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Feature article

Biomedical applications of boronic acid polymers

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ABSTRACT

Boron-containing organic compounds have found widespread use in synthetic organic chemistry. More recently, boronic acid-containing polymers have proven valuable in a variety of biomedical applications, including the treatment of HIV, obesity, diabetes, and cancer. However, as compared to many other classes of functional polymers, boronic acid-containing (co)polymers remain underutilized, despite their unique reactivity, solubility, and responsive nature. This Feature Article highlights research in this area, with particular focus on recent developments in synthesis, processing, and materials development that have enabled the preparation of new biomaterials. In addition to providing an overview to the current state of the art, we emphasize the versatility of boronic acid polymers and suggest routes for their further employment in other potential biomedical applications.

1. Introduction

Boronic acids contain trivalent boron atoms bonded to one alkyl/aryl substituent and two hydroxyl groups (R–$B(OH)_2$) [1]. Unlike carboxylic acids, boronic acids are not naturally occurring, though they have appeared in the literature since at least 1860 [2]. Unique and versatile reactivity [3] and stability [4] of boronic acids have led to uses in numerous areas, including C–C bond formation, acid catalysis, asymmetric synthesis, carbohydrate analysis, metal-catalysis, molecular sensing, and as therapeutic agents, enzyme inhibitors, and novel materials (Fig. 1) [3].

Several unique characteristics of boronic acids make them well suited for biomedical applications [5]. The empty *p*-orbital on boron leads to Lewis acidity and facile interconversion from sp^2 to sp^3 hybridization in the presence of Lewis bases. In aqueous media, this interconversion can readily occur by reaction with water, such that neutral and trigonal boron is converted to an anionic tetrahedral geometry. The pH at which this reaction occurs for 50% of the boronic acid groups is defined as the pK_a, with most boronic acids having $pK_a \approx 4.5–10$ [5–7]. Most of the polymeric boronic acids reported in the literature contain phenylboronic acid moieties (-Ph-$B(OH)_2$) [8,9]. Addition of various substituents on the phenyl ring allows the pK_a to be tuned so that boronic acid-containing polymers can be employed in a physiologically relevant pH range [5,10,11].

Perhaps the most important chemical characteristic that has led to boronic acids finding utility in a plethora of biomedical applications is the ability to form reversible covalent complexes with 1,2- or 1,3-diols [4,7]. In aqueous systems, boronic acids exist in equilibrium between an undissociated neutral trigonal form (**1**) and a dissociated anionic tetrahedral form (**2**) (Scheme 1) [10,12–15]. In the presence of 1,2- or 1,3-diols, cyclic boronate esters formed by reaction of the neutral boronic acid with a diol are generally considered hydrolytically unstable [13]. On the other hand, reaction of the anionic boronate anion (**2**) with a diol leads to stable boronate esters (**3**). Therefore, the net effect of adding reactive diols to boronic acids (**1**) in aqueous media is a shift in equilibrium to the anionic forms (**2** and **3**) [10]. For polymeric boronic acids, this transition from a neutral, and often hydrophobic polymer to a hydrophilic polyanion can lead to useful "diol-responsive" behavior.

Also of importance for biological applications, many boron compounds exhibit unique neutron bombardment behavior [5]. Boron naturally consists of two non-radioactive isotopes, boron-10 and boron-11. Boron-10 is in ~20% natural abundance and has the ability to capture low energy thermal neutrons to release lithium-7 nuclei and alpha particles capable of low penetration of alpha radiation [17]. Because these particles are capable of moving a distance approximately the width of a cell, boron neutron capture therapy (BNCT) is particularly well suited for localized radiation therapy [17–21].

An encouraging sign for the use of boronic acids in medical applications is a lack of apparent toxicity or *in vivo* instability issues. Bortezomib (Velcade®), a boronic acid-based proteasome inhibitor,

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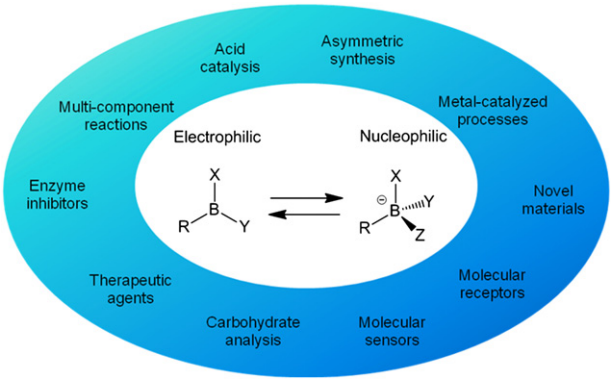


Fig. 1. Various uses of boronic acids [3]. Adapted from Aust. J. Chem., 60, Petasis, N.A., "Expanding roles for organoboron compounds – Versatile and valuable molecules for synthetic, biological, and medicinal chemistry", 795–798. Copyright (2007), with permission from CSIRO.

was approved by the US Food and Drug Administration in May 2003 for the treatment of multiple myeloma with no unacceptable toxicity issues [5,22,23]. The eventual end product in the breakdown of boronic acid-containing compounds is generally boric acid, which is not particularly toxic to humans [5,24,25]. Boron is present in various foods [26] and a variety of consumer products [27]. However, despite these encouraging signs, ultimately the toxicity of each boronic acid considered for biological use requires individual assessment.

