Hetero-arylboroxines: the first rational synthesis, X-ray crystallographic and computational analysis†

Peter M. Iovine,*[a] Charles R. Gyselbrecht,[a] Emily K. Perttu,[a] Cole Klick,[a] Alexander Neuwelt,[a] Jason Loera,[a] Antonio G. DiPasquale,[b] Arnold L. Rheingold[b] and Jeremy Kua[a]

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A novel series of hetero-arylboroxines were synthesized and structurally characterized by X-ray diffraction, NMR and computational analysis. The solid-state structures of the hetero-arylboroxines represent the first report of AB_2-type hetero-arylboroxines.

Boroxines, sometimes termed boronic acid anhydrides or boroxins, are the dehydration products of organoboronic acids (see Fig. 1). Historically, there were two common themes in boroxine-related research. First was the question of aromaticity in boroxine ring compounds.[1–4] The second line of investigation focused on the propensity of arylboroxines to form Lewis acid–base adducts with nitrogen-containing ligands.[5–10] More recently, however, boroxine research has been invigorated by a flurry of tantalizing papers. Notably, the Yaghi group has synthesized and characterized 2D[11] and 3D[12] arylboroxine materials that function as permanently porous organic frameworks with high thermal stabilities and large surface areas. Additionally, arylboroxine ring motifs have been important in the facile and reversible assembly of arylboronic acid end-functionalized telechelic polymers,[13] the development of arylboroxine-based nonlinear optical materials,[14] polymer electrolytes for lithium-ion battery applications,[15] flame-retardant materials,[16] and the immobilization of oligofluorene chromophores in networked matrices.[17]

In contrast to homo-arylboroxines, there are no published reports (to our knowledge) of hetero-arylboroxines, *i.e.* arylboroxine rings containing two or three different aryl substituents. Developing rational methods to synthesize and control hetero-arylboroxine structure will significantly expand the impact of these boron-containing species in areas such as solid-state design, porous organic materials and dynamic combinatorial chemistry. In this paper we outline a novel synthetic approach toward the rational synthesis of hetero-arylboroxines that relies on arylboroxine–ligand interactions to control the substitution pattern on the arylboroxine ring. A full computational analysis complements the experimental work and further dissects the thermodynamics of hetero-arylboroxine formation.

[a]*Department of Chemistry and Biochemistry, University of San Diego, 5998 Alcala Park, San Diego, CA, 92110, USA. E-mail: piovine@sandiego.edu; Fax: +1 (1)619 260 2211; Tel: +1 (1)619 260 4028; Web: http://web.mac.com/tetrakis*

[b]*Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA, 92093, USA*

† Electronic supplementary information (ESI) available: Experimental details, NMR spectra, crystallographic experimentals for **3a**–**c**, along with details of the DFT computational methods (B3LYP/6-311+G*) with implicit solvent, zero-point energy and thermal-enthalpy corrections. CCDC reference numbers 671272–671274. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b804705g

We began our investigation into hetero-arylboroxines armed with two conclusions from our previous arylboroxine-based thermodynamic studies.[18,19] First, arylboronic acids can be smoothly and efficiently converted to 1 : 1 arylboroxine–ligand adducts. Second, 1 : 1 arylboroxine–ligand adducts are thermodynamically favored over 1 : 2 or 1 : 3 adducts. In an equilibrating mixture of two arylboronic acids (*e.g.* A and B), if one of the arylboronic acids contains an intramolecular ligand (denoted A in this example) then there will be a thermodynamic preference for the AB_2 hetero-arylboroxine over the A_2B or A_3 arylboroxines as binding one ligand is energetically more favorable than binding two or three. In addition, the AB_2 stoichiometry should dominate over the B_3 arylboroxine because there is a thermodynamic preference for ligated arylboroxine over unligated.

The synthesis of hetero-arylboroxines **3a–c** is shown in Fig. 1. The reaction conditions are straightforward and parallel known procedures employing mild chemical dehydrating agents.[20,21] Commercially available *ortho*-(*N*,*N*-dimethylaminomethyl)phenylboronic acid (**1**) was refluxed with two molar equivalents of arylboronic acids (**2a–c**) in the presence of magnesium sulfate. Fig. 1 shows the ^{19}F NMR spectrum of the solid obtained after concentrating the reaction of **1** and **2a**.

Based on both the ^{19}F and ^{1}H NMR data, a 9 : 1 : 1 molar ratio of **3a** : **4a** : **2a** was found. Although two arylboronic acid building blocks can lead to four arylboroxine products, only two such arylboroxine products, **3a** and **4a**, were detected by both ^{1}H and ^{19}F NMR. The ^{19}F resonances attributed to **4a** and **2a** were made by comparison to authentic samples while the assignment of **3a** was made in the following manner. First, binding Lewis basic species such as the *N*,*N*-dimethylaminomethyl group of **3a** to arylboroxine rings decreases arylboroxine Lewis acidity and generally results in upfield ^{19}F NMR shifts relative to the corresponding unligated arylboroxine.[22] Therefore, the chemical shift of the −110 ppm ^{19}F resonance, assigned as **3a**, is justified based on the relative position of the resonances of **4a** and **2a**. In addition, the chemical shift of the resonance assigned as **3a** in Fig. 1 correlates well with known mono-ligated fluoro-containing arylboroxines such as **4a**–pyridine.[22] Although Fig. 1 shows only arylboroxines **3a** and **4a**, two additional arylboroxine products are possible. Compound **5a** (see Fig. 4), an A_2B hetero-arylboroxine, would also have one unique ^{19}F resonance just as in **3a**. However, integration data from the ^{1}H NMR supports the formation of **3a** and not **5a**. In addition, integration of the ^{1}H NMR supports the existence of **3a** and not fluorine-free A_3 homo-arylboroxine **6a**. We therefore conclude that arylboroxines **5a** and **6a** were not formed in sufficient concentration to be measured by NMR.

Purification of the individual arylboroxine products was not possible by standard bench-top methods such as column

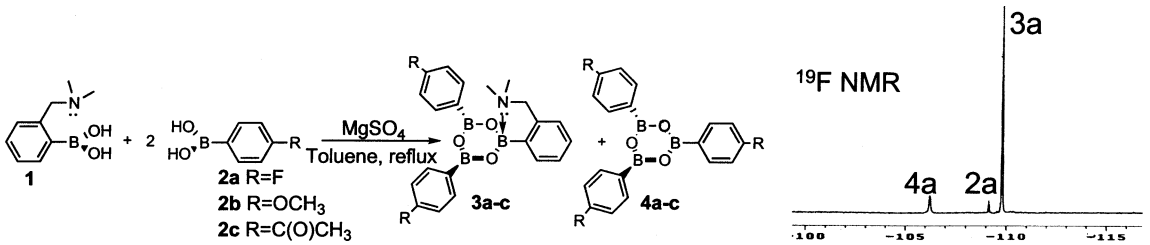

Fig. 1 The syntheses of hetero-arylboroxines **3a–c**. The ^{19}F NMR ($CDCl_3$, 25 °C) is shown for the reaction of **1** and **2a** and shows a 9 : 1 : 1 molar ratio of **3a** : **4a** : **2a**.

chromatography. Arylboroxines, including hetero-arylboroxines **3a–c**, rapidly hydrolyze on silica gel and in wet polar solvents. As solids, however, these arylboroxine-based materials are robust and no degradation is observed over long periods under standard atmospheric conditions. In an effort to corroborate the solution NMR data and obtain the first known X-ray structure of a hetero-arylboroxine, single crystals of **3a–c** were grown by diffusion of pentane into a 1,2-dichloroethane solution of the reaction mixture. The structures of **3a–c** are shown in Fig. 2.† In all three structures the arylboroxine ring adopts a planar conformation and the AB_2 stoichiometry is observed. The B–N bond lengths are 1.70 Å for both **3a** and **3b** and 1.68 Å for **3c**. The average O–B1–O bond angle (where B1 represents the sp^3-hybridized boron atom in **3a**, **3b** and **3c**, see Fig. 2) was 113.1° whereas the average O–B2–O and O–B3–O bond angle (where B2 and B3 represent the sp^2-hybridized boron atoms in **3a**, **3b** and **3c**) was 120.8°. As expected, coordination of B1 by the nitrogen ligand results in a lengthening of the B1–O bond lengths (average B1–O bond length for **3a**, **3b** and **3c** is 1.45 Å) relative to the B2–O or B3–O bond lengths (the average sp^2 B–O bond length is 1.37 Å). A table summarizing key X-ray crystallographic parameters can be found in the ESI.†

