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Boronic Acids as Molecular Sensors

NBO Analysis and ^{13}C Chemical Shifts as Tools for Evaluation of DFT Geometry Optimization of Complexes of Diphenylmethane 3,3'-Diboronic Acids and Glucose

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Abstract: - Studies on the formation of bisdentate complexes of diphenylmethane-3,3'-diboronic acid **1** and glucose were carried out using DFT methods. A 1,2- and 5,6-coordinated complex (*i.e.* **2**) was chosen (on the basis of a recent NMR spectroscopic study) as a most probable model of plausible isomeric structures which **1** could form as reacting with hydroxylic positions (total of 5) of glucose (in the furanose form). The optimized structure of **2** was found to be closely similar to that proposed on the basis of the earlier NMR study. The calculated ^{13}C NMR shifts were closely similar to the measured ones. A more glucose selective analog of the sensor **1** was proposed.

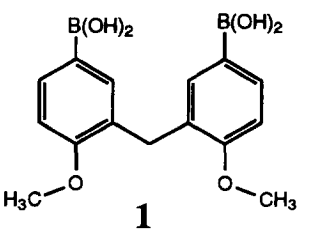
INTRODUCTION

During this decade, there has been a continuously growing interest in the use of boronic acids in the construction of molecular devices such as carriers for membrane transport, solid supports for chromatography, enzyme inhibitors, and chemosensors (molecular sensors).[1] In the field of molecular sensors, aromatic boronic acids (e.g. **1**; Scheme I) have shown great potential in the (enantio)selective recognition of sugars (*e.g.* based on the formation of chiral analogs of diboronate **2**; Scheme I) in aqueous solution.[1,2] Recently, discrimination of very 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.[3]

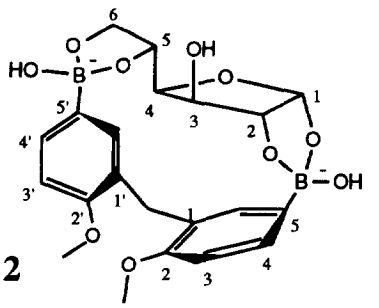
In the case of enantioselective recognition of sugars a sensor molecule is required to have two chelating functional groups.[2a] These groups can be either boronic acids or a boronic acid and a metal chelate (*e.g.* a metalloporphyrin)[3] possessing Lewis acidic properties. Detection of the formation of these complexes is normally based on the change of the coordination of one or both of the chelating groups.[2a] In the case of boronic acids, two of the boronate hydroxyl groups would be alkylated (formation of a 1,3-dioxaborolane ring) and, furthermore, in the presence of strong nucleophiles, the nucleophile adds to the Lewis acidic boron of the newly formed dioxaborolane ring.[2a] In consequence of the addition, the empty 2p-orbital of the dioxaborolane (of which the boron was able to interact with the adjacent aromatic π-system) would be occupied by the electron pair donated by the coordinating base (2p - π interactions decrease substantially).

Therefore, as the 2p - π interaction is not possible in the tetrahedral adduct, polarization of the π-electron system of the adjacent aryl group will decrease. This change of polarization can be detected using spectroscopic (*e.g.* circular dichroism or fluorescence spectroscopy)[2a,2d] methods.

Scheme I



1



2

Although the formation of boronic acid derivatives of diols has been known for almost 50 years and crystal (and molecular) structures of many boronate esters of polyols (trigonal geometry of boron in the absence of coordinating Lewis bases) have been determined by X-ray diffraction, structures of these complexes in solution are poorly characterized and still a matter of debate.[2] As one of the recent attempts to determine a solution structure of a bisdentate boronate complex of a sugar, the NMR study of a glucose complex of 2,2'-dimethoxydiphenylmethane-5,5'-diboronic acid **1** was carried out by Norrild and Eggert (Scheme I).[2c] The complex was proposed to have a structure corresponding to that of **2** (Scheme I). This doubly negatively charged complex (*i.e.* **2**) poses many interesting questions: 1) can the charge be localized in some atom(s), and if not, how is the charge delocalized then; 2) what is the role of the phenyls (Shinkai *et al.*[2a] have reported a very high circular dichroism of solutions of these complexes, originating from aromatic absorptions); 3) electronic structure of the boronate groups; 4) how stable is the macro cyclic ring of the diboronate in a conformation such as that of **2** [*i.e.* does the structure of **2** (Scheme I) represent a minimum of the energy hypersurface of the glucose complex of 2,2'-dimethoxydiphenylmethane-5,5'-diboronic acid **1**]. The aim of this work was to approach (the answers of) these questions using the methods of theoretical chemistry.

COMPUTATIONAL METHODS

The structure of **2** was optimized employing density functional (DFT) theories (at the DN level, using the Janak - Morruzi - Williams functional).[4] The program DMol (versions 2.2 and 2.3 on Convex C3840) was used in the DFT calculations.[4a-d] We turned to the Gaussian 94 package[5] in order to carry out an NBO analysis[6] of the electron structure of **2** (on Cray X-MP) because NBO analysis is not implemented in DMol. The structure of **2** (optimized using DMol)[4a-d] was used as such to perform the NBO analysis. The basis set (HF/6-31G) for the NBO analysis[6] was chosen to correspond (as closely as possible) to the description of electron structure obtained by DMol. In order to more thoroughly compare the optimized structure and the rough model proposed by Norrild and Eggert,[2c] ^{13}C NMR shifts of **2** were calculated[5,6] using Gaussian 94.[5] The chemical shifts were calculated at the HF/6-31G level of theory by applying the Gauge-Independent Atomic Orbitals

(GIAO) method. A reference of the ^{13}C shifts was provided in the same way as the shifts of **2** [shifts of the structure of tetramethylsilane (TMS) optimized (Dmol) without symmetry were calculated using Gaussian 94; the shifts averaged to 206.1 ± 0.25 ppm].

DFT methods were preferred in the structure optimization for several reasons. The DFT calculations include correlation, and the results are comparable to those obtained by MP2 level of theory. Since the complex **2** studied here is a dianion, the use of diffusion functions in *the ab initio* methods is obligatory. This in turn would require computational resources beyond those available. Moreover, the geometry optimizations [especially for electron-rich compounds, like metals, metal complexes and related (ionic) species][4c-d] obtained by DFT methods are generally considered to be more reliable than those calculated by *ab initio* methods.[4c-d]

RESULTS AND DISCUSSION

The optimized structure of **2** shown in Figure 1 resembles much that proposed by Norrild and Eggert (Scheme I).[2c] A comparison of the most important charges of the optimized structure of **2** is depicted in Figure 2. The calculated ^{13}C NMR shifts are shown (Fig. 3). A new glucose sensor was proposed (Fig. 4).

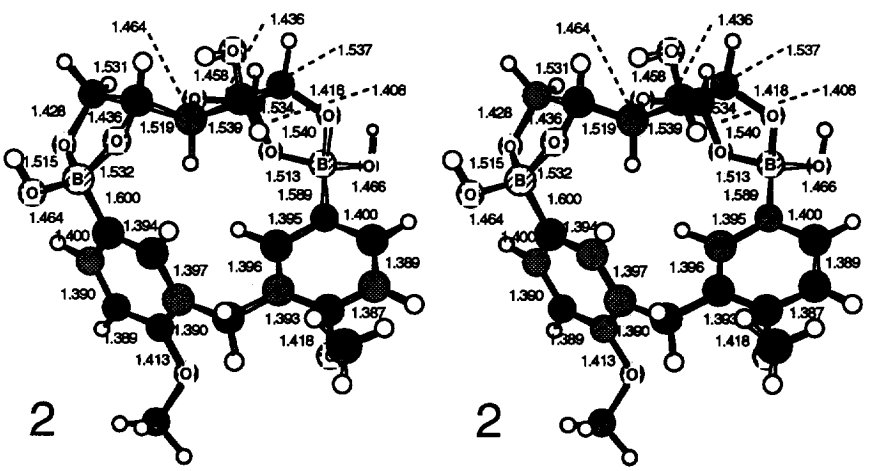


Figure 1. Stereoscopic view of the optimized structure of **2**. Some of the most importantbond lengths [in Å] are shown. The energy of **2** was -1604.161572 a.u. and the dipolemoment 12.6 debyes (DMol).