Several reviews describe the use of small molecule boronic acids in medical applications [3–5,28], but significantly less attention has been dedicated to summarizing the biological utility of boronic acid-containing polymers. The use of polymers in biotechnology, particularly drug delivery, provides several well-known benefits, including increased activity caused by multivalency and the possibility of slow and controlled drug release with targeted biodistribution. Macromolecular drug delivery vehicles can provide increased circulation time in the body since their relatively large size significantly limits rates of glomerular filtration [29]. Additionally, small molecules can be readily removed from the body by the reticuloendothelial system (RES), while large hydrophilic polymer-based systems may not be as readily detected, thus increasing their circulation time [30].

Boronic acid-containing polymers with their unique reactivity and stimuli-responsive behavior have potential applications as self-healing materials, therapeutic agents, self-regulated drug delivery systems, nucleotide adsorbents, and sensors for sugars and glycoproteins [8,28,31–39]. In this Feature Article, we highlight recent reports of boronic acid-containing polymers being used in biomedical applications. Focus will be given to materials that serve as lipase inhibitors, human immunodeficiency virus (HIV) inhibitors, glucose sensors, insulin delivery systems, dopamine sensors, supports for cell growth, and BNCT agents.

2. Lipase inhibition

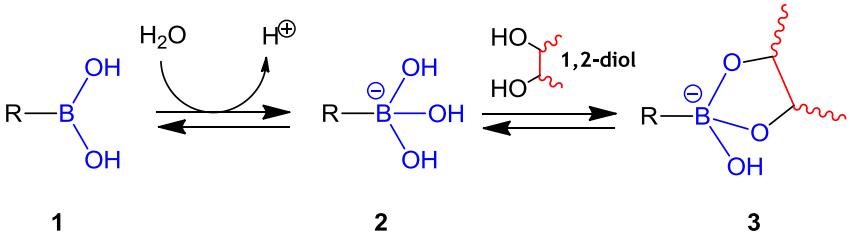
Obesity, defined as abnormal or excessive fat that has accumulated to an extent that may have an adverse effect on health, is a major problem, particularly in the developed world. Obesity can lead to increased risk for cardiovascular disease (*e.g.*, heart disease and stroke), diabetes, musculoskeletal disorders, and some forms of cancers, such as endometrial, breast, and colon. To combat obesity, diets low in fat and calories are often recommended, but the incidence of compliance and maintenance of these diets is often low [40]. Several chemical approaches, such as anorectic drugs, have been used in an attempt to reduce appetite and food consumption. However, all of these methods have associated risks and complications, and the most successful technique for controlling obesity is currently controlled diet [40].

Dietary fat must be hydrolyzed prior to absorption by the digestive tract. Lipases are enzymes responsible for the hydrolysis of insoluble hydrophobic lipids [41]. Lipases hydrolyze lipids to enable absorption by the digestive tract. Phenylboronic acid groups have been shown to inhibit hydrolases, including lipases [42,43] and proteases [44–46]. The ability of boronic acids to readily convert between a neutral trigonal sp^2 and anionic tetrahedral sp^3 geometry is similar to that of an sp^2 carbonyl carbon converting to a tetrahedral sp^3 carbon during the hydrolysis of amide or ester bonds [5]. The inhibitory action of boronic acids is generally thought to occur by the trigonal boronic acid forming a negatively charged tetrahedral complex with a serine hydroxyl group in the lipase active center (Scheme 2) [47]. The affinity of the enzymes for the boronic acid residues is greater than that for typical lipid substrates by a factor of 10^2-10^4 [48].

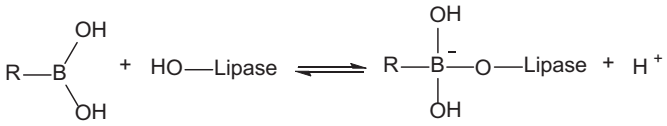
Lipase inhibitors can be used to prevent the hydrolysis of lipids and thereby reduce fat absorption in the digestive tract. Undigested triglycerides and diglycerides are then removed from the body without significant absorption. While caloric intake is decreased as a result, an unfortunate side effect is the occurrence of subsequent leaky or oily stools. Therefore, fat-binding polymers can be administered in combination with lipase inhibitors to stabilize/complex the undigested oils [49]. Polymers with electron withdrawing groups either *para* or *meta* to pendent aryl boronic acids have been shown to be effective lipase inhibitors while simultaneously serving as fat binders to help reduce the occurrence of these unpleasant side effects [40].

3. HIV inhibition

HIV is the virus that leads to acquired immune deficiency syndrome (AIDS) [50]. In 2009, there were an estimated 2.6 million people newly infected with HIV, 1.8 million in sub-Saharan Africa alone. While HIV can spread by a variety of mechanisms, unprotected heterosexual intercourse is the dominant mode of HIV transmission. Considering this, a clear need exists for women-controlled prophylactics or microbicides that prevent HIV infection [51]. The design of effective microbicides requires understanding of vaginal physiology and the mechanism of heterosexual



Scheme 1. Ionization equilibria of boronic acids in aqueous media [16].



Scheme 2. Lