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## Metal-Stabilized Boronate Ester Cages

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ABSTRACT: Molecular cages with arylboronate ester caps at the vertices are described. The cages were obtained by metal-templated polycondensation reactions of a tris(2-formylpyridine oxime) ligand with arylboronic acids. Suited templates are triflate or triflimide salts of Zn<sup>II</sup>, Fe<sup>II</sup>, Co<sup>II</sup>, or Mn<sup>II</sup>. In the products, the metal ions are coordinated internally to the pyridyl and oximato N atoms adjacent to the boronate ester, resulting in an improved hydrolytic stability of the latter. It is possible to decorate the cages with cyano or aldehyde groups using functionalized arylboronic acids. The aldehyde groups allow for a postsynthetic modification of the cages via an imine bond formation.



#### INTRODUCTION

Boronate esters are formed by condensation of boronic acids with diols.<sup>1</sup> Despite the high thermodynamic stability of the B-O bond, most boronate esters undergo rapid exchange reactions. Therefore, boronate esters can be used as dynamic covalent links in polymer chemistry<sup>2–4</sup> and in structural supramolecular chemistry.<sup>5–9</sup> Molecular cages containing boronate ester links can be obtained by [x+y] polycondensation reactions of appropriately designed polyboronic acids and polyalcohols. Cages with different geometries have been reported, including heterodimeric [1 + 1] cages,<sup>10</sup> trigonal bipyramidal or trigonal prismatic [2 + 3] cages,<sup>11-15</sup> cavitand-based [2 + 4] cages,<sup>16-20</sup> tetrahedral [4 + 6] cages (an example is depicted in Figure 1a),<sup>21-23</sup> cubic [8 + 12] cages,<sup>24,25</sup> and a complex interlocked [16 + 24] cage.<sup>26</sup> Boronate esters have also been combined with dynamic covalent imine bonds to make cages in three-component [2 + 3 + 6] polycondensation



Figure 1. Examples of molecular cages containing boronate ester links (a), or dative B-N bonds to boronate esters (b).

reactions.<sup>27,28</sup> Furthermore, it is possible to obtain molecular cages with boroxine links by a self-condensation of diboronic acids.<sup>29,30</sup>

Boronate esters and boroxines are Lewis acidic compounds, which can form adducts with N-donor ligands.<sup>31,32</sup> The formation of dative B-N bonds can trigger the formation<sup>33</sup> or the interconversion of cages.<sup>30</sup> Dative B–N bonds can also be employed as a structure-directing element for the formation of boronate ester-based cages (an example is depicted in Figure 1b).<sup>34-37</sup>

A characteristic feature of molecules with a cage-like shape is the presence of an internal cavity, which allows an accommodation of guest molecules. Cages featuring boronate ester groups were found to act as hosts for ammonium<sup>10</sup> and cesium ions,<sup>33</sup> for fullerenes,<sup>11</sup> and for (poly)aromatic compounds.<sup>14,16–20,36</sup> Materials based on boronate ester cages are of interest for gas sorption or separation, and cages with Brunauer-Emmett-Teller (BET) surface areas of more than 3400 m<sup>2</sup> g<sup>-1</sup> have been reported.<sup>25</sup> A potential drawback for applications is the susceptibility of boronate ester- and boroxine-based cages toward hydrolytic degradation. Attempts have been made to stabilize boronate ester cages by a postsynthetic modification (intramolecular alkene metathesis),<sup>24</sup> but the required synthetic efforts are substantial.

Below, we describe the synthesis and characterization of boronate ester cages, which are stabilized by a coordination to

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internal metal ions. The cages are less prone to hydrolytic degradation, and the vertices of the cages can be decorated in a flexible fashion with different functional groups.

#### RESULTS AND DISCUSSION

Boronate ester-capped metal complexes of type A (Figure 2) were first described by Bosten and Rose in 1968.<sup>38</sup> These



Figure 2. General structure of boronate ester-capped clathrochelates (A) and monocapped pyridyloximato complexes (B).

complexes classify as "clathrochelates"<sup>39,40</sup> because the central metal ion is completely surrounded by a macrobicyclic ligand framework.

