Acta Chemica Scandinavica, 1999: 53: 34–40
Printed in UK – all rights reserved

ACTA
CHEMICA SCANDINAVICA
ISSN 0904–213X

Diphenylmethane 3,3′-Diboronic Acid as a Model of Molecular Sensors for Sugars. Recognition of Glucose in a Furanose or Pyranose Form?

Rolf Uggla,[a] Markku R. Sundberg[a] and Vesa Nevalainen[b,*]

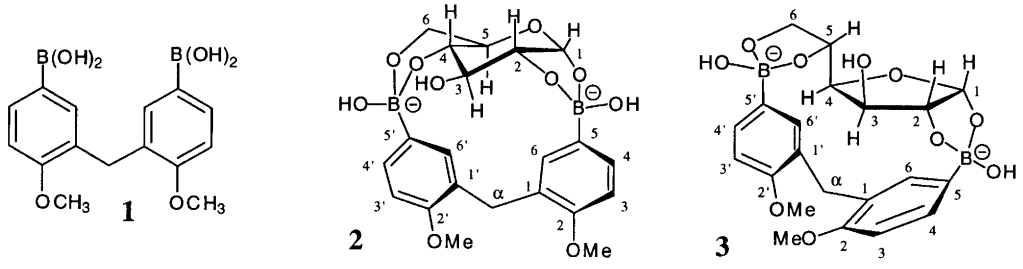
[a]Laboratory of Inorganic Chemistry and [b]Laboratory of Organic Chemistry, PO Box 55, FIN-00014 University of Helsinki, Finland

Uggla, R., Sundberg, M. R. and Nevalainen, V., 1999. Diphenylmethane 3,3′-Diboronic Acid as a Model of Molecular Sensors for Sugars. Recognition of Glucose in a Furanose or Pyranose Form? – Acta Chem. Scand. 53: 34–40. © Acta Chemica Scandinavica 1999.

The structures of the doubly negatively charged glucose 6,6′-dimethoxydiphenylmethane-3,3′-diboronates **2** (glucose in the pyranose form) and **3** (glucose in a furanose form) have been optimized by density functional theory (DFT) methods. In a vacuum, the optimized structure of **2** was found to be 0.65 kcal mol^{-1} more stable than that of **3**. Inclusion of solvent (water) effects, using the conduction-like-screening-model (COSMO) method, increases the stability of **2** to the level of 1.0 kcal mol^{-1} (relative to **3**). Although the values of ^{13}C nuclear NMR chemical shifts calculated (in a vacuum and in water) by using gauge-independent atomic orbitals (GIAO) method at the RHF/6-31G and RHF/6-31G** levels of theory support the furanose form (i.e. **3**; when the shifts were compared with the experimentally determined ones), the differences of the ^{13}C shifts of **2** and **3** can, on the other hand, be related to the lack of basis sets to describe the dianionic structures of **2** and **3**. Furthermore, this might reflect the possibility that neither **2** nor **3** corresponds to the real structure of the glucose–**1** complex formed under basic conditions.

Over the past decade, there has been a continuously growing interest in the use of boronic acids in the construction of molecular devices such as molecular sensors.[1–10] Aromatic boronic acids (e.g. **1**, Scheme 1) have shown great potential in the (enantio)selective recognition of sugars (e.g. based on the formation of chiral analogs of diboronate **2** or **3**; Scheme 1) in aqueous solution.[1–15] Recently, discrimination of highly sensitive sugar derivatives (e.g. D-glucose 1-phosphate and 6-phosphate) and important amino acids [e.g. 3,4-dihydroxyphenylalanine (DOPA)] has been achieved.[16] Also model systems imitating changes induced by cell membranes (covered by saccharides) in the morphology of surrounding solids (e.g. porphyrin-containing oriented aggregates) have been devised utilizing the high affinity of boronic acids to 1,2-diols (e.g. sugars).[1]

Although the formation of boronic acid derivatives of diols has been known for almost 50 years structures of these complexes (e.g. **2**, **3** and other related diboronates) in solution are poorly characterized and still a matter of debate.[11–15] The NMR studies carried out by Tsukagoshi and Shinkai[14] on a glucose complex of diboronic acid **1** indicate that the complex could have a pyranose structure corresponding to that of **2** whereas an isomeric furanose



Scheme 1.

* To whom correspondence should be addressed.

complex **3** was proposed by Norrild and Eggert.[13] Recently, Shinkai *et al.* again described sugar complexes of diboronic acids of which the mode of chelation remains uncertain (involvement of an α-pyranose adduct is proposed but, on the other hand, the authors also state that the related furanose form cannot be ruled out).[15] Therefore, as it would appear difficult to determine experimentally the kinds of adduct that could form when diboronic acids such as **1** react with polyhydroxy compounds (e.g. sugars), we have undertaken theoretical studies on these dianionic complexes. As a first step in this direction we have evaluated the structure of **3** using density functional methods.[3] Here we report a comparative study on the two structures (i.e. **2** and **3**) of which the formation has been proposed earlier on the basis of experimental[13,14] studies.

