

# BORONIC ACIDS AS VERSATILE SUPRAMOLECULAR REAGENTS

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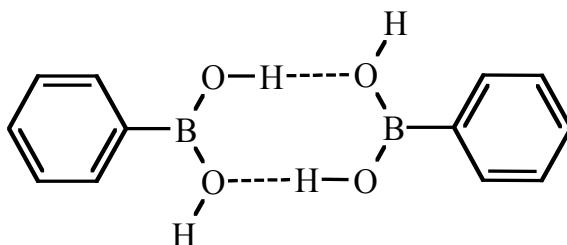
## 1. ABSTRACT

Crystal engineering and supramolecular synthesis is governed by the structural consequences of intermolecular forces, and by the way in which such interactions are utilized for controlling the assembly of molecules into predictable structural motifs. A vital part of crystal engineering is thus dedicated to identifying robust intermolecular synthons that can be used as reliable connectors between molecules. In this paper we describe how the hydrogen-bond capabilities of boronic acids  $R-B(OH)_2$  can be translated into versatile co-crystallizing tools capable of forming heteromeric structure-directing hydrogen-bond interactions with a variety of complementary structural partners e.g. 2-aminopyrimidine and 4,4'-bipyridine.

## 2. INTRODUCTION

The synthesis of supramolecular assemblies composed of several different molecular fragments [1] held together by non-covalent forces is still a relatively young discipline and our understanding of how groups of molecules communicate, bind, organize, and function, is still incomplete [2]. Despite recent advances in supramolecular synthesis, the detailed control over the assembly of molecules into ordered solids remains an elusive goal, and we are rarely able to predict the structure of a simple crystalline material. Much more work is required to increase the choice of reliable building blocks of low-dimensional architectures and, more importantly, to allow us to rationalize and predict structural arrangements of molecules within new crystalline materials. An enhanced understanding of intermolecular forces may also enable us to better address crucial questions about polymorphism and crystal morphology.

Boronic acids are receiving considerable attention from the synthetic community due to the fact that they are invaluable intermediates in very versatile and useful aryl-aryl cross-coupling reactions [3]. However, the same chemical functionalities have, by and large [4, 5], remained unexplored as supramolecular connectors despite the fact that aryl-boronic acids can produce hydrogen-bonded dimers and ladders akin to motifs observed in carboxylic acids and carboxamides, Scheme 1 [6].



**Scheme 1.** Head-to-head hydrogen-bonded motif common among phenylboronic acids.

The boronic acid moiety may represent a potentially versatile supramolecular synthetic tool but there are still no systematic structural studies that have examined how this particular moiety competes or interacts with other hydrogen-bond functionalities e.g. carboxylic acids, carboxamides, oximes, 2-aminopyridines, *etc.*

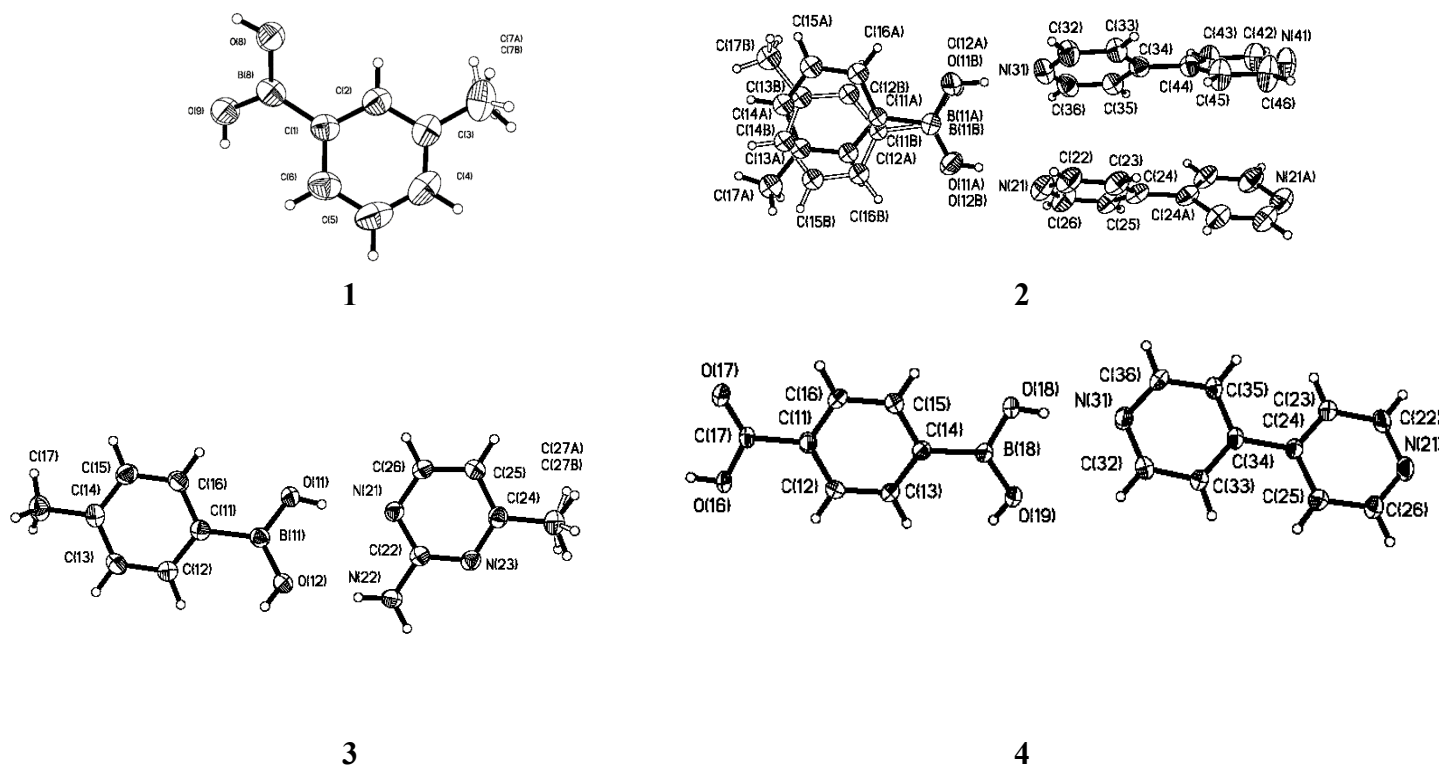
In this study we employ co-crystallization techniques as a way of probing the supramolecular behavior of boronic acids, and we demonstrate that they are capable of engaging in a variety of predictable structure-directing intermolecular interactions. These results indicate that boronic acids may become an important addition to the tools employed in hydrogen-bond based crystal engineering and supramolecular synthesis. Here we present the crystal structures of 3-methylphenylboronic acid **1**, (4,4'-bipyridine)<sub>3</sub>:(3-methylphenylboronic acid)<sub>2</sub> **2**, 2-amino-4-methylpyrimidine:(4-methylphenylboronic acid)<sub>2</sub> **3**, and 4,4'-bipyridine:4-carboxyphenyl boronic acid **4**, Table 1.

### 3. EXPERIMENTAL

#### 3.1 Crystallography

X-ray data were collected on a Bruker SMART 1000 four-circle CCD diffractometer using a fine-focus molybdenum K $\alpha$  tube. Data were collected using SMART [7]. Initial cell constants were found by small, widely separated “matrix” runs. Preliminary Laué symmetry was determined from axial images. Generally, an entire hemisphere of reciprocal space was collected regardless of Laué symmetry. Scan speed and scan width were chosen based on scattering power and peak rocking curves. Unless otherwise noted, 0.3 ° scans were used.