Boronate-ester capped clathrochelate complexes feature remarkably inert B–O bonds. On the one hand, as a consequence, they do not degrade in an aqueous solution, enabling biological applications.<sup>41</sup> On the other hand, they are not suited as constitutionally dynamic links in supramolecular chemistry. However, clathrochelates with additional donor groups in an apical position can be used as versatile metalloligands.<sup>42,43</sup>

Complexes of type **A** are obtained by a metal-templated condensation reaction of a 1,2-dioxime with a boronic acid.<sup>39,40</sup> Using a pyridyloxime instead of a dioxime leads to monocapped, cationic complexes of type **B** (Figure 2).<sup>44,45</sup> The reported synthetic procedures indicate that the monocapped complexes are not prone to hydrolytic degradation (e.g.,  $CH_2Cl_2$  solutions of the Ni<sup>II</sup> complex can be washed with water).<sup>44</sup>

We recently described first attempts to integrate compounds of type **B** into more complex molecular architectures. In particular, we have shown that dinuclear complexes with a helicate-like structure can be obtained when ditopic bispyridyloxime ligands were employed instead of simple pyridyloximes.<sup>46</sup> However, there was no information on whether the helicates were formed under kinetic or (partial) thermodynamic control.

Prior to targeting even more elaborate cage structures, we decided to examine the structures and the dynamic behavior of monocapped pyridyloximato complexes. For this purpose, we synthesized the new complexes **1-Fe** and **1-Zn** by a reaction of pyridine-2-aldoxime (3 equiv) with phenylboronic acid (1 equiv) and  $M(OTf)_2$  (1 equiv; M = Fe or Zn) (Scheme 1). For the synthesis of **1-Fe**, acetonitrile was used as the solvent (reflux, 90 min, 82% yield). The synthesis of the Zn<sup>II</sup> complex **1-Zn** was accomplished in ethanol in the presence of NaHCO<sub>3</sub> (reflux, 3 h, 85%).

The complexes were characterized by NMR spectroscopy, high-resolution mass spectrometry, and by single-crystal X-ray diffraction (Figure 3). Whereas the Zn–N bonds in **1-Zn** are all of a similar length (2.13–2.19 Å), one can observe distinct



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**Figure 3.** Molecular structure of **1-Fe** (a) and **1-Zn** (b) in the crystal, with views from the side and along the  $M \cdots B$  axis. Triflate anions and hydrogen atoms are not shown for clarity.

differences between the lengths of the Fe–N<sub>oximato</sub> and the Fe–N<sub>pyridyl</sub> bonds, with the former being 0.1 Å shorter (1.89 vs 1.99 Å). Another noteworthy difference between 1-Fe and 1-Zn is the coordination geometry of the metal ion. For 1-Zn, one can observe a distorted trigonal prismatic geometry with an average twist angle<sup>47</sup> of  $\varphi_{av} = 14^{\circ}$ . The coordination geometry of the Fe<sup>II</sup> complex, however, is better described as distorted octahedral with an average twist angle of  $\varphi_{av} = 40^{\circ}$ . The different coordination environments of the two complexes also influences the boronate ester capping groups. Because of the increased octahedral character of 1-Fe, the boron atom is closer to the metal center than in 1-Zn (2.98 Å for 1-Fe vs 3.27 Å for 1-Zn).

Next, we investigated the lability of 1-Zn by performing exchange reactions. Solutions of the complex in methanol or acetonitrile (13 mM) were mixed with 4-*tert*-butylphenylboronic acid (1 equiv) or 2-acetylpyridine oxime (3 equiv) (Scheme 2).

After an equilibration time of 15 min at 30  $^{\circ}$ C, the resulting mixtures were investigated by mass spectrometry. For the reactions with the boronic acid, we observed approximately equally intense peaks for complexes with a phenylboronate ester and with a 4-*tert*-butylphenylboronate ester cap (see the Supporting Information, Figures S49 and S50). For the reaction with 2-acetylpyridine oxime, we observed peaks for complexes containing zero, one, two, or three 2-acetylpyridine oximato ligands. These experiments indicate that ligand exchange reactions involving B–O bond rupture are possible for monocapped pyridyloximato complexes.