Structural characterization of 2: Being inspected on the basis of bond lengths both of the aromatic rings of **2** (Fig. 1, see the numbering in Scheme I) look very similar. The maximum deviation of the aryl *C-C* bonds is 0.003 Å (the *C1-C2* bond is 0.003 Å longer than the *C1'-C2'* one). Both of the aryls are also highly planar (maximum deviations of the aryl carbons from the plane of the aromatic rings was 0.008 and 0.009 Å, Fig. 2). The charge of the H_3CO-C_6H_3 moiety of the 5,6-coordinated boronate is only 0.039 units more negative than that of the 1,2-coordinated one (Fig. 2). Interestingly, the planes of the aromatic rings appear to be almost in a perpendicular arrangement [e.g. the torsion angles *C(2)-C(1)-C-C(1')* and *C(2')-C(1')-C-C(1)* of **2** are -168.5° and +94.4°, respectively (Fig. 1)]. However, although both of the borons of **2** appear to be equally and

highly sp^3-hybridized ($sp^3 : sp^2 = 87 : 13$, Fig. 2),[7] other factors related to the binding of the borons indicate more differences (than seen in the case of the aryl groups).

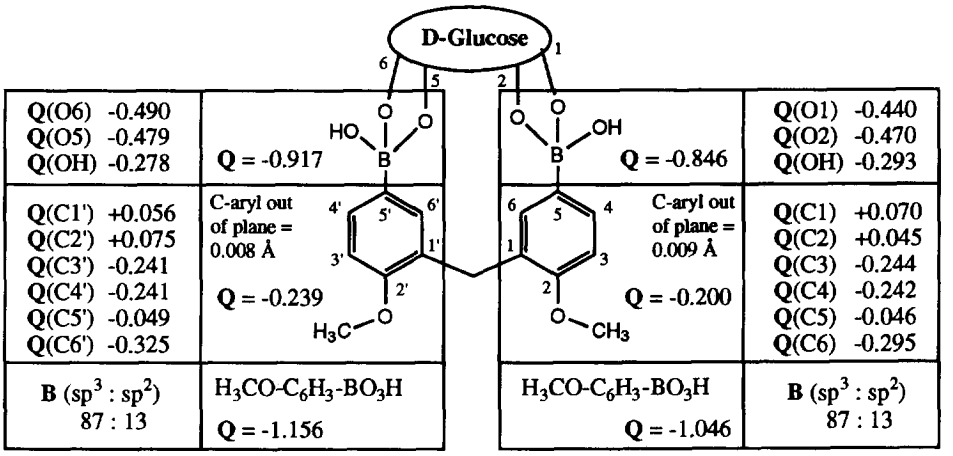
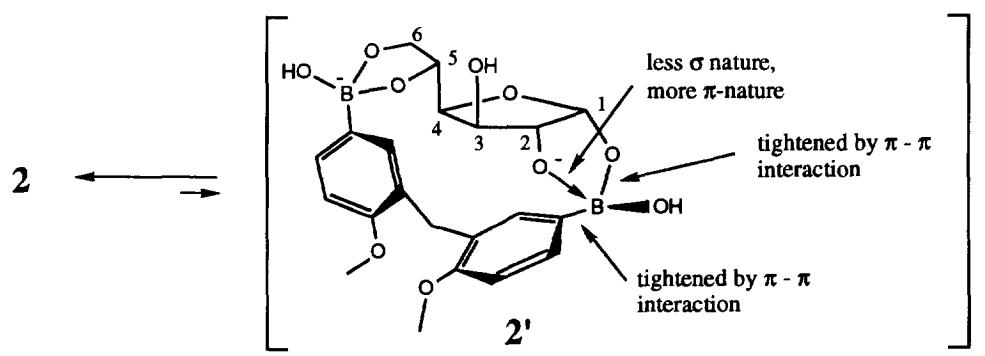


Figure 2. Selected atomic and other charges (obtained using DMol) of the optimized structure of **2**.