The B–N bond lengths in compounds **3a–c** are typical for arylboroxines having one ligand. Considering structures **3a–c** are the first reported hetero-arylboroxines, a comparative B–N bond length analysis of **3a–c** can only be done with published homo-arylboroxines. The James group has reported an *ortho*-(N-phenylmethylamino)-homo-arylboroxine containing one B–N interaction[26] while the Sotofte[27] and Anslyn[28] groups have reported homo-arylboroxines with two and three B–N interactions. A general trend emerges where B–N bond lengths increase with increasing number of arylboroxine–nitrogen interactions. Bond lengths vary from 1.68 to 1.84 Å with the shorter bond lengths being associated with arylboroxines showing one B–N bond[26] and the 1.84 Å upper limit associated with arylboroxines having three B–N bonds.[27] It is important to note that despite the relative lengthening of B–N bonds with increasing number of B–N bonds, all the bond lengths cited above fall within the 1.5–1.8 Å range expected for strong B–N bonds.[29]

In the case of **3c**, crystals from the same batch as those used for the X-ray structure determination were isolated and examined by ^{1}H NMR. The upfield portion of the ^{1}H NMR spectrum for **3c** is shown in Fig. 3a and highlights the benzylic protons of the *N*,*N*-dimethylaminomethyl moiety. Upon addition of 4-methoxyphenylboronic acid to a chloroform solution of **3c**

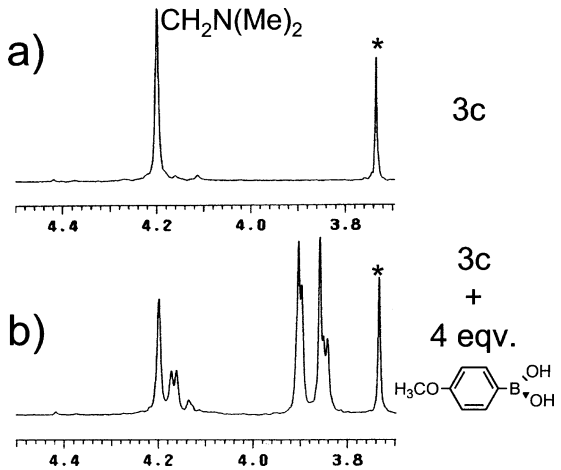

Fig. 3 ^{1}H NMR ($CDCl_3$, 25 °C) spectra showing the room-temperature scrambling of hetero-arylboroxine **3c** upon addition of excess 4-methoxyphenylboronic acid (**2b**). Scrambling is observed in both the benzylic (~4.2 ppm) and methoxy (~3.8 ppm) regions of the spectrum (panel b). The peak marked with an asterisk (*) is residual 1,2-dichloroethane.

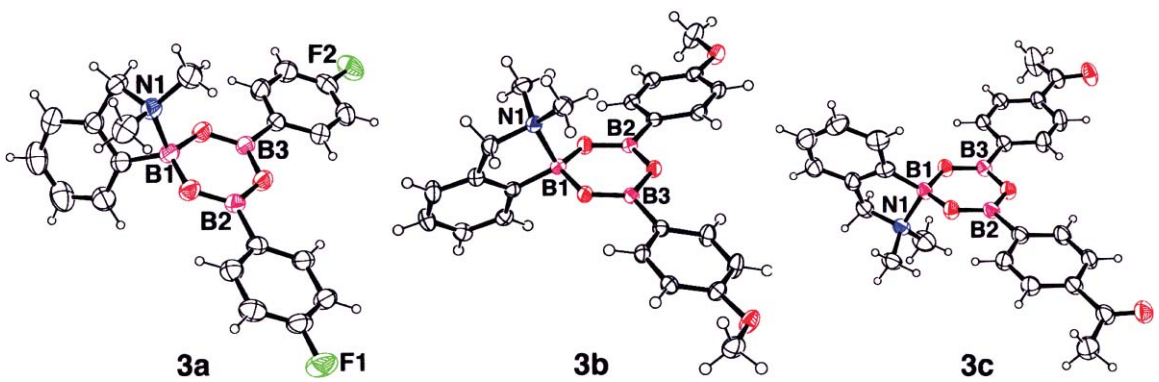

Fig. 2 X-Ray structures of **3a**,[23] **3b**[24] and **3c**[25] with thermal ellipsoids at the 50% probability level.