Encouraged by these results, we set out to explore if boronate ester cages can be obtained with capped pyridyloximato complexes as links. For this purpose, we used the tritopic ligand 2 (Scheme 3). This ligand was obtained from the pubs.acs.org/IC

Scheme 2. Exchange Reactions with 4-*tert*-Butylphenylboronic Acid (a) and with 2-Acetylpyridine Oxime (b)



corresponding trialdehyde<sup>48</sup> by a condensation with hydroxylamine hydrochloride.

#### Scheme 3. Synthesis of the Tetrahedral Cages 3-M<sup>a</sup>



 $^{a}M = Fe, Zn, Co, Mn.$ 

First test reactions with  $MX_2$  salts (X = OTf or  $NTf_2$ ) and phenylboronic acid showed that tetranuclear condensation products had formed (NMR and/or MS data), but the polycondensation reactions were incomplete. Using the slightly more soluble 3-bromophenylboronic acid and a more forcing reaction condition (dry acetonitrile, microwave heating, 120 °C, 4 h) gave improved results, and we were able to obtain the cages 3-M (M = Fe, Zn, Co, Mn) with isolated yields of ~50% after a precipitation with diethyl ether (Scheme 3). NMR characterization in solution was possible for the diamagnetic complexes 3-Fe and 3-Zn, whereas the paramagnetic<sup>44</sup> complexes 3-Co and 3-Mn were analyzed by mass spectrometry. The high-resolution electrospray ionization (ESI) mass spectrum of cage 3-Mn is characteristic for this kind of assembly and presents three major peaks corresponding to the cationic cage with a variable number of anions, namely, [3-Mn-4OTf]<sup>4+</sup>, [3-Mn-3OTf]<sup>3+</sup>, and [3-Mn-2OTf]<sup>2+</sup> (Figure 4).



**Figure 4.** HR-MS of cage **3-Mn**, with an enlargement of the isotopic distribution at m/z = 926 (inset).

The molecular structures of **3-Zn** and **3-Mn** were determined by single-crystal X-ray diffraction (Figure 5). The diffraction data were of moderate quality, and most of the triflate ions could not be located with accuracy. Only one encapsulated TfO<sup>-</sup> ion in the cavity of **3-Mn** could be refined (Figure 5b). The coordination environment of the Zn<sup>II</sup> ions in **3-Zn** is similar to what was observed for the mononuclear complex **1-Zn**: the six N-donor atoms are arranged in a distorted trigonal prismatic fashion ( $\varphi_{av} = 19^{\circ}$ ) with an average Zn–N bond length of 2.16 Å. Slightly shorter metal–nitrogen bond distances of Mn–N<sub>av</sub> = 2.11 Å are found for the Mn<sup>II</sup> complex **3-Mn**, but the coordination geometry is very similar, with an average twist angle of  $\varphi_{av} = 19^{\circ}$ .

The distortion from an ideal trigonal prismatic geometry implies that the four metal centers in 3-Zn and 3-Mn are chiral, and they display the same chirality in the crystal  $(4 \times \Delta \text{ or } 4 \times \Lambda)$ .

An interesting feature of boronate ester-capped metal complexes is the possibility to introduce addition functional groups by using a functionalized boronic acid during the synthesis.<sup>40-43</sup> Tetrahedral cages can also be decorated with pending functional groups, as evidenced by the synthesis of cages with cyano (4-Zn) and aldehyde (5-Zn and 6-Zn, Scheme 4) groups.<sup>49</sup>

The complexes **4-Zn**, **5-Zn**, and **6-Zn** were characterized by NMR spectroscopy and high-resolution mass spectrometry. In addition, we were able to determine the solid-state structures of **4-Zn** and **6-Zn** by single-crystal X-ray diffraction (Figure 6).



Figure 5. Molecular structure of the cationic cages of 3-Zn (a) and of 3-Mn with encapsulated  $TfO^{-}$  (b) in the crystal. Hydrogen atoms are not shown for clarity.