Unit cell constants and orientation matrices were improved by least-squares refinement of reflections thresholded from the entire dataset. Integration was performed with SAINT [8] using this improved unit cell as a starting point. Precise unit cell constants were calculated in SAINT from the final merged dataset. Lorenz and polarization corrections were applied, but data were not corrected for absorption. Laué symmetry, space group, and unit cell contents were found with XPREP. Data were reduced with SHELXTL [9]. The structures were solved in all cases by direct methods without incident. In general, hydrogen atoms were assigned to idealized positions and were allowed to ride. Unless otherwise noted, the coordinates of hydrogen atoms engaged in hydrogen-bonding were allowed to refine. Thermal ellipsoids and labeling schemes are shown in **Figure 1** a-d and the crystallographic data are listed in Table 1.



**Figure 1.** Thermal ellipsoids and labeling schemes for 1-4.

Table 1

Structure code	1	2	3	4
Systematic name	3-methylbenzeneboronic acid	(3-methylbenzeneboronic acid) <sub>2</sub> , (4,4'-bipyridine) <sub>3</sub>	2-amino-4-methylpyrimidine, 4-methylbenzeneboronic acid	4-carboxybenzeneboronic acid, 4,4'-bipyridyl
Formula moiety	C <sub>7</sub> H <sub>9</sub> B O <sub>2</sub>	(C <sub>7</sub> H <sub>9</sub> O <sub>2</sub> B) <sub>2</sub> (C <sub>10</sub> H <sub>8</sub> N <sub>2</sub> ) <sub>3</sub>	(C <sub>5</sub> H <sub>7</sub> N <sub>3</sub> ) (C <sub>7</sub> H <sub>9</sub> B O <sub>2</sub> )	(C <sub>7</sub> H <sub>7</sub> B O <sub>4</sub> ) (C <sub>10</sub> H <sub>8</sub> N <sub>2</sub> )
Empirical formula	C <sub>7</sub> H <sub>9</sub> B O <sub>2</sub>	C <sub>44</sub> H <sub>42</sub> B <sub>2</sub> N <sub>6</sub> O <sub>4</sub>	C <sub>12</sub> H <sub>16</sub> B N <sub>3</sub> O <sub>2</sub>	C <sub>17</sub> H <sub>15</sub> B N <sub>2</sub> O <sub>4</sub>
Molecular weight	135.95	740.46	245.09	322.12
Color, Habit	colorless prism	colorless prism	amber prism	colorless prism
Crystal system	Monoclinic	Monoclinic	Monoclinic	Triclinic
Space group, Z	P2(1)/c, 4	C2/c, 4	P2(1)/c, 4	P1, 1
a, Å	15.063(4)	20.2663(10)	9.5084(10)	3.9552(8)
b, Å	5.6710(17)	9.2707(5)	11.9386(12)	8.3612(16)
c, Å	9.101(3)	22.3043(11)	11.2657(12)	11.670(2)
a, °	90.00	90.00	90.00	101.613(3)
b, °	94.854(5)	113.787(2)	102.717(2)	98.910(4)
g, °	90.00	90.00	90.00	98.038(4)
Volume, Å <sup>3</sup>	774.6(4)	3834.6(3)	1247.5(2)	367.59(13)
Density (g/cm <sup>3</sup> )	1.166	1.283	1.305	1.455
Temperature (K)	203(2)	163(2)	203(2)	203(2)
X-ray wavelength	0.71073	0.71073	0.71073	0.71073
m, (mm <sup>-1</sup> )	0.081	0.083	0.089	0.104
Q <sub>min</sub> (°)	2.71	2.00	2.20	1.81
Q <sub>max</sub> (°)	27.45	28.26	28.28	28.23
Reflections				
collected	4389	13899	9199	2657
independent	1677	4428	2873	2225
observed	656	2332	2009	1860
Threshold expression	I > 2s(I)	I > 2s(I)	I > 2s(I)	I > 2s(I)
R <sub>1</sub> (observed)	0.0387	0.0514	0.0474	0.0446
wR <sub>2</sub> (all)	0.0997	0.1381	0.1407	0.1085

