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Influence of the diol structure on the Lewis acidity of phenylboronates

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A series of cyclic esters of pentafluorophenylboronic acid have been obtained and their Lewis acidity evaluated experimentally by a modified Gutmann method. The results based on ³¹P NMR measurements were compared with those determined by quantum mechanical calculations at the DFT-VSXC/pcS-2 level of theory. The differences in Lewis acidity are discussed on the basis of electronic and geometric parameters. The calculations revealed that the complexes of investigated esters with Et₃PO have multiple conformers of a wide range of calculated ³¹P NMR shielding constants. Additionally, a correlation between the calculated O-B-O angle of esters and the experimental acceptor number was found. Copyright © 2013 John Wiley & Sons, Ltd. Supporting information may be found in the online version of this paper.

Keywords: acceptor number; boronic esters; Laplacian; NMR shielding constants calculation

INTRODUCTION

The formation of cyclic esters in the reaction of phenylboronic acids with diols is the basis of their several beneficial applications, including sensing of biologically important species as probably the most spectacular one.^[1] The esterification reaction is useful in boronic unit protection, dopamine detection,^[2] affinity chromatography,^[3] and solid-state synthesis of saccharides.^[4] Other interesting applications of that process are the formation of self-repairing polymers^[5] or glucose-sensitive materials.^[6] Phenylboronic esters themselves are also very advantageous species. They usually display higher stability at elevated temperatures as well as increased solubility in organic solvents in comparison with phenylboronic acids.^[7,8] Phenylboronates are also stronger Lewis acids than the parent acids. All those issues result in wide applications of phenylboronates,^[9] including binding of electron-rich molecules, e.g. in fluoride anion sensing^[10,11] or anion complexation, improving properties of polymer electrolytes.^[12-14] The advantage of the use of phenylboronates over other anion complexing agents are: low expenses, lack of reactive groups (like -OH), and low toxicity.

The Lewis base complexation changes the geometry of the boron center from planar to tetrahedral. Therefore, the Lewis acidity of a trigonal organoboron compound depends on the degree in which its geometry is close to the tetrahedral one. This is related to the energy barrier of geometry conversion (planar to tetrahedral). The dependence of Lewis acidity from the O-B-O angle as well as the concept of THC index are well known.^[15] This has been given as an explanation of stronger Lewis acidity of boronic esters in comparison with corresponding acids.^[16] Lewis acidity of the boron center influences affinity towards electron-rich species and has been the subject of intense studies.^[17,18] It also stands for useful properties of phenylboronic esters; therefore, quantitative evaluation of this property is of crucial importance. In spite of that, no systematic study of the acidity of phenylboronic esters has been reported until recently, when the influence of

number and position of electron-withdrawing substituents in the aromatic ring has been investigated.^[9] The influence of a diol structure is the subject of the present paper. A combination of experimental and theoretical methods has been used to evaluate acceptor number (*AN*) of several phenylboronic esters to get insight into various factors that affect their Lewis acidity.

EXPERIMENTAL SECTION

Synthesis

Pentafluorophenylboronic acid was synthesized according to a known procedure.^[19] Neopentyl glycol, 1,2-benzenedimethanol, ethylene glycol, and Et₃PO were purchased from Sigma-Aldrich. *meso*-Hydrobenzoin was purchased from Alfa Aesar. All reagents where used as received. The synthesis of catechol esters was described previously.^[9] All solvents and auxiliary materials were purchased from POCH and used as received.

2-(Pentafluorophenyl)-1,3,2-dioxaborolane (**2**): An equimolar amount of ethylene glycol and pentafluorophenylboronic acid were dissolved in 100 cm³ of toluene in a two-necked flask (150 cm³) supplied with a thermometer and a Dean–Stark trap for azeotropic water removal. The solution was refluxed for 6 h. The solvent was then removed under vacuum to give a white slurry. Sublimation under vacuum gave the ester as a white solid. Yield: 88%. (Found: C, 40.35; H, 1.76. Calc. for $C_8H_4BF_5O_2$: C, 40.39; H, 1.69%) ¹H NMR (CDCl₃, 400 MHz): 4.38 (s, 4H) ppm, ¹⁹F NMR (CDCl₃, 376.3 MHz): -128.73, -148.35, -161.27 ppm, ¹¹B NMR (CDCl₃, 64 MHz): 29.0 ppm.