Computational methods

Two major methods of computation were used: density functional theory (DFT)[17–23] and restricted Hartree–Fock[24] combined with natural bond order (NBO) analyses[25] and ^{13}C chemical shift[26] calculations. DFT geometry optimizations of **2**, **3**[27] and tetramethylsilane (TMS) were performed with the DMol program (versions 2.2 and 2.3, on a Convex C3840),[17–20] including the Janak–Morruzi–Williams functional with the local density approximation. No gradient corrections were applied. The basis sets were either DN or DNP. DN uses double-numeric quality basis sets; approximately 2 atomic orbitals for each occupied in free atom. DNP in turn uses a DN basis with polarization functions; i.e. functions with angular momentum one higher than that of highest occupied orbital in free atom. The DN and DNP basis sets are comparable to Gaussian 6-31G* and 6-31G** basis sets, respectively.

The logarithm of the equilibrium constant (the equilibrium between **2** and **3**) is related to ΔG° which in turn is linearly dependent on ΔH° and $T\Delta S^\circ$. As the computational methods applied do not take into account the role of entropy (ΔS°) we note that energies provided will be somewhat uncertain. On the other hand, as we are comparing energies of two isomers, the error related to entropy is likely to be negligible.

The COSMO method (COnduction-like-Screening-MOdel)[27] installed in the DMol Package (version 950 on an SGI Power Onyx VTX)[28] was applied to study the solvent effects on the dianions. In COSMO, the solute is situated in a cavity, inside the homogeneous dielectric continuum of the solvent. There are both electrostatic and non-electrostatic interactions between solute and solvent. Both dianions were surrounded by simulated water molecules in the calculations. The numerical values for the input parameters were those given by the program for water as default.

Restricted Hartree–Fock calculations for the NBO analyses[25] of **2** and **3** optimized at the DN level were carried out with the Gaussian 94 program with the 6-31G basis set. The same basis was used for the ^{13}C NMR chemical shift calculations by applying the Gauge-Independent Atomic Orbitals (GIAO)[26] method. For the purposes of the NBO analysis and determination of the ^{13}C chemical shifts we did not reoptimize the structures of **2** or **3** (optimized at the DN level using DMol) using Gaussian. Therefore, results related to the NBO analysis and determination of the chemical shifts should be considered only as estimates. A reference for the chemical shifts was obtained by optimizing the structure of TMS by DFT methods[17–20] and by subsequent GIAO calculations [TMS (optimized at the DN level using DMol v2.2, GIAO at the 6-31G level) $^{13}C = 206.1$ ppm; TMS (optimized at the DN level using DMol v2.36, GIAO at the 6-31G level) $^{13}C = 205.9$ ppm; TMS (optimized at the DN level using DMol v2.36, GIAO at the 6-31G** level) $^{13}C = 200.1$ ppm; TMS (optimized at the DNP level using DMol v2.36, GIAO at the 6-31G** level) $^{13}C = 200.3$ ppm, respectively].

In order to assess the performance of the computational methods used we carried out (using DMol)[17–20] a limited geometry optimization of one of the complexes at the much more demanding DNP level. The optimization was limited in that the exact positions of the rotating methoxy groups were not determined (the molecular skeleton together with all hydroxy groups was fully optimized). The rationale of this limitation assumes that the energies related to the rotation of C–O bonds of ethers are small. Therefore, a potentially lengthy and computationally expensive optimization of the position the rotating methoxy groups would provide us with only a minimal decrease of the total energy of the complex. Chemical shifts of the partially optimized structure were then calculated using the Gaussian 94 package[24,26] at the HF/6-31G and HF/6-31G** levels.

Initial structures of **2** and **3** were generated using Chem3D Plus (Cambridge Scientific Computing, Inc., Cambridge, Mass.). Because the energy minimization of these charged systems (**2** and **3**) was not directly achievable using Chem3D Plus, neutral analogs of **2** and **3** (carbons in place of the borons) were constructed and optimized by use of standard molecular mechanics. For the DFT calculations, the carbons (of the optimized analogs) were changed back to borons. We considered this approach reasonable because Norrild *et al.*[19] report the structure of the diboronate (**3**) to resemble that of neutral carbon analogs.

Results

The optimized structures of **2** (in a vacuum and in water, Fig. 1) resemble that proposed by Tsukagoshi and Shinkai.[14] The same conclusion can be drawn when the optimized structures of **3** (in vacuum and in water, Fig. 2) are compared with that suggested by Norrild and Eggert (Scheme 1).[13] Interestingly, despite the considerable topological difference between the structures of **2** and **3** the difference in total energies of **2** and **3** was only