The *B-O* bond lengths of the borolane ring of the 1,2-coordinated boronate (of **2**) are mutually more dissimilar than those of the 5,6-coordinated one. The $B\text{-}O_{C1}$ bond of the 1,2-boronate is shorter than any other of the *B-O* bonds of **2** (as is the adjacent *C1-O* bond shorter than any other of the *C-O* bonds of **2**). The $B\text{-}O_{C2}$ bond of the 1,2-boronate, on the other hand, appears to be longer than any other of the *B-O* bonds of **2**. Therefore, it looks as if the *B-O* bonds closer to the outer surface of **2** (*e.g.* the $B\text{-}O_{C1}$ bond, Fig. 1) would be tighter than those (*e.g.* the $B\text{-}O_{C2}$ bond) buried into inner parts of the complex **2**. Interestingly, similar conclusions can be drawn as binding of the 5,6-coordinated boronate is inspected. The $B\text{-}O_{C5}$ bond (buried in) is longer than the $B\text{-}O_{C6}$ bond (near the outer surface, Fig. 2). The differences related to the $B\text{-}O_C$ bonds could be evaluated also on the basis of the resonance shown in Scheme II.

Scheme II



The resonance **2** <-> **2'** (Scheme II) could be rationalized in the light of the following observations: **a**) the $B\text{-}O_{C2}$ bond (resonance lengthens) is longer than any other of the *B-O* bonds of the borolane rings; **b**) the $B\text{-}O_{C2}$ bond is almost in a perpendicular (*e.g.* $O_{C2}\text{-}B\text{-}C_5\text{-}C_4 = 82.0°$) arrangement relative to the plane of the

adjacent phenyl ring [in contrast to the related bonds of the 5,6-coordinated boronate where the $B\text{-}O_{OH}$ bond is almost perpendicular (*e.g.* $O_{OH}\text{-}B\text{-}C_{5'}\text{-}C_{4'}$ = -97.5°) to the plane of the adjacent aromatic ring; Fig. 1] allowing electrons of the $B\text{-}O_{C2}$ bond to interact with the π-system of the aromatic ring; **c**) the $B\text{-}O_{C1}$ bond is shorter (resonance shortens) than any other of the *B-O* bond of the borolane rings; **d**) the $B\text{-}C_5$ bond (resonance shortens) is shorter than the $B\text{-}C_{5'}$ bond (no resonance, none of the $B\text{-}O_C$ bonds of the 5,6-coordinated boronate is perpendicular to the plane of the adjacent phenyl); **e**) the negative charge (Fig. 2) of the O_{C2} atom (resonance enhances) is higher than that of the O_{C1} atom (resonance diminishes); **f**) no separation of charges similar to that of O_{C1} and O_{C2} atoms (charges differ by 0.030, Fig. 2) can be seen in the case of O_{C5} and O_{C6} atoms (no similar resonance, charges differ by 0.011, Fig. 2).

There could be also other factors (*e.g.* strain) related to the differences of the $B\text{-}O_C$ bonds discussed above. A brief analysis of bond angles (of **2**) imply that there could be more strain related to the 1,2-coordinated boronate than to the 5,6-coordinated one. This strain can be seen best by comparing the *B-C-C* bond angles. The *B-C-C* angles (*B-C5'-C6'* = 121.8° and *B-C5'-C4'* = 121.0°) of the 5,6-coordinated boronate of **2** are almost equal whereas the related angles (*B-C5-C6* = 123.7° and *B-C5-C4* = 118.6°) of the 1,2-coordinated counterpart differ by 5.1 degrees! This strain could also lengthen the $B\text{-}O_{C2}$ bond (Fig. 1).