(4R,5S)-2-(Pentafluorophenyl)-4,5-diphenyl-1,3,2-dioxaborolane (**3**), 2-(2,3,4,5,6-pentafluorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (**4**), and 3-(pentafluorophenyl)-3,5-dihydro-1*H*-2,4,3-benzodioxaborepine (**5**) were obtained by a solid-phase esterification.^[20] The reactions were performed

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Figure 1. Pentafluorophenylboronates of catechol (1), ethylene glycol (2), *meso*-hydrobenzoin (3), neopentyl glycol (4), and 1,2-di(hydroxymethyl) benzene (5)

in an ordinary mortar, which was heated to about 60°C. The substrates were mixed in equimolar amounts and ground manually for about an hour to give the products in satisfying to excellent yields. (**3**): yield: 99%, (Found: C, 61.57; H, 3.12. Calc. for $C_{20}H_{12}BF_5O_2$: C, 61.58; H, 3.10%) ¹H NMR (CDCl₃, 400 MHz): 6.00 (s, 2H), 6.95 (m, 4H), 7.09 (m, 6H) ppm, ¹⁹F NMR (CDCl₃, 376.3 MHz): -127.94, -147.69, -160.81 ppm, ¹¹B NMR (CDCl₃, 64 MHz): 29.8 ppm. (**4**): yield: 98%, (Found: C, 47.05; H, 3.43. Calc. for $C_{11}H_{10}BF_5O_2$: C, 47.19; H, 3.60%) ¹H NMR (CDCl₃, 400 MHz): 1.07 (m, 6H), 3.81 (s, 4H) ppm, ¹⁹F NMR (CDCl₃, 376.3 MHz): -131.36, -151.18, -161.42 ppm, ¹¹B NMR (CDCl₃, 64 MHz): 28.0 ppm. (**5**): yield: 84%, (Found: C, 53.46; H, 2.59. Calc. for $C_{14}H_8BF_5O_2$: C, 53.55; H, 2.57%) ¹H NMR (CDCl₃, 400 MHz): 5.28 (s, 4H), 7.38 (m, 4H), ¹⁹F NMR (CDCl₃, 376.3 MHz): -131.49, -151.74, -161.72 ppm, ¹¹B NMR (CDCl₃, 64 MHz): 28.3 ppm.

³¹P NMR measurements

All samples were prepared in atmosphere of dry argon. To the 0.297 mol/dm³ solution of Et₃PO in benzene-d₆ (0.4 cm³), variable amounts of boronic esters were added. The ³¹P NMR spectra were recorded on a Varian Unity Plus 200 MHz spectrometer using BF₃*Et₂O in CDCl₃ and 95% D₃PO₄ in D₂O as external reference, respectively. The shift of the complex ($\delta_{complex}$) was extrapolated from the concentration-shift dependence to infinite excess of the ester over Et₃PO and used for calculation of *AN*.

Calculations

All starting geometries of the complexes were prepared manually and submitted for full optimization at the B3LYP/6-311G(2df,p) level of theory with the use of IEFPCM model of solvent influence (Integral Equation Formalism variant of the Polarizable Continuum Model)^[21] to simulate the benzene solution. Frequencies were calculated for all found conformations to ensure that the optimized structure is not a transition state. All presented relative energies were corrected for Zero Point Energy. The σ (³¹P) were calculated using Gauge-Independent Atomic Orbital method and VSXC^[22] pure DFT functional in pcS-2 basis set. Polarization consistent basis set family was optimized for DFT by Jensen^[23] for calculating NMR shielding constants. Those computations were carried out using Gaussian 09.^[24] The 2D and 3D Laplacian of the electron density was calculated (for optimized geometries of the isolated esters) using CheckDen^[25] software from wave functions extracted from the Gaussian checkpoint files. The valence shell charge concentrations (VSCCs) differ in size around the B-O and B-C_{Ar} bonds (shown in Fig. 7). Thus, the 2D-Laplacian cross-section maps along these bonds

(Fig. 5 and Fig. 6) were calculated perpendicular to the plane fixed by O-B-O atoms (*VSCC's* maximum).

RESULTS AND DISCUSSION

In order to investigate the influence of the diol structure on the Lewis acidity of esters, pentafluorophenylboronates of five diols have been studied (Fig. 1). The esters were selected to probe the influence of different possible structural aspects: from the previously reported^[9] flat and aromatic catechol (1), relatively small and aliphatic ethylene glycol (2), one-side hindered *meso*-hydrobenzoin (3), six-membered ring neopentyl glycol (4) to seven-membered ring of 1,2-di(hydroxymethyl)benzene ester (5).