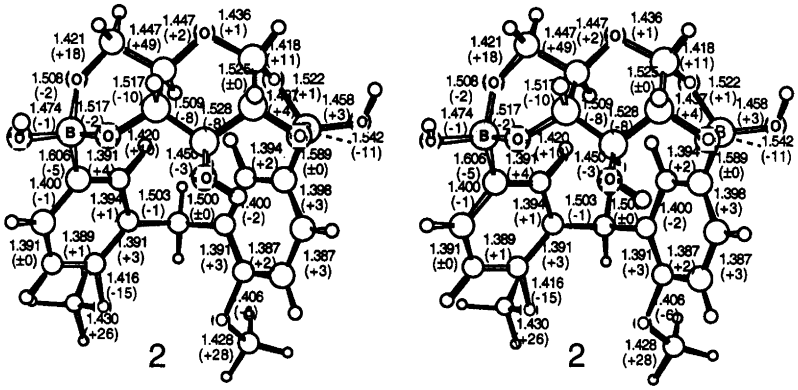


Fig. 1. Stereoscopic view of the optimized structure of **2**. Some of the most important bond lengths (in Å) are shown. Changes in the bond lengths observed with inclusion of solvent effects (using the COSMO model) are shown in parentheses (positive/negative signs indicate lengthening/shortening of the bonds). In a vacuum the energy of **2** was −1604.16260 a.u. and the dipole moment 16.8 D (DMol). In water the corresponding values were −1604.48016 a.u. and 13.5 D, respectively.

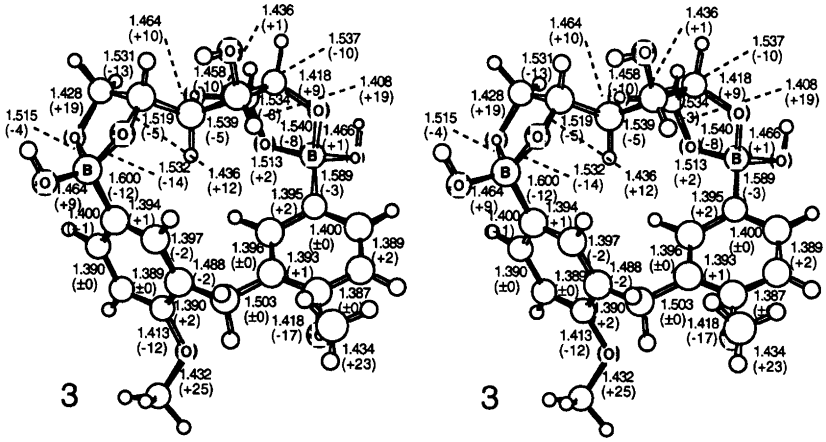


Fig. 2. Stereoscopic view of the optimized structure of **3**. Some of the most important bond lengths (in Å) are shown. Changes of the bond lengths observed with inclusion of solvent effects (using the COSMO model) are shown in parentheses (positive/negative signs indicate lengthening/shortening of the bonds). The energy of **3** was −1604.16157 a.u. and the dipole moment 12.6 D (DMol). In water the corresponding values were −1604.47858 a.u. and 12.4 D, respectively.

0.65 kcal mol^{-1} in a vacuum (Figs. 1 and 2). This corresponds to a relative ratio of 66:34 for **2**:**3** (at 300 K) indicating the isomer proposed by Shinkai *et al.* to be favored over that of Norrild *et al.* In water the ratio **2**:**3** (i.e. 84:16) is even more favorable to **2** ($\Delta E_{2,3} = 1.0$ kcal mol^{-1}; Figs. 1 and 2). The contribution of non-electrostatic energies was negligible (and similar in the case of both **2** and **3**) and therefore it was not taken into consideration.

A comparison of the calculated ^{13}C NMR shifts of the structures of **2** and **3** (suggesting the opposite relative abundance of **2** and **3**) optimized (in a vacuum and in water) at the DN level are shown in Fig. 3. The influence of the quality of computational methods (DN vs. DNP) on the goodness of the calculated ^{13}C NMR shifts was assessed as depicted in Fig. 4.

Discussion

Structure and solvation of **2** *and* **3**. On the basis of bond lengths (calculated in a vacuum and in water) the aromatic rings of **2** (Fig. 1) are very similar to those of **3** (Fig. 2). The maximum deviation of the lengths of aryl C–C bonds is 0.004 Å [the C1–C2 bond of **2** is 0.004 Å (in a vacuum) longer than that of **3**]. The planes of the aromatic rings of **3** (Fig. 2) appear to be almost in a perpendicular arrangement whereas those of **2** (Fig. 1) lie more 'symmetrically' [the torsion angles C(2)–C(1)–C(α)–C(1′) and C(2′)–C(1′)–C(α)–C(1) of **3** are −168.5° and +94.4°; the corresponding values of **2** are +87.5° and −112.3°, respectively]. The borons of **2** and **3** appear to be highly sp^3-hybridized ($B_{1,2\text{-coord}}$ of **2** is sp$^{2.9}$-hybridized whereas the other borons are all fully sp^3-hybridized).[29,30] Inspection of the changes of bond lengths of **2** (Fig. 1) and **3** (Fig. 2) reveals that changing the conditions of these anions from a vacuum to water does not affect bonding in either the aromatic rings or the bridge (C_α) connecting the rings, but does in the neighborhood of the heterocyclic 5- and 6-rings and methoxyl (and hydroxy) groups.