Scheme 4. Synthesis of Zinc Cages with Pendent Cyano (a) and Aldehyde Groups in Para (b) and Meta Position (c)



The overall geometry of these cages is similar to what was found for **3-Zn**. The cyano groups in **4-Zn** are 2.8 nm apart from each other. It is worth noting that clathrochelate complexes with pendent cyano groups have been used in the past for the synthesis of coordination polymers with unusual network topologies.<sup>50</sup> Cage **4-Zn** could potentially be used as a nanoscale link for creating 4-connected networks. The aldehyde-functionalized cages **5-Zn** and **6-Zn**, on the one hand, could serve as building blocks in reactions with amines.<sup>51</sup> On the other hand, amine-aldehyde condensations liberate water, and the presence of boronate ester groups in **5-Zn** and **6-Zn** presents a potential obstacle. We thus examined the



Figure 6. Molecular structure of the cationic cages of 4-Zn (a) and of 6-Zn (b) in the crystal. Hydrogen atoms are not shown for clarity.

hydrolytic stability of the cages using **6-Zn** as a representative example. Increasing amounts of  $D_2O$  were added to a solution of **6-Zn** in CD<sub>3</sub>CN (2.5 mM). Up to 10 vol %  $D_2O$  were welltolerated. With 15 vol %  $D_2O$ , small amounts of decomposition products could be detected by NMR spectroscopy (Figure S47). Cage **6-Zn** also displays an increased kinetic inertness when compared to the mononuclear complex **1-Zn**: the addition of 4-*tert*-butylphenylboronic acid (4 equiv) to a solution of **6-Zn** in CH<sub>3</sub>CN (5 mM) did lead to only a minor exchange of the boronate ester cap, as evidenced by an MS analysis after the mixture was tempered for an hour at 50 °C.

To demonstrate the feasibility of a postsynthetic functionalization<sup>52</sup> via an imine bond formation, we examined the reaction of **5-Zn** with 4-pentylaniline. An imine formation was achieved by heating a solution of the two compounds in acetonitrile for 48 h. The resulting imine-decorated cage **7-Zn** was obtained after a precipitation with diethyl ether with an isolated yield of 65% (Scheme 5).

#### CONCLUSION

We have shown that arylboronate ester-capped pyridyloximato complexes are constitutionally dynamic compounds, which are able to undergo exchange reactions with boronic acids and pyridyl oxime ligands. This feature makes them well-suited for the construction of complex supramolecular structures. By using a tris(2-formylpyridine oxime) ligand, we have been able to obtain tetrahedral cages with boronate ester caps in metaltemplated polycondensation reactions. Because of the presence

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#### Scheme 5. Postsynthetic Modification of 5-Zn



of internally coordinated M<sup>II</sup> ions, the cages display an increased hydrolytic stability when compared to purely organic cages with boronate ester or boroxine links. However, the presence of metal ions introduces charges and counterions. The latter can occupy the cage cavity and potential external voids. Consequently, it is unlikely that assemblies based on boronate ester-capped pyridyloximato complexes will lead to materials with permanent porosity, as it was observed for some charge-neutral boronate ester cages.<sup>25</sup> It is also worthwhile to compare the new cages with a tetrahedral imine cage (8-Zn), which was obtained by a Zn<sup>2+</sup>-templated condensation of a phenyl-centered tris(2-formylpyridine) ligand with tris(2aminoethyl)amine (tren).53 This imine cage is structurally similar to the Zn<sup>2+</sup> cages described here, even though its cavity is a bit smaller (see Figure S54). One difference is the reduced charge of our cages (4+) compared to the charge of the imine cage (8+), which could influence the solubility and host-guest chemistry. An advantage of boronate ester caps compared to tren-based caps is the possibility to introduce functional groups at the cage vertices by using an appropriate boronic acid. Functionalized cages could be used as nanoscale building blocks for more complex molecular assemblies or polymeric materials.54,55

#### ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.inorgchem.1c01719.

Experimental procedures and analytical data of the ligands and cages (<sup>1</sup>H, <sup>13</sup>C, DOSY NMR, HRMS) (PDF)

#### Accession Codes

CCDC 2061750–2061753 and 2080461–2080462 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/ data\_request/cif, or by emailing 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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#### Notes

The authors declare no competing financial interest.

Crystallographic data for the structures reported in this paper have been deposited at the Cambridge Crystallographic Data Center (CCDC) as supplementary publications CCDC 2061750 (3-Zn), 2061751 (3-Mn), 2061752 (4-Zn), 2061753 (6-Zn), 2080461 (1-Fe), 2080462 (1-Zn).

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