Relative Lewis acidity of the studied compounds (1–5) has been experimentally evaluated in terms of the AN,^[26,27] which is the affinity towards triethylphosphine oxide (Et₃PO). The ANs were calculated according to the following formula: $AN = [(\delta_{complex} - \delta_{(1)})/(\delta_{(2)} - \delta_{(1)})] \times 100$, where $\delta_{(1)}$ and $\delta_{(2)}$ are the ³¹P NMR chemical shifts of Et₃PO in hexane (41.0 ppm) and in SbCl₅ (86.1 ppm), respectively. All five compounds are solids at room temperature; thus, the AN measurement was conducted in benzene-d₆ according to the previously described procedure.^[9] Among the investigated compounds, neopentyl glycol ester (**4**) is the weakest Lewis acid with the experimental $\delta(^{31}P)$ NMR of Et₃PO complex equal to 47.2 ppm.

Simultaneously, DFT computations were performed to find out whether such calculations can serve as a prediction tool in designing compounds of desired Lewis acidity. The Et_3PO itself has four conformations (A–D, Fig. 2).

The molecular structures of complexes of esters with all the four forms of Et₃PO were analyzed for possible geometries, and each was submitted for geometry optimization on B3LYP/6-311G(2df,p) level of theory. In all cases, multiple conformations were found and characterized as true minima as the frequency calculations showed no imaginary frequencies. In the majority of cases, the minimum energy conformations of complexes correspond to the Et₃PO conformation B (Fig. 2). This conformer is unsymmetrical and has one ethyl group rotated upwards, away from the oxygen atom. This geometry is in agreement with the Et₃PO geometry observed in the crystal structure of the Et₃PO*B(C₆F₅)₃^[28] complex, which is the only example of a crystal structure of a Et₃PO complex with organoboron Lewis acid.

The NMR calculations were performed for all the found complex conformations on the VSXC/pcS-2 level of theory. The calculated shielding constant was converted to chemical shift using the following constant and scaling factor $\delta_{calc.} = (361.04 - \sigma_{calc.})^*$ 0.91. The calculated ³¹P NMR chemical shifts were averaged assuming a Boltzmann distribution of the conformers, which was calculated using the $\Delta\Delta G_{conf.}$ values displayed in Table S1 (Supplementary Data). The same procedure – conformational analysis, NMR calculations, population analysis, and scaling – was



Figure 3. Catechol esters: phenylboronate (**1a**), 2-fluorophenylboronate (**1b**), 3-fluorophenylboronate (**1c**), 4-fluorophenylboronate (**1d**), 2,4-difluorophenylboronate (**1e**), 2,6-difluorophenylboronate (**1f**), 3,4,5-trifluorophenylboronate (**1g**), 2,4,6-trifluorophenylboronate (**1h**)

applied for fluorinated catechol esters investigated previously (Fig. 3) ^[9] (Table S2, Supplementary Data).

Figure 4 shows data points for the minimal energy conformers which display better correlation of the DFT NMR calculated and experimental data ($R^2 = 0.91$, RMSD = 1.03 ppm) in comparison with the averaged ones ($R^2 = 0.88$, RMSD = 1.57 ppm). One can easily notice that the shifts for the lowest energy conformers of compounds **4** and **5** are significantly deviated from the correlation line. In the case of **4**, the minimum energy conformer is about 12 ppm above the line. In the case of **5**, the difference is smaller (about 4 ppm). Similar situation is observed, considering the whole population of the conformers (Fig. S3, S4, Supplementary Information). The results show that the correlativity of the experimental and computational NMR data is fair enough for complexes of five-atom ring esters (**1**, **1a–h**, **2**, and **3**) but rather poor for those of six (**4**) or seven-member rings (**5**). The calculated energies of complexation (Table 1) qualitatively reflect

the experimentally determined relative Lewis acidity. The weakest acid (4) displays a positive energy of complexation, whereas the strongest acid (1) displays the most negative energy of complexation. The calculated energies of complexation of compounds 2, 3, and 5 are moderate and close to each other, similar to the experimental δ^{31} P NMR of the complex.

The diol structure can affect the Lewis acidity of phenylboronates in different ways. The first factor concerns the steric hindrance in the interaction with Lewis base. It is obvious that this issue affects only those Lewis bases which are of considerable volume themselves (e.g. Et₃PO), but not small molecules like fluorine anion. The differences in the measured AN of the investigated compounds can be explained only partially on the basis of different bulkiness of the diol moieties. The influence of the steric hindrance in the case of 1 and 4 is not surprising. The flat and rigid catechol residue of 1 causes the smallest hindrance; thus, this ester is the strongest Lewis acid. The branchy neopentyl residue in the six-membered ring of 4 causes a great steric hindrance, resulting in the lowest Lewis acidity. In the rest of the cases, the relative differences in measured AN are not so self-evident. The glycol ester 2 bears only four hydrogen atoms that can repulse the upcoming Lewis base, whereas the ester 3 is strongly hindered from one side, so the overall Lewis acidity of 2 should be higher than that of 3. However, it is not the case, the measured AN of 3 is about six points higher that of 2 (Table 1).



Figure 4. Measured ³¹P NMR δ of ester–Et₃PO complexes against DFT-GIAO-calculated minimal energy conformer values. The line shows correlation of the data for compounds **1**, **1a–h**, **2**, and **3**

Table 1. Ester*Et₃PO complex ³¹P NMR measured shift (δ_{exp}), acceptor number (*AN*), calculated shift of minimum energy conformer of complex, Boltzman population averaged calculated shift, calculated complexation energy

Cmpd	$\delta_{\rm exp.}/{\rm ppm}$	AN	Min. energy δ $_{\rm calc.}/{ m ppm}$	Averaged δ _{calc.} /ppm	Complexation energy ^a /kJ/mol
1	77.8	81.5	70.7	68.8	-32.87
2	51.5	23.3	60.6	61.0	-4.81
3	54.2	29.2	59.8	59.9	-9.57
4	47.2	13.7	70.3	69.3	3.71
5	54.8	30.6	65.1	64.5	-7.54

^aCalculated for the reaction between the minimum energy conformer of Et_3PO (A) and an ester leading to minimum energy conformer of the complex. The isolated esters have only one stable form each.

The other reason of acidity differences can be the electronic one, changing electron density of the boron center. This can be analyzed by the Laplacian of the electron density, which reveals the localization of the charge accumulation (and depletion) that can shield the acidic center and, in result, lower the Lewis acidity. The two-dimensional Laplacian maps in Fig. 5 and Fig. 6 were calculated for optimized geometries of isolated esters along B-C_{Ar} bond and one of the B-O bonds, in both cases perpendicular to the plane fixed by the O-B-O atoms. The *VSCCs* are of the same size for all cases along both planes. This shows that the charge concentration in the close vicinity of boron center does not depend on the structure of the diol moiety. Hence, the differences in the *AN* of investigated compounds are not caused by any electronic effect originating from the diol moiety. An example of three-dimensional Laplacian is shown in Fig. 7.

The other factor is the previously mentioned geometrical one, which seems to be the reason of acidity differences among the investigated species besides the simple steric hindrance of the boron center. The differences in the relative Lewis acidity of the investigated compounds are easy to explain when one correlates *AN* with the calculated O-B-O angle in the ester. Figure 8



Figure 7. An overview of the 3D Laplacian of the electron density of the neopentyl pentafluorophenylboronate (**4**)

presents measured *AN* plotted against O-B-O angle from optimized geometries of isolated esters. The *AN* rises rapidly with the reduction of the O-B-O angle. For the glycol ester (**2**), it is equal to 23.3 (113.8°) and for the catechol ester (**1**) it is 81.5 (111.2°). However, above 120° the *AN* rises with increasing angle. This is due to the reduction of the two O-B-C_{Ar} angles upon increasing the O-B-O angle, what makes the planar-to-tetrahedral interconversion also easier. This effect is weaker, for upon



Figure 5. Laplacian of the electron density along B-O bond perpendicular to O-B-O plane. The horizontal line indicates equality of the VSCCs. The length unit is in Å



Figure 6. Laplacian of the electron density along B-C_{Ar.} bond perpendicular to O-B-O plane. The horizontal lines indicate equality of the VSCCs. The length unit is in Å





Figure 8. O-B-O angle from optimized structures of investigated phenylboronates against their measured Lewis acidity expressed as δ^{31} P NMR. The dashed line represents a polynomial correlation function ($\delta = -0.03\theta^3 + 12.68\theta^2 - 1562.12\theta + 64094.75$) for which R² = 0.998

widening the O-B-O angle the two oxygen atoms get closer to the fluorine atoms, what can result in repulsion. The easiest way to lower the strain is to twist the ester ring along the B- $C_{Ar.}$ bond. This reduces the overall Lewis acidity because it reduces somewhat the access window to the boron for the upcoming Lewis base.

CONCLUSIONS

The overall Lewis acidity of equally fluorinated diol phenylboronates is significantly affected by the structure of the diol. The measured *AN* of the investigated pentafluoroboronates cover almost the whole acidity scale. The explanation is more than just simple steric bulk, but rather geometric parameters of the ester ring which affect the geometry of the boronate group. The comparison of the experimentally assessed Lewis acidity with the geometrical parameters drawn from DFT optimizations confirmed that the alteration of the boron configuration towards tetrahedral geometry increases the acidity.

SUPPORTING INFORMATION

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Supporting information may be found on the online version of this article.

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