The lengths of the B–O bonds (calculated in a vacuum) of the borolane 5-rings of **2** (Fig. 1) and **3** (Fig. 2) vary

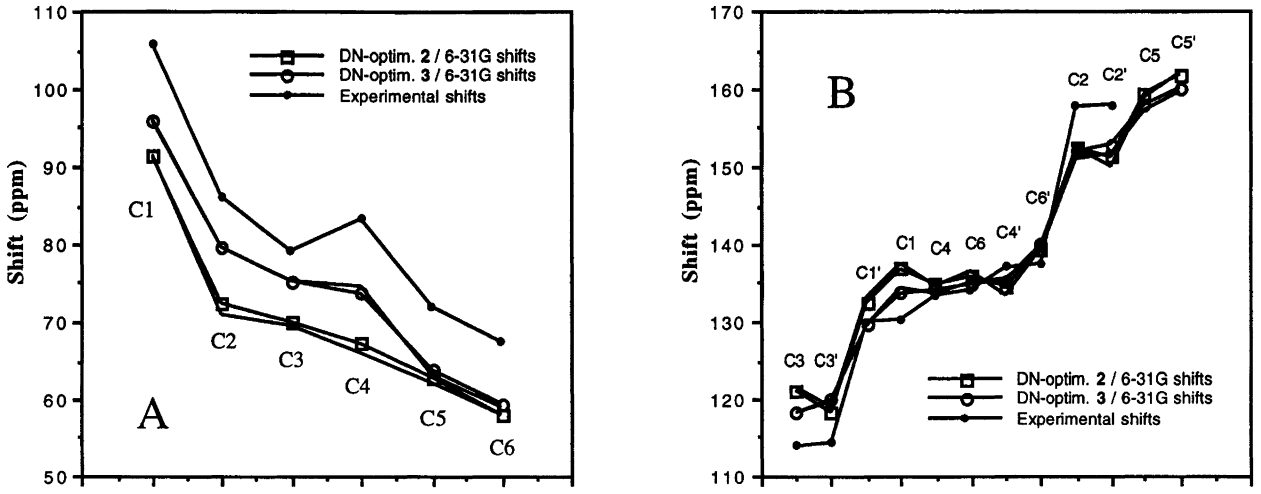


Fig. 3. Correlation of the calculated ^{13}C NMR chemical shifts (GIAO/HF/6-31G) of **2** (Fig. 1) and **3** (Fig. 2) with the measured shifts. (**A**) Shifts of the sugar moiety. (**B**) Shifts of the phenyl rings. Lines without the dots indicate the effect of solvation (shifts of the structures optimized with COSMO).

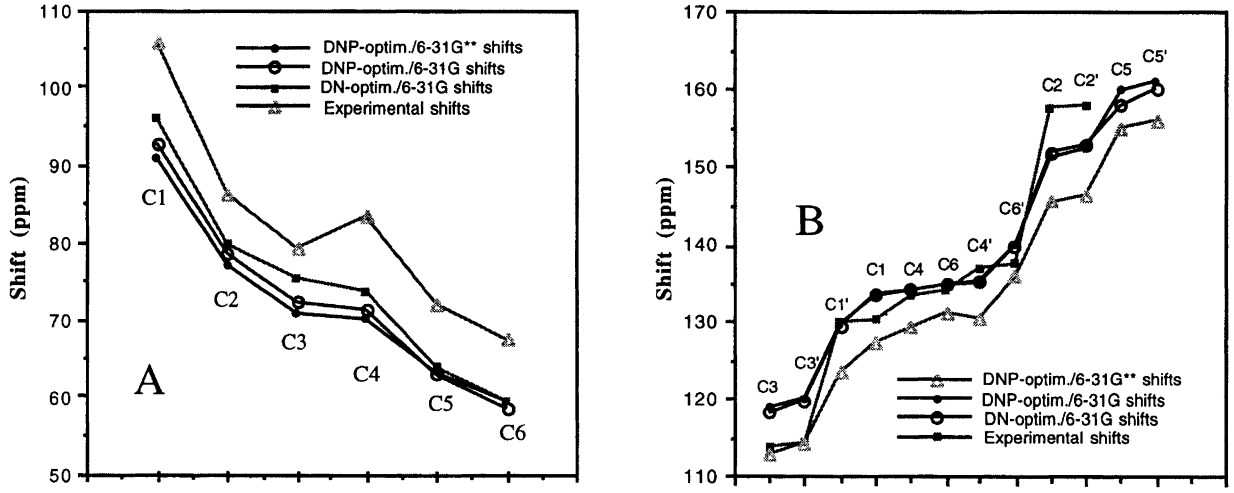


Fig. 4. Correlation of the calculated ^{13}C NMR chemical shifts of **3** with the measured shift. (**A**) Shifts of the sugar moiety. (**B**) Shifts of the phenyl rings.