Natural Bond Orbital (NBO) analysis of **2**: A rough[6] NBO analysis [at the 6-31G level, single point calculation on the structure of **2** optimized using DMol[4]] indicates that there are no intramolecular hydrogen bonds in **2**. Within the framework of 3C bonding (*no B-C-C* bonds were found in the set 3C bonds) the weakest bond seems to be the *C4-C5-C6* bonds (HOMO). If the bonding is analysed on the normal 2C - 2e basis, the weakest bonds are the *C3-C4* (-0.096) and *C3'-C4'* (-0.094). All these carbons (*C3*, *C3'*, *C4*, *C4'*, *C6*, *C6'*) are bearing negative charges (Fig. 2) significantly higher than those of the other aromatic carbons (of which the *C1*, *C2*, *C1'* and *C2'* are positively charged, Fig. 2). This implies, that in the presence of cations (counter ions of **2** in a solution), interactions between the cations and the aromatic π-system are not all necessarily repulsive. Nevertheless, the most ionic bonds of **2** appear to be the *B-O* bonds (e.g. the electron density of the $B\text{-}O_{C5}$ bond is shared between the boron and oxygen atoms in the ratio of 17 : 83).

The resonance described in Scheme II (interaction of one of the 2p orbitals of the boron of the $B\text{-}O_{C2}$ bond with the adjacent aromatic π-system) is supported by the NBO analysis. The $B\text{-}O_{C1}$ bond is stronger (and the $B\text{-}O_{C2}$ bond weaker) than the other $B\text{-}O_C$ bonds. The NBO analysis also indicates that the $B\text{-}O_{C2}$ bond contains (from both of the boron and O_{C2} atoms) more 2p-functions (needed for the 2p - π interaction) and less 2s-functions (indicating weakened σ-interaction, Scheme II) than any of the related *B-O* bonds of **2**. Furthermore, lengthening of the $B\text{-}O_{C2}$ bond is related to the enhanced role of 2p-functions (in contrast to s-functions, p-functions are not centered to the atomic nucleus; therefore lengths of σ-bonds increase with increasing amount of p-functions). The length of $B\text{-}O_{C1}$ bond (shorter than any of the related *B-O* bonds) could be rationalized in the light of the NBO analysis (compositions of the $B\text{-}O_{C1}$, $B\text{-}O_{C5}$ and $B\text{-}O_{C6}$ bonds were all found to be very similar). Although the boron and O_{C1} atoms are forming a ($B\text{-}O_{C1}$) bond similar to the $B\text{-}O_{C5}$ *and* $B\text{-}O_{C6}$ bonds, the distance of the boron and O_{C1} atoms can be shorter because there would be less repulsion between the boron and O_{C1} atoms. The length of the $B\text{-}C_5$ bond (shorter than the $B\text{-}C_{5'}$ bond) can be rationalized in the same manner as that of the $B\text{-}O_{C1}$ bond discussed above [NBO analysis indicates that the *B-C* bonds have very similar compositions; i.e. the $B\text{-}C_5$ bond is shorter than the $B\text{-}C_{5'}$ bond because there would be less repulsion related to the former].

In addition to the analysis of *B-O* bonds discussed above, some interesting observations can be made related to the *C-O* bonds. Namely, not only was the $B\text{-}O_{C1}$ bond found stronger than the other $B\text{-}O_C$ bonds but also the the *adjacent* $C1\text{-}O_B$ bond is stronger than any of the other related $C\text{-}O_B$ bonds of **2**. Both of these observations imply, that 1,2-coordinated boronates would be more stable than the related 5,6-coordinated ones. Interestingly, on the basis of NMR studies on a number of boronic acid - glucose complexes Norrild and Eggert[2c] propose formation of the 1,2-coordinated boronic acid derivatives to be favoured over the others.

^{13}C NMR chemical shifts of 2: In order to compare the structure of **2** (Fig. 1) with that (Scheme I) proposed by Norrild and Eggert (^{13}C NMR chemical shifts of **2** reported)[2c] we calculated the ^{13}C shifts of **2**. The calculated shifts (compared with those reported by Norrild and Eggert)[2c] are shown in Figure 3. The maximum difference (10.0 ppm) can be seen in the value of *C1* of the glucose unit. Although the difference (9.6 ppm) related to the shift of *C4* is also near to the maximum difference, values of the other carbons are surprisingly similar to those reported by Norrild and Eggert.[2c] Therefore, it looks as if the calculated chemical shifts could support the proposed similarity of the optimized geometry of **2** and that predicted by Norrild and Eggert.[2c]

