1
Structure, Properties, and Preparation of Boronic Acid Derivatives
Overview of Their Reactions and Applications

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1.1
Introduction and Historical Background

Structurally, boronic acids are trivalent boron-containing organic compounds that possess one carbon-based substituent (i.e., a C−B bond) and two hydroxyl groups to fill the remaining valences on the boron atom (Figure 1.1). With only six valence electrons and a consequent deficiency of two electrons, the sp^2-hybridized boron atom possesses a vacant p-orbital. This low-energy orbital is orthogonal to the three substituents, which are oriented in a trigonal planar geometry. Unlike carboxylic acids, their carbon analogues, boronic acids, are not found in nature. These abiotic compounds are derived synthetically from primary sources of boron such as boric acid, which is made by the acidification of borax with carbon dioxide. Borate esters, one of the key precursors of boronic acid derivatives, are made by simple dehydration of boric acid with alcohols. The first preparation and isolation of a boronic acid was reported by Frankland in 1860 [1]. By treating diethylzinc with triethylborate, the highly air-sensitive triethylborane was obtained, and its slow oxidation in ambient air eventually provided ethylboronic acid. Boronic acids are the products of a twofold oxidation of boranes. Their stability to atmospheric oxidation is considerably superior to that of borinic acids, which result from the first oxidation of boranes. The product of a third oxidation of boranes, boric acid, is a very stable and relatively benign compound to humans (Section 1.2.2.3).

Their unique properties and reactivity as mild organic Lewis acids, coupled with their stability and ease of handling, are what make boronic acids a particularly attractive class of synthetic intermediates. Moreover, because of their low toxicity and their ultimate degradation into boric acid, boronic acids can be regarded as "green" (environment-friendly) compounds. They are solids, and tend to exist as mixtures of oligomeric anhydrides, in particular the cyclic six-membered boroxines (Figure 1.1). For this reason and other considerations outlined later in this chapter, the corresponding boronic esters are often preferred as synthetic intermediates. Although other classes of organoboron compounds have found tremendous utility

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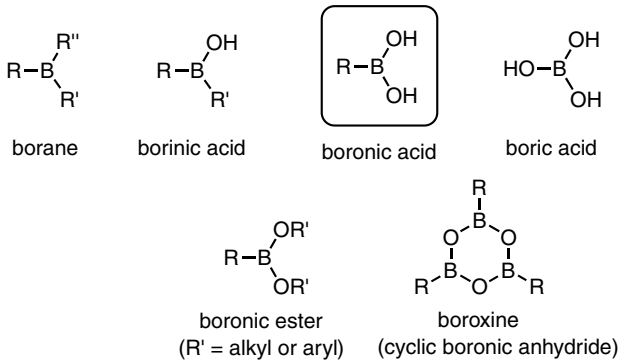

Figure 1.1 Oxygen-containing organoboron compounds.

in organic synthesis, this book focuses on the most recent applications of the convenient boronic acid derivatives. For a comprehensive description of the properties and reactivity of other classes of organoboron compounds, interested readers may refer to a selection of excellent monographs and reviews by Brown [2], Matteson [3], and others [4–8]. In the past two decades, the status of boronic acids in chemistry has gone from that of peculiar and rather neglected compounds to that of a prime class of synthetic intermediates in their own right. The attribution of the 2010 Chemistry Nobel Prize for palladium-catalyzed cross-coupling reactions to Professor Akira Suzuki and other pioneers recognized the great importance of boronic acids in this revolutionary class of C–C bond forming processes. In the past 5 years, impressive advances have been made in the use of boronic acids in molecular recognition, materials science, and catalysis. The approval of the anticancer agent Velcade®, the first boronic acid-containing drug to be commercialized (Section 1.6.5), further confirms the growing status of boronic acids as an important class of compounds in chemistry and medicine. This chapter describes the structural and physicochemical properties of boronic acids and their many derivatives, as well as modern methods for their preparation. A brief overview of their synthetic and biological applications is presented, with an emphasis on topics that are not covered in other chapters of this book.

1.2 Structure and Properties of Boronic Acid Derivatives

1.2.1 General Types and Nomenclature of Boronic Acid Derivatives

The reactivity and properties of boronic acids highly depend upon the nature of their single variable substituent, more specifically, on the type of carbon group (R, Figure 1.1) directly bonded to boron. In the same customary way employed for

other functional groups, it is convenient to classify boronic acids into subtypes such as alkyl-, alkenyl-, alkynyl-, and arylboronic acids.