more [one of the bonds is always 0.020 ± 0.003 Å longer than the other (adjacent) bond] than the corresponding bonds of the 6-ring (1.512 ± 0.005 Å, Fig. 1) of **2**. On the other hand, the B–O_{OH} bond of the 4,6-boronate of **2** (1.474 Å) is longer than the corresponding bonds of the 1,2- and 5,6-boronates of **2** and **3** (all within 1.462 ± 0.004 Å). Despite these differences, changes in the lengths of the B–O bonds related to solvation are surprisingly similar in the case of both **2** and **3**. Average changes of the lengths of B–O bonds (Figs. 1 and 2) of the boronate groups fall all in the range -0.007 ± 0.002 Å, respectively. This (i.e. shortening of the B–O) implies that solvation strengthens the B–O bonds. The adjacent C–O bonds, however, appear to lengthen.

Solvation-related lengthening of the C6–O bond (of **2** and **3**) is larger than that of the C5–O (of **3**) or C4–O (of **2**) bond. Analogously the change in the length of the C1–O bond is larger than that of the C2–O bond (in the case of both **2** and **3**). These observations could be rationalized in the light of steric crowding related to these bonds; the C6–O and C1–O bonds are more exposed to the solvent (and can interact more favorably with the electric dipoles of the solvent) than are the C5–O (of **3**), C4–O (of **2**) or C2–O bonds. Furthermore, strengthening of the B–O bonds and weakening of the adjacent C–O bonds indicates that the solvent enhances the anionic nature of the boronate groups (i.e. the groups which were the most negative in a vacuum will be even more negative in water). If the anionic nature of the boronate groups (of **2** or **3**) increases, then electronic repulsion in the rest of the structure (of **2** or **3**) should decrease and the bonds being influenced by the decrease should shorten. Indeed, all C–C bonds of the sugar moieties of **2** (Fig. 1) and **3** (Fig. 2) shorten (except the C5–C6 and C1–C2 bonds of **2**) when **2** and **3** are

transferred from a vacuum to water. In contrast with the C–C bonds, C–O bonds of the pyranose and furanose rings lengthen.

The above discussed similarity between the structures of **2** and **3** is consistent with the close similarity of the energies of **2** and **3**. Although this conclusion might appear as contradictory to the previous observations[13] that 5-rings are favored over 6-rings in the formation of tetrahedral boronates, the result indicates only that effects other than the electron distribution between the boron and oxygen atoms are responsible for the observed favorability of formation of the 5-rings.

Charge distributions of **2** *and* **3**. Hardly anything is known in the literature about the electronic structure of dianionic complexes such as **2** or **3**. Therefore, and in order to gain a better insight into the solvent–complex interactions, we inspected the charge distributions of **2** and **3**. A rough[25] NBO analysis [single point calculations at the HF/6-31G level, Table 1] of **2** and **3** indicates the absence of short-range intramolecular interactions (including hydrogen bonds). Furthermore, the small difference in energies of **2** and **3** indicates that intramolecular interactions must be similar in the case of both complexes (our NBO calculations do not take into account intermolecular interactions). The highest occupied molecular orbital (HOMO) can be located in one of the aromatic rings in the case of both **2** (the highest density on C1, C5, and C6) and **3** (the highest density on C4, C5, and C6). The negative charges of the C3, C3′, C4, C4′, C6 and C6′ atoms of the phenyl rings of **3** and **2** were substantially higher than those of the other atoms of the aromatic systems. E_{HOMO} of **3** is 0.35 eV less negative than that of **2**. Solvation, however, appears to equalize these energies; charges on the oxygens of **2** (Table 1) change more than those of **3** and E_{HOMO} of **3** (calculated using the COSMO model) is 0.16 eV more negative than that of **2**.

The difference in the negative charges of the phenyl groups was found to be considerably higher in **2** (than in **3**). Also the phenyl group of the 4,6-bound boronate of **2** appeared to be less negatively charged than the 1,2-bound one. In **3** the relative order of polarity of the groups is the opposite of that of **2**. This implies that the phenyl group which is more exposed to the solvent would, not surprisingly, be bearing more negative charge than the less exposed one. Nevertheless, the most ionic bonds of **2** and **3** appear to be the B–O bonds (e.g. the electron density of the $B–O_{C5}$ bond of **3** is shared between the boron and oxygen atoms in a ratio of 17 : 83).

The oxygens of B–OH groups are the most negatively charged atoms of **2** and **3** (in a vacuum and in water, Table 1). Interestingly, differences in the negative charges of the B–OH groups disappear as a consequence of solvation. Namely, the difference in the charges of the 1,2-bound boronates of **2** and **3** is 0.024 (i.e. 0.639–0.615, Table 1) in a vacuum but only 0.006 [i.e. (0.639 + 0.098) – (0.615 + 0.116), Table 1] in water. The corresponding differences of the 4,6- and 5,6-bound boronates are 0.038 (in a vacuum) and 0.006 (in water).