Table 1 Enthalpy for the formation of arylboroxines of the structural type B_3, AB_2, A_2B and A_3 where A is arylboronic acid monomer **1** and B represents non-coodinating arylboronic acid monomers **2a–c**. Calculations were performed using chloroform as an implicit solvent

Reaction	ΔH°_{soln}/kcal mol^{-1}
$3B \rightarrow B_3$ (**4a**) + $3H_2O$	4.38
$A + 2B \rightarrow AB_2$ (**3a**) + $3H_2O$	−2.56
$2A + B \rightarrow A_2B$ (**5a′**) + $3H_2O$	2.06
$2A + B \rightarrow A_2B$ (**5a**) + $3H_2O$	−0.10
$3A \rightarrow A_3$ (**6′**) + $3H_2O$	15.25
$3A \rightarrow A_3$ (**6**) + $3H_2O$	6.50
$3B \rightarrow B_3$ (**4b**) + $3H_2O$	4.09
$A + 2B \rightarrow AB_2$ (**3b**) + $3H_2O$	−1.26
$2A + B \rightarrow A_2B$ (**5b′**) + $3H_2O$	3.06
$2A + B \rightarrow A_2B$ (**5b**) + $3H_2O$	1.22
$3B \rightarrow B_3$ (**4c**) + $3H_2O$	8.07
$A + 2B \rightarrow AB_2$ (**3c**) + $3H_2O$	−0.99
$2A + B \rightarrow A_2B$ (**5c′**) + $3H_2O$	2.47
$2A + B \rightarrow A_2B$ (**5c**) + $3H_2O$	0.11

(see Fig. 3b), new peaks immediately appear in the benzylic (see Fig. 3b), methoxy (see Fig. 3b) and aromatic (see ESI,† Fig. S1) regions. These results and similar results with **3a** and **3b** suggest that, at room temperature and in the presence of excess 4-methoxyphenylboronic acid, hetero-arylboroxine **3c** scrambles with 4-methoxyphenylboronic acid forming an assortment of new homo- and hetero-arylboroxines.

Computational methods were used to examine the thermodynamic profile of arylboroxine products derived from the reaction of two different arylboronic acid monomers. As described earlier, "A" is used to denote self-coordinating arylboronic acid **1** while "B" denotes non-coordinating arylboronic acids **2a–c**. The calculated solution-phase enthalpies for the formation of A_3, A_2B, AB_2 and B_3 arylboroxines are shown in Table 1.

As expected, AB_2 (**3a–c**) was the most stable for all three *para* substituents studied. Formation of all AB_2 structures is exothermic. A_2B (**5a–c**) was the next lowest in stability from our calculations. With two pendant *N*,*N*-dimethylaminomethyl groups, two possible isomers can be formed: both pendants on opposite sides of the ring (**5a**) or on the same side (**5a′**). Both structures are shown in Fig. 4. **5a** is energetically more stable than **5a′** for two reasons: less steric hindrance from the amine's methyl groups, and a lower net dipole in a less polar solvent. ΔH is close to zero for the formation of A_2B.

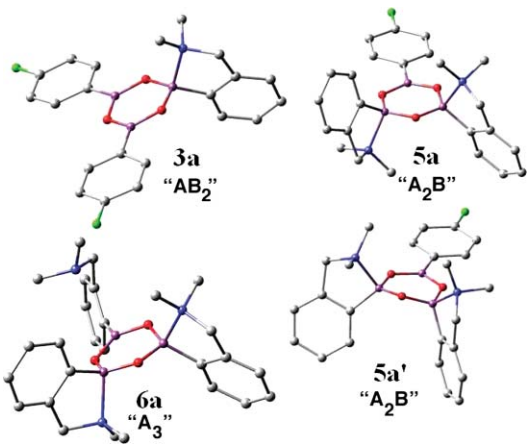

Fig. 4 Calculated structures of AB_2, A_2B and A_3 arylboroxine rings.

The homo-arylboroxines B_3 and A_3 were calculated to be less stable than the hetero-arylboroxines A_2B and AB_2, and their formation is endothermic. Experimentally, small amounts of B_3 are observed but not A_2B. We think there are two reasons for the difference between the computational and experimental results. First, the ratio of B to A monomers is higher in experiment, thus favoring the chemical potential of B over A. This is not taken into account in the calculations. Second, there may be small amounts of A_2B formed but not detected by NMR. In any case, A_2B crystals were not isolable and AB_2 is the dominant product from both experiment and calculation. A_3 is not observed experimentally and is predicted to be much less stable from our calculations. Having all three pendant groups on the same side of the ring is very unfavorable ($\Delta H = +15.3$ kcal mol^{-1}). Alternatively, when two of these pendant groups are on the same side and one opposite, only two B–N bonds are formed as shown for **6a** in Fig. 4.

As the number of pendant *N*,*N*-dimethylaminomethyl groups increases, the computed B–N bond distances also increase. For AB_2, A_2B and A_3 the average calculated distances are 1.76, 1.82 and 1.87 Å respectively. When the pendant groups are bound on opposite faces, one B–N bond is on average 0.4 Å shorter than the other. The AB_2 ring (**3a**) remains relatively planar although having one tetrahedral boron results in a slight pucker with an O–B–O–B dihedral angle of 4.3° (directed toward the pendant group) compared with the planar **4a** structure. With an additional pendant group, the A_2B ring still remains relatively planar (the average dihedral is 2.7°) if the amine groups are on opposite faces (**5a**). However, significant puckering of the ring is observed for amine groups on the same face of the boroxine ring (**5a′**) and the average dihedral is 17°. The structural trends for varying the A group are reproduced in the methoxy and acetyl series of arylboroxines.

In conclusion, we have synthesized and characterized a series of AB_2-type hetero-arylboroxines using a straightforward experimental procedure. Both the experimental and DFT calculations suggest that equilibrating mixtures of arylboroxine ring compounds can be biased by modulating the coordination environment of the arylboroxine ring itself. The hetero-arylboroxine structural motif represents an entirely untapped, yet accessible, reservoir of structural diversity that may further expand the utility of arylboroxines in areas such as crystal engineering, boron-containing materials, dynamic combinatorial chemistry and supramolecular chemistry.

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23 Crystal data for **3a**: $C_{21}H_{20}B_3F_2NO_3$ (M_r = 404.81), 0.20 × 0.20 × 0.20 mm, orthorhombic, space group *Pbca* (No. 61), a = 11.5420(10) Å, b = 18.9350(15) Å, c = 19.6870(17) Å, α = 90°, β = 90°, γ = 90°, volume = 4302.5(6) Å^3, Z = 8, calculated density = 1.250 Mg m^{-3}, absorption coefficient = 0.092 mm^{-1}, T = 298 K, 23 336 reflections collected, 3806 reflections were independent, R_{int} = 0.0450. Final R values were $R1$ = 0.0510, $wR2$ = 0.1180 [$I > 2\sigma(I)$], R indices (all data) $R1$ = 0.0697, $wR2$ = 0.1281, GOF = 1.058.
24 Crystal data for **3b**: $C_{23}H_{26}B_3NO_5$ (M_r = 428.88), 0.20 × 0.16 × 0.12 mm, monoclinic, space group $P2_1/n$ (No. 14), a = 12.8312(13) Å, b = 12.0846(12) Å, c = 15.7327(16) Å, α = 90°, β = 112.252(2)°, γ = 90°, volume = 2257.8(4) Å^3, Z = 4, calculated density = 1.262 Mg m^{-3}, absorption coefficient = 0.086 mm^{-1}, T = 100(2) K, 9555 reflections collected, 4959 reflections were independent, R_{int} = 0.0263. Final R values were $R1$ = 0.0506, $wR2$ = 0.1255 [$I > 2\sigma(I)$], R indices (all data) $R1$ = 0.0758, $wR2$ = 0.1378, GOF = 1.005.
25 Crystal data for **3c**: $C_{25}H_{26}B_3NO_5$ (M_r = 452.90), 0.12 × 0.08 × 0.04 mm, monoclinic, space group $P2_1/n$ (No. 14), a = 13.0525(12) Å, b = 12.2950(11) Å, c = 16.2138(14) Å, α = 90°, β = 111.504(2)°, γ = 90°, volume = 2420.9(4) Å^3, Z = 4, calculated density = 1.243 Mg m^{-3}, absorption coefficient = 0.084 mm^{-1}, T = 208 K, 14 020 reflections collected, 4286 reflections were independent, R_{int} = 0.0351. Final R values were $R1$ = 0.0616, $wR2$ = 0.1710 [$I > 2\sigma(I)$], R indices (all data) $R1$ = 0.0943, $wR2$ = 0.1975, GOF = 1.033.
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