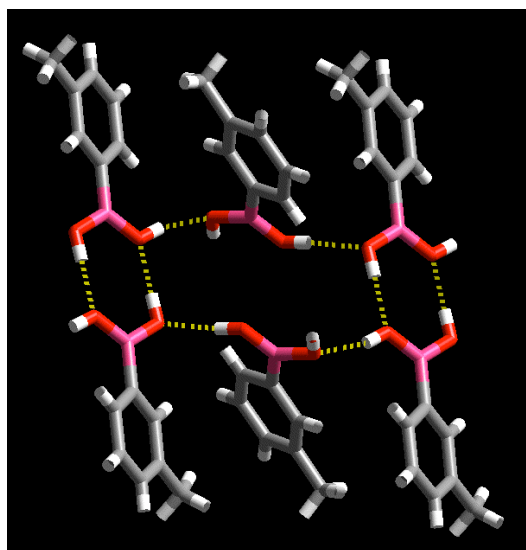
### 3.3 Synthesis

3-Methylphenylboronic acid was synthesized by adding the Grignard reagent of 3-bromotoluene to a THF solution of triisopropyl borate. The mixture was stirred at -78 °C for one hour, whereupon the reaction was quenched with sulfuric acid and the desired product was subsequently extracted with ether and recrystallized from hot water to produce colorless needles; yield: 84%; mp: 160-163 °C. 4-Methylphenylboronic was prepared in the same way; yield 83%; m.p. 244-246 °C. 4-carboxyphenyl boronic acid was synthesized by oxidation with potassium permanganate of 4-methylphenyl boronic acid; yield 59%; m.p. 232-233 °C.

The crystal structure determination of **1** shows that the two hydroxyl groups are arranged in a *syn* and *anti* manner, respectively. [10] The primary hydrogen-bond motif in this structure, Table 2, is a head-to-head dimeric interaction composed of two symmetry related O-H...O interactions (similar to a classic dimeric carboxylic acid motif) **Figure 2**.

**Table 2.**  
*Hydrogen-bond geometries for 1-4*

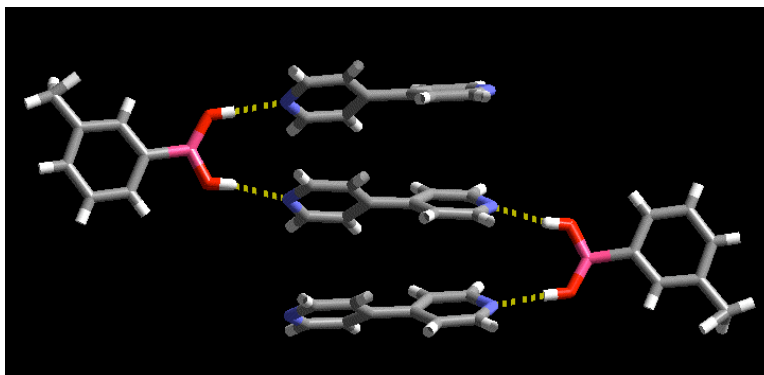
	D-H	H...A	D...A	<(DHA)	Generator for A
1					
O8-H8...O9	0.922(19)	1.804(19)	2.7241(19)	175.5(18)	-x, -y, -z
O9-H9...O8	0.873(19)	1.848(19)	2.7024(19)	165.6(18)	X, -y-1/2, z-1/2
2					
O11A-H11C...N21	0.83(3)	1.99(2)	2.80(2)	170(3)	
O12B-H12D...N21	0.86(4)	1.99(2)	2.83(3)	167(3)	
O11B-H11D...N31	0.92(4)	1.793(19)	2.70(3)	169(2)	
O12A-H12C...N31	0.98(3)	1.793(19)	2.76(2)	169.9(18)	
3					
O11-H11...N21	0.85(2)	1.93(2)	2.7719(16)	169.8(18)	
N22-H22A...O12	0.894(19)	2.131(19)	2.9987(17)	163.4(16)	
N22-H22B...O11	0.90(2)	2.19(2)	3.0003(18)	151.0(16)	x, -y-1/2, z-1/2'
O12-H12...N23	0.80(2)	2.03(2)	2.8094(17)	164.3(18)	-x, y+1/2, -z+1/2
4					
O16-H16...N21	0.82	1.85	2.667(3)	173.9	
O18-H18...N31	0.82	2.00	2.813(3)	173.0	
O19-H19...O17	0.82	2.11	2.839(2)	148.8	