On the basis of both NBO analysis and inspection of atomic charges the 1,2-bound boronate is predicted to be less Lewis acidic and therefore to interact less with the counter ions than the 4,6- or 5,6-bound ones. However, on the basis of NMR studies, Norrild and Eggert propose that the 1,2-bound boronic acid derivatives of glucose are more stable than the others.[13] Our results are consistent with that proposal in that, as the 4,6- or 5,6-bound boronates can interact more with counter ions, the propensity of 4,6- and 5,6-bound

Table 1. Total atomic charges (Q)[a] and binding energies (E)[b] of the lone pairs[c] of the oxygen atoms of **2** and **3**.

	Environment							
	In vacuum				COSMO (rel. to vacuum)			
Atom	$Q(\mathbf{2})$[a]	$Q(\mathbf{3})$[a]	$E_{LP}(\mathbf{2})$[b]	$E_{LP}(\mathbf{3})$[b]	$Q(\mathbf{2})$[d]	$Q(\mathbf{3})$[d]	$E_{LP}(\mathbf{2})$[d]	$E_{LP}(\mathbf{3})$[d]
O_1	−0.458	−0.440	−6.23	−5.82	−0.075	−0.102	+0.16	+0.16
O_2	−0.476	−0.470	−5.74	−5.52	−0.063	−0.084	+0.07	+0.08
O_3	−0.514	−0.553	−6.97	−7.81	−0.087	−0.063	+0.07	−0.03
O_4	−0.492	−0.363	−5.31	−6.91	−0.074	−0.052	+0.34	+0.18
O_5	−0.333	−0.479	−7.13	−5.55	−0.052	−0.074	+0.12	+0.13
O_6	−0.474	−0.490	−5.20	−5.28	−0.102	−0.090	+0.05	+0.22
$O_{B1,2}$ (OH)	−0.615	−0.639	−5.74	−5.61	−0.116	−0.098	+0.17	+0.16
$O_{B4,6}$ (OH)	−0.656	—	−5.12	—	−0.090	—	+0.10	—
$O_{B5,6}$ (OH)	—	−0.618	—	−5.42	—	−0.122	—	+0.17
O_{Me2}	−0.368	−0.429	−8.06	−9.12	−0.094	−0.041	−0.33	−0.61
$O_{Me2'}$	−0.390	−0.391	−8.05	−8.95	−0.080	−0.080	−0.06	−0.15
Sum of charges:	−4.776	−4.872	—	—	−0.833	−0.806	—	—

[a]Calculated at the DN-level using DMol. [b]On the basis of NBO analysis. Energies given in electron volts (eV). The HOMO-1 and HOMO-2 energies of **2** were −4.16 and −4.49 eV (−2.32 and −2.67 eV in water); the corresponding values of **3** were −3.81 and −4.35 eV (−2.48 and −2.59 eV in water). [c]The value of the more Lewis basic one of the two lone pairs of each oxygen. [d]The values given are relative to those calculated in a vacuum; negative/positive sign indicates that the negative value increases/decreases.

boronates to participate in hydrolytic cleavage reactions (leading to the opening of the cyclic boronate system) would be higher than that of the 1,2-bound ones.

NMR shifts of **2** *and* **3**. To assess the structures of **2** (Fig. 1) and **3** (Fig. 2) in the light of the experimental data (^{13}C NMR chemical shifts of a glucose complex of **1**)[13] a graphical presentation of the shifts was constructed (Fig. 3).

The calculated shifts of **3** are clearly and systematically closer to the measured ones than are those of **2** are, suggesting the structure proposed by Norrild and Eggert[13] to be that formed as glucose reacts with 2,2′-dimethoxydiphenylmethane-5,5′-diboronic acid **1**. This results in a conclusion different from that drawn on the basis of the relative energies of **2** and **3**. On the other hand, the difference in the energies (0.65 kcal mol^{-1} in a vacuum) of **2** and **3** does not have to be particularly high (4–5 kcal mol^{-1} would be enough to decrease the concentration of the less favored isomer to the level at which it cannot be detected by NMR spectroscopy). As the shifts calculated for the structures (of **2** and **3**), optimized with inclusion of the COSMO model, deviate only a few ppm units from the corresponding values calculated in a vacuum (Fig. 3), the systematic error (i.e. the difference between the calculated and measured shifts; Fig. 3) is probably attributable to the missing counter ions (because of limited computational resources counter ions were not taken into account).

Assessment of the calculated chemical shifts could be based on the experimental data of **3** (**2**) and the related dianionic and neutral *p*-tolylboronates (two monodentate *p*-tolylboronates reacting with one glucose) reported[2c] by Norrild *et al.* A comparison of the ^{13}C-chemical shifts of the glucose moieties of **3** (**2**) with the neutral and dianionic *p*-tolylboronates indicates that the chemical shift of C2 is relatively insensitive to environmental effects. The C2 shift of **3** (**2**) has been measured to be 86.1 ppm whereas the corresponding values of the dianionic *p*-tolylboronate and its neutral analog were 85.7 and 85.8 ppm.[13] While the measured values (of neutral and dianionic species) differ by less than 0.5 ppm, our calculated shifts of C2 of **2** and **3** differ by 7.1 ppm (the calculated shift of C2 of **3** differs from the experimental one by 6.5 ppm). Therefore, we believe that the difference between the calculated shifts is genuine.