When treated as an independent substituent, the prefix borono is employed to name the boronyl group (e.g., 3-boronoacrolein). For cyclic derivatives such as boronic esters, the IUPAC RB-1-1 rules for small heterocycles (i.e., the Hantzsch–Widman system) are employed along with the prefix "boro." Thus, saturated five- and six-membered cyclic boronic esters are, respectively, named as dioxaborolanes and dioxaborinanes. For example, the formal name of the pinacol ester of phenylboronic acid is 2-phenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. The corresponding nitrogen analogues are called diazaborolidines and diazaborinanes, and the mixed nitrogen–oxygen heterocycles are denoted by the prefix oxaza. Unsaturated heterocycles wherein the R group and the boron atom are part of the same ring are named as boroles.

1.2.2 Boronic Acids

1.2.2.1 Structure and Bonding

The X-ray crystal structure of phenylboronic acid (**1**, Figure 1.2) was reported in 1977 by Rettig and Trotter [9]. The crystals are orthorhombic, and each asymmetric unit was found to consist of two distinct molecules, bound together through a pair of O−H−O hydrogen bonds (Figure 1.3a and b). The CBO_2 plane is quite coplanar with the benzene ring, with a respective twist around the C−B bond of 6.6° and 21.4° for the two independent molecules of $PhB(OH)_2$. Each dimeric ensemble is also linked with hydrogen bonds to four other similar units to give an infinite array of layers

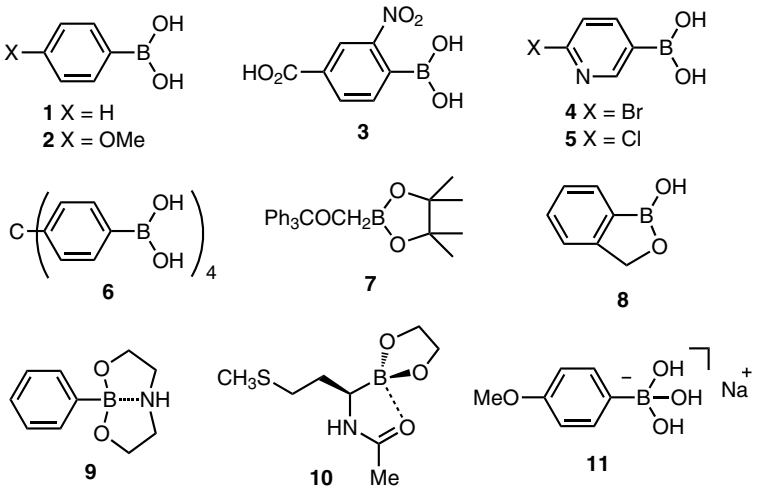

Figure 1.2 Boronic acid derivatives analyzed by X-ray crystallography.

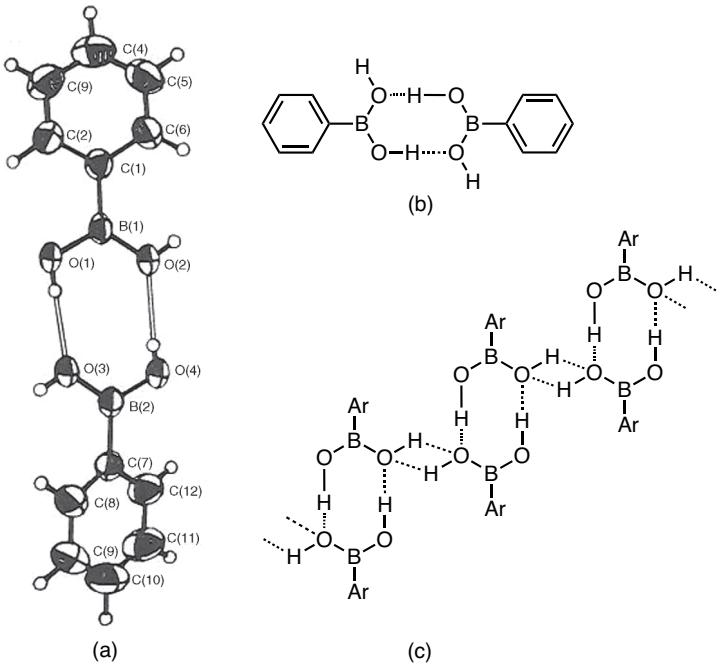

Figure 1.3 Representations of the X-ray crystallographic structure of phenylboronic acid. (a) ORTEP view of a dimeric unit. (b) Structure of the dimeric unit showing hydrogen bonds. (c) Structure of the extended hydrogen-bonded network.

