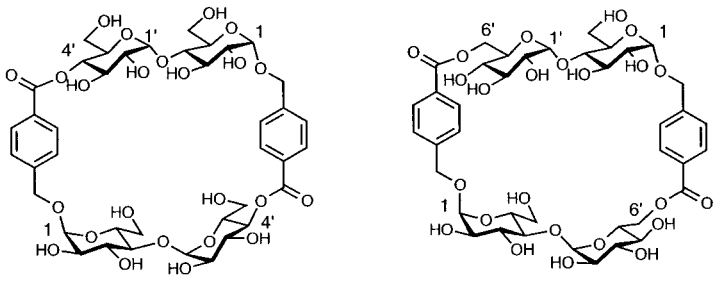
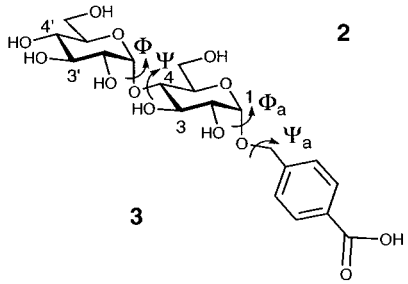
Model systems can also help to understand all these molecular aspects of carbohydrate recognition. In previous work we have designed and synthesized a new type of model receptor (glycophanes) to study carbohydrate binding in water.[6] Glycophanes consist of disaccharides and aromatic segments, and may be considered as cyclodextrin – cyclophane hybrids. With these receptors we have shown, for the first time, the existence of lipophilic interactions in water between carbohydrate surfaces.[7] We have now prepared two new glycophanes **1** and **2**, made up from maltose (4-*O*-(α-D-glucopyranosyl)-D-glucopyranose), the constituent disaccharide of cyclodextrins, and (4-hydroxymethyl)benzoic acid as aromatic segment. The linkage of the aromatic ring to either position 4′ or 6′ of the maltose molecule confers different flexibility on the receptors and different topologies than those present in cyclodextrins. This will allow us to compare the influence of the maltose presentation on the interactions of these receptors with a series of common ligands. In this paper we present evidence that carbohydrate – arene stacking is more important that hydrogen-bonding interactions for the dynamic behavior of the more flexible glycophane **2**. This glycophane adopts a folded conformation in water as a result of intramolecular interactions between a glucose moiety and a phenyl ring. This interaction induces a change in the maltose conformer distribution that is not observed in the more rigid glycophane **1**. Water is necessary for this hydrophobic collapse, which is not observed in methanol or dimethylsulfoxide. The conformational properties of **1** and **2** were assessed by NMR spectroscopy, as well as molecular mechanics and dynamics simulations. Model systems for binding carbohydrate in water based on sugar – arene interactions have been previously reported.[8]

Glycophane **1** was synthesized from maltose, and glycophane **2** was obtained in almost quantitative yield by spontaneous transacylation of glycophane **1** in water.[9] Significant upfield shifts (up to $\Delta\delta = 0.4$) were observed for the H1, H2, and H4 protons of **2** relative to the corresponding protons of the reference compounds **1** and **3**, indicating close proximity of the aromatic rings to the β face of the glucose



1 **2**



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