Evaluation of the performance of the computational methods. In order to assess the reliability of the results leading to the above conclusion (drawn on the basis of chemical shifts) the partially optimized (at the DNP level) structure of **3** was inspected. The structural changes observed as the structure of **3** (optimized at the DN level; Fig. 2) was optimized further (partial optimization to the level at which only some gradients related to the rotation of the methoxy groups were slightly higher than the threshold value of DMol) at the higher (DNP) level were small. The overall shape of the complex was retained. A comparison of the bond lengths of **3** (Fig. 2) with those of the partially optimized structure revealed that the (polar) B–O and C–O bonds shorten slightly (max. shortening 0.035 Å), the B–C bonds lengthen slightly (max. lengthening 0.024 Å), the C–C bonds of the sugar moiety hardly change (max. change 0.012 Å), and the C–C bonds of the phenyl groups are practically not affected at all (max. change 0.003 Å).

Results of the partial optimization of **3** at the JMW/DNP level were also evaluated by calculating the ^{13}C NMR chemical shifts[26] of **3** at the HF/6-31G and HF/6-31G** levels. A comparison of the shifts of the sugar moiety of **3** is shown in Fig. 4.

The chemical shifts calculated at the JMW/DNP//RHF/6-31G** level deviate systematically more from the experimental ones than the related values calculated at the JMW/DN//RHF/6-31G or JMW/DNP//RHF/6-31G levels (Fig. 4). The chemical shifts of the phenyl groups calculated at the JMW/DNP//RHF/6-31G** level deviate particularly from the measured ones and other calculated shifts (Fig. 4).

Although the results depicted in Fig. 4 look strange the variation of the chemical shifts calculated at different levels of theory is clearly less than the difference between the values of isomers (**2** and **3**). This is particularly true for C2, of which the chemicals shifts vary only within 78.3 ± 1.3 ppm (Fig. 4). The significance of C2 has been discussed above in the context of the general assessment of the predictive value of the calculated chemical shifts. On the other hand, although the differences of the ^{13}C shifts can be related to the quality of basis sets to describe the dianionic structures of **2** and **3** the differences might, however, reflect the possibility that neither **2** nor **3** corresponds to the real structure of the glucose–**1** complex formed under basic conditions. Furthermore, the surprisingly small difference (only about 1.0 kcal mol^{-1}) of the relative energies of **2** and **3** supports this conclusion. Namely, NMR spectrometric studies reveal that there will be only one complex formed when glucose reacts with **1** under basic conditions whereas the small difference in energies between **2** and **3** suggests that both **2** and **3** should be seen in an NMR experiment (detection limit normally about 5%).

As the ^{13}C shifts of the aromatic moieties [Fig. 3(B) and Fig. 4(B)] deviate much less from the measured ones, we may conclude that our results related to the aromatic counterparts of **2** and **3** describe much more closely the real structure of the glucose complex of **1** (than does the sugar moiety). Therefore, the conformation and/or topology of the glucose moiety of the real complex could be different from that of **2** or **3**. Furthermore, the results related to the aromatic counterparts indicate that the computational methods we have used are suitable for dianionic structures such as **2** and **3**.

Conclusions

Results of this work indicate that the doubly negatively charged complexes **2** and **3** of glucose and 2,2′-

dimethoxydiphenylmethane-5,5′-diboronic acid **1** have closely similar energies of formation (in a vacuum and in water). Therefore, which of the dianionic structures (**2** or **3**) is formed (or predominates) in a mixture of glucose, **1**, and an inorganic base will apparently be determined partly by the nature of the counter ions (i.e. the cationic moiety of the base). In this light it would appear that one could construct molecular sensors which (with appropriately chosen topology and rigidity of the molecular skeleton of the sensor) could recognize glucose selectively either in furanose or in pyranose form.

Both in water and in a vacuum (in both cases in the absence of counter ions) the ^{13}C NMR shifts of **3** correspond better to the related experimental data reported by Norrild and Eggert.[13] Nevertheless, results of this study also suggest that the conformation and/or topology of the glucose moiety of the real complex could be different from that of **2** or **3**. In order to reveal the correct structure of the complex glucose forms with **1** under basic conditions one should inspect hundreds of topological isomers and conformers. That would require tremendous computational resources which were not available for us for this study. Further studies on the structure and function of these molecular sensors for the (enantio)selective discrimination of biologically significant molecules are in progress.

Acknowledgments. The Physics Computation Unit (DEC 3000 M400 Alpha; University of Helsinki), the Computing Center (VAX 6000–610; University of Helsinki) and The Center of Scientific Computing (Cray X-MP, Convex C3840 and SGI Power-Challenge, Computing Center of the Finnish State) are acknowledged for providing computational resources needed to carry out this study. We are grateful to Dr. Tuija Raaska (The Center of Scientific Computing) for her help related to the use of DMol.