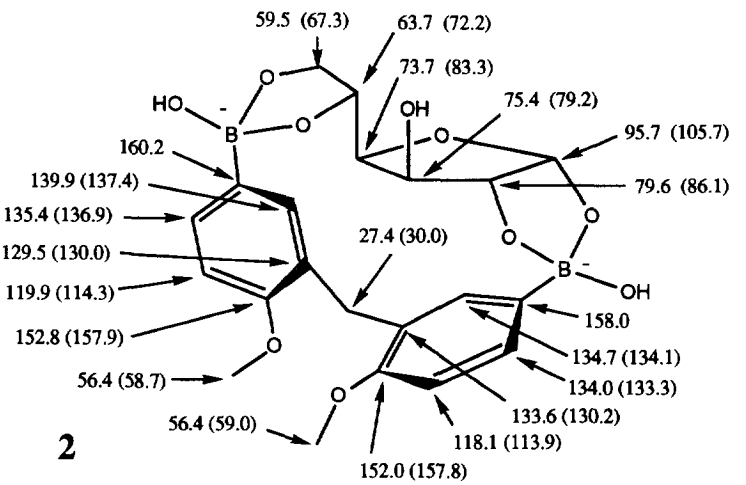
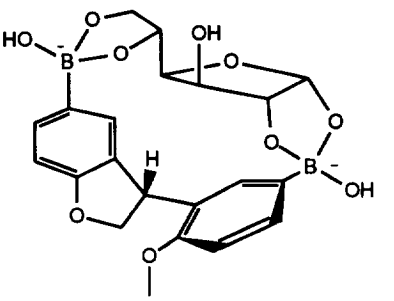


Figure 3. Calculated and measured (in parentheses, reported by Norrild and Eggert, ref. 2c) ^{13}C NMR chemical shifts [ppm] of **2**. Assignation of the shifts of 1,2- and 5,6-coordinated phenyls completed on the basis of these calculations.

CONCLUSIONS

Results of this work indicate that the doubly negatively charged complex **2** of glucose and 2,2'-dimethoxydiphenylmethane-5,5'-diboronic acid **1** can exist in a conformation which is structurally closely similar to that proposed earlier[2c] on the basis of an NMR study. Binding of the boronate on the 1,2-position of glucose was predicted to be tighter than that on the 5,6-position. The somewhat higher negative charge of the 5,6-coordinated boronate moiety (of **2**) located mainly in the oxygens adjacent to the borons (about 25% of the negative charge of the $H_3CO\text{-}C_6H_3\text{-}BO_3H$ moieties found in the phenyl groups) indicates that electronic properties of the 1,2- and 5,6-coordinated phenylboronates could be distinguishable. The equal sp^3:sp^2-

hybridization ratios of both borons of **2** indicate that (in the case of strong nucleophiles, e.g. hydroxyl anion) the differences in the electron distribution of the arylboronate groups would not be related to the hybridization of the boron centers, but more probably, to the differences of angle strain in the aryl - boronate junctions.



A

Figure 4. An analog (shown as a glucose complex **A**) of **1** proposed to functions as a molecular sensor potentially more efficient than the less rigid 2,2'-dimethoxydiphenylmethane-5,5'-diboronic acid **1**.

The geometry of the diboronic acid moiety of the optimized structure of **2** (Fig. 1) indicates that analogs (Fig. 4) of **1** could form chelates similar to **2**, but potentially more selectively [the geometry of the phenyl rings would be fixed (by the 5-ring) in the neighborhood of conformations feasible for the formation of the glucose adduct, Fig. 4]. Further studies on the structure and function of these tetradentate molecular sensors for the (enantio)selective discrimination of biologically significant molecules are in progress.

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6. For the purposes of the NBO analysis and determination of the ^{13}C chemical shifts we did not reoptimize the structure of **2** (optimized at the DN level using DMol) using Gaussian. Therefore, results related to the NBO analysis and determination of the chemical shifts could be considered only as estimates.
7. Determined on the basis of bond angles of the boron atoms as described in the literature (*e.g.* Nevalainen, V.; Uggla, R.; Sundberg, M. *Tetrahedron: Asymm.* **1995**, *6*, 1431).

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