**Figure 2.** Head-to-head hydrogen-bonded dimers interconnected into an infinite ladder in the crystal structure of **1**.

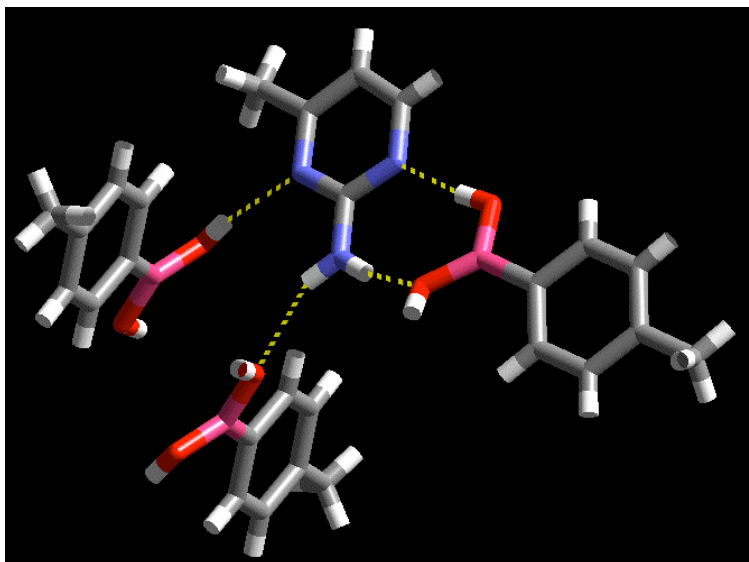
The centrosymmetric dimers are further connected into a ladder like structure with the same connectivity as the motif commonly displayed by primary amides [11]. However, whereas the latter are often more or less planar, the boronic acid ladder is composed of dimers that are arranged in alternating perpendicular fashion along the ladder.

The crystal structure of **2** [12] demonstrates that a pyridyl moiety is capable of breaking the boronic acid dimer and replacing it with near-linear O-H...N hydrogen bonds (Table 2), which is similar to the well-known structure-directing COOH...py [13] and R-OH...py synthons, **Figure 3**[14].



**Figure 3.** Discrete pentameric supermolecule in **2** assembled via four (two equivalent) O-H...N hydrogen-bond interactions.

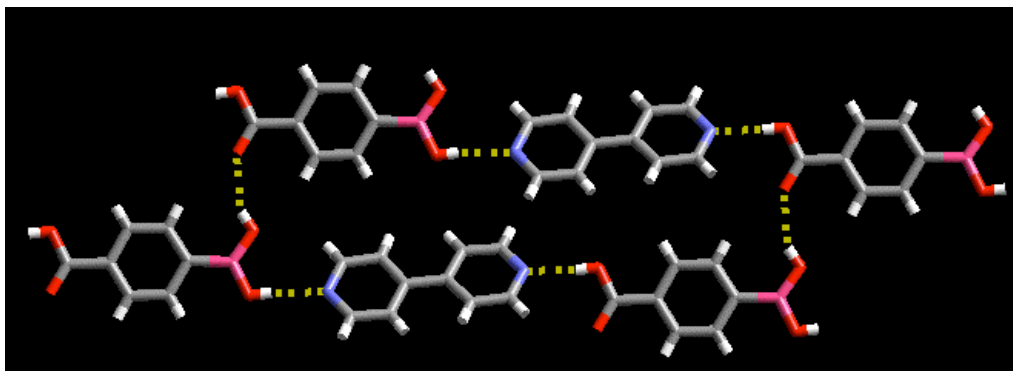
One part of the hydrogen-bonded motif in **2** is akin to the interactions that commonly take place between resorcinol-based components and bipyridyl-type compounds [15]. However, the separation between OH groups in boronic acid is not sufficient to allow for the formation of a discrete tetramer as observed in resorcinol:4,4'-bipy [16]. The end result is a discrete pentameric supermolecule that leaves two terminal nitrogen atoms, N(41) without any strong hydrogen-bond interactions. There are also no C-H...N interactions involving this nitrogen atom (the shortest N(41)...C distance is over 3.4Å).