References

1. Arimori, S., Takeuchi, M. and Shinkai, S. *J. Am. Chem. Soc. 118* (1996) 245.
2. Riggs, J. A., Litchfield, R. K. and Smith, B. D. *J. Org. Chem. 61* (1996) 1148.
3. Uggla, R., Sundberg, M. R. and Nevalainen, V. *Tetrahedron: Asymm. 7* (1996) 1741.
4. James, T. D., Sandanayake, K. R. A. S. and Shinkai, S. *Angew. Chem., Int. Ed. Engl. 35* (1996) 1910.
5. Sarson, L. D., Ueda, K., Takeuchi, M. and Shinkai, S. *J. Chem. Soc., Chem. Commun.* (1996) 619.
6. Suenaga, H., Arimori, S. and Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* (1996) 607.
7. Takeuchi, M., Mizuno, T., Shinmori, H., Nakashima, M. and Shinkai, S. *Tetrahedron 52* (1996) 1195.
8. James, T. D., Shinmori, H., Takeuchi, M. and Shinkai, S. *J. Chem. Soc., Chem. Commun.* (1996) 705.
9. James, T. D., Shinmori, H. and Shinkai, S. *J. Chem. Soc., Chem. Commun.* (1997) 71.
10. Kondo, K., Shiomi, Y., Saisho, M., Harada, T. and Shinkai, S. *Tetrahedron 48* (1992) 8239.
11. James, T. D., Sandanayake, K. R. A. S. and Shinkai, S. *Nature 374* (1995) 345.
12. Suenaga, H., Mikami, M., Sandanayake, S. and Shinkai, S. *Tetrahedron Lett. 36* (1995) 4825.
13. Norrild, J. Chr. and Eggert, H. *J. Am. Chem. Soc. 117* (1995) 1479.
14. Tsukagoshi, K. and Shinkai, S. *J. Org. Chem. 56* (1991) 4089.
15. James, T. D., Sandanayake, K. R. A. S., Iguchi, R. and Shinkai, S. *J. Am. Chem. Soc. 117* (1995) 8982.
16. Imada, T., Kijima, H., Takeuchi, M. and Shinkai, S. *Tetrahedron 52* (1996) 2817.
17. DMol, User Guide, Version 2.2, Biosym Technologies, San Diego, CA 1992.
18. DMol, User Guide, Version 2.3, Biosym Technologies, San Diego, CA 1993.
19. DMol, User Guide, Version 2.36, Biosym Technologies, San Diego, CA 1994.
20. DMol, Biosym Technologies on Internet: *www.biosym.com.*
21. Ziegler, T. *Chem. Rev. 91* (1991) 651.
22. Llamas-Saiz, A. L., Foces-Foces, C., Mo, O., Yanez, M., Elguero, E. and Elguero, J. *J. Comput. Chem. 16* (1995) 263.
23. Trickey, S. B. In: Kryachko, E. S. and Calais, J. L., Eds., *Conceptual Trends in Quantum Chemistry*, Kluwer Dordrecht 1994.
24. GAUSSIAN 94, Revision B.1, Frisch, M. J., Trucks, G. W., Schlegel, H. B., Gill, P. M. W., Johnson, B. G., Robb, M. A., Cheeseman, J. R., Keith, T., Petersson, G. A., Montgomery, J. A., Raghavachari, K., Al-Laham, M. A., Zakrzewski, V. G., Ortiz, J. V., Foresman, J. B., Cioslowski, J., Stefanov, B. B., Nanayakkara, A., Challacombe, M., Peng, C. Y., Ayala, P. Y., Chen, W., Wong, M. W., Andres, J. L., Replogle, E. S., Gomperts, R., Martin, R. L., Fox, D. J., Binkley, J. S., Defrees, D. J., Baker, J., Stewart, J. P., Head-Gordon, M., Gonzalez, C. and Pople, J. A. Gaussian, Inc., Pittsburgh, PA 1995.
25. Carpenter, J. E. and Weinhold, F. *J. Mol. Struct. (Theochem) 169* (1988) 41; NBO is a subprogram in GAUSSIAN 94.
26. Wolinski, K., Hilton, J. F. and Pulay, P. *J. Am. Chem. Soc. 112* (1990) 8251; the GIAO method is implemented in GAUSSIAN 94.
27. Klamt, A. and Schüürmann, G. *J. Chem. Soc., Perkin Trans. 2* (1993) 799.
28. Dmol 95.0, User Guide, Version 3.0.0, Biosym Technologies, San Diego, CA 1995.
29. Determined on the basis of bond angles of the boron atoms as described in the literature [e.g. Nevalainen, V., Uggla, R. and Sundberg, M. *Tetrahedron: Asymm. 6* (1995) 1431].
30. van den Berg, R., Peters, J. A. and van Bekkum, H. *Carbohydr. Res. 253* (1994) 1.

Received March 6, 1998.