(Figure 1.3c). The X-ray crystallographic analysis of other arylboronic acids like *p*-methoxyphenyl boronic acid (**2**) [10] and 4-carboxy-2-nitrophenylboronic acid (**3**, Figure 1.2) [11] is consistent with this pattern. The structures of heterocyclic boronic acids such as 2-bromo- and 2-chloro 5-pyridylboronic acids (**4** and **5**) were reported [12]. Although the boronate group has a trigonal geometry and is fairly coplanar with the benzene ring in structures **1**, **2**, **4**, and **5**, it is almost perpendicular to the ring in structure **3**. This observation is likely due to a combination of two factors: minimization of steric strain with the *ortho*-nitro group, and because of a possible interaction between one oxygen of the nitro group and the trigonal boron atom. Based on the structural behavior of phenylboronic acid and its propensity to form hydrogen-bonded dimers, diamond-like porous solids were designed and prepared by the crystallization of tetrahedral-shaped tetraboronic acid **6** (Figure 1.2) [13]. With a range of approximately 1.55–1.59 Å, the C–B bond of boronic acids and esters is slightly longer than typical C–C single bonds (Table 1.1). The average C–B bond energy is also slightly smaller than that of C–C bonds (323 versus 358 kJ/mol) [14]. Consistent with strong B–O bonds, the B–O distances of tricoordinate boronic acids such as phenylboronic acid are fairly short, and lie in the range of 1.35–1.38 Å (Table 1.1). These values are slightly larger than those observed in boronic esters. For example, the B–O bond distances observed in the X-ray crystal-

Table 1.1 Bond distances from X-ray crystallographic data for selected boronic acid derivatives (Figure 1.2).

Compound	B–C (Å)	B–O^1 (Å)	B–O^2 (Å)	B–X (Å)	Reference
1	1.568	1.378	1.362		[9]
2	1.556				[10]
3	1.588	1.365	1.346		[11]
4	1.573	1.363	1.357		[12]
5	1.573	1.362	1.352		[12]
7	1.560	1.316	1.314		[15]
8	1.494	1.408	1.372		[16]
9	1.613	1.474	1.460	1.666	[18]
10	1.613	1.438	1.431	1.641	[22]
11	1.631	1.492	1.487	1.471	[23]

lographic structures of the trityloxymethyl pinacolate boronic esters (e.g., **7** in Figure 1.2) are in the range of 1.31–1.35 Å (Table 1.1), and the dioxaborolane unit of these derivatives is nearly planar [15]. The X-ray crystallographic structure of cyclic hemiester **8** (Figure 1.2) was described [16]. Like phenylboronic acid, this benzoxaborole also crystallizes as a hydrogen-bonded dimer, however without the extended network due to the absence of a second hydroxyl group. The cyclic nature of this derivative induces a slight deviation from planarity for the tricoordinate boronate unit, as well as a distortion of the bond angles. The endocyclic B–O bond in **8** is slightly longer than the B–OH bond. This observation was attributed to the geometrical constraints of the ring, which prevents effective lone pair conjugation between the endocyclic oxygen and the vacant orbital of boron. The unique properties and reactivity of benzoxaboroles along with their preparation were recently reviewed [17].

In order to complete boron's octet, boronic acids and their esters may also coordinate basic molecules and exist as stable tetracoordinated adducts. For example, the X-ray crystallographic structure of the diethanolamine adduct of phenylboronic acid (**9**, Figure 1.2) [18] confirmed the transannular B–N bridge long suspected from other spectroscopic evidence such as NMR [19, 20]. This dative B–N bond has a length of 1.67 Å (Table 1.1), and it induces a strong $N^{\delta+}-B^{\delta-}$ dipole that points away from the plane of the aryl ring. This effect was elegantly exploited in the design of a diboronate receptor for paraquat [21]. Chelated boronic ester **10** presents characteristics similar to that of **9** [22]. Trihydroxyborate salts of boronic acids are discrete, isolable derivatives that had not been characterized until recently [23]. The sodium salt of *p*-methoxyphenyl boronic acid (**11**) was recrystallized in water and its X-ray structural elucidation showed the borate unit in the expected hydrogen bonding network accompanied with the sodium cation coordinated with six molecules of water. In principle, the boron atom in tetrahedral complexes can be stereogenic if it is bonded to four different ligands. Hutton and coworkers recently reported the first example of one such optically pure complex stereogenic at boron only [24]. Stable complex **12** (Figure 1.4) was made through a chirality transfer process described in

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