**Figure 4.** The complementarity of 2-aminopyrimidine:boronic acid drives the formation of the co-crystal in **3**. The additional proton on boronic acid provides a crosslink.

A paper by Etter *et al* [17] reporting the crystal structure of a carboxylic acid: 2-aminopyrimidine co-crystal provided a classic example of how heteromeric complementary hydrogen-bond interactions can be employed as the driving force for binary molecular solids. The crystal structure of **Figure 4** shows that the boronic acid moiety engages in an  $R_2^2(8)$  motif with 2-aminopyrimidine (as do carboxylic acids), Table 2. However, the additional hydrogen-bond donor on boronic acid creates a more complex 3-D motif compared with the discrete 0-D motif (between 2-aminopyrimidine and monocarboxylic acids) or 1-D motif (in the case of 2-aminopyrimidine and dicarboxylic acids).

Finally, given the fact that both carboxylic acids and boronic acids are capable of forming strong and directional O-H $\cdots$ N hydrogen bonds to a pyridyl moiety, the crystal structure of **4** [18], does not reveal any surprising primary intermolecular interactions, **Figure 5**. The primary interaction is likely to be the py $\cdots$ COOH hydrogen bond; a common supramolecular interaction that has been instrumental in the design of one- and two-dimensional supramolecular architectures, such as infinite chains, [19] honeycomb layers, [20] and sheets, [21]. Since the reaction was carried out in a 1:1 ration, this leaves a good hydrogen-bond donating moiety, the B(OH)<sub>2</sub> group) and one good hydrogen-bond acceptor, the remaining pyridyl moiety. As demonstrated in previous studies [4, 5] the self-complementary boronic acid dimer can be broken in favor of a B(OH)<sub>2</sub> $\cdots$ py interaction, which is exactly what happens in the crystal structure of **4**.



**Figure 5.** Horizontal infinite chains of bipy and 4-carboxyphenylboronic molecules in the crystal structure of **4** connected through O-H $\cdots$ N hydrogen bonds.

The combination of the acid $\cdots$ py, B(OH)<sub>2</sub> $\cdots$ py, and B(OH)<sub>2</sub> $\cdots$ acid hydrogen bonds leads to infinite chains of alternating bipy and 4-carboxyphenyl boronic acid held together via COOH $\cdots$ py and R-OH $\cdots$ py, which are cross-linked by O-H $\cdots$ O interactions (from boronic acid to carboxylic acid) resulting in a 2-D hydrogen-bonded sheet. All primary hydrogen-bond donors and acceptors are satisfied and the main intermolecular interactions in **4** are readily rationalized based upon existing structural information.

This study has demonstrated that the boronic acid moiety may be incorporated into more complicated modular supramolecular synthetic strategies by virtue of its ability to form predictable hydrogen-bond interactions with a variety of well-known acceptor sites. It remains to be seen how reliable this moiety is, or how it can be made to fit in a hierarchical approach to the assembly of ternary and higher-order supermolecules and molecular solids. However, these results indicate that it can become a useful building block along the lines of carboxylic acids, carboxamides and oximes in the construction of robust and reliable extended architectures.

#### 4. ACKNOWLEDGEMENTS

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CCDC 249705 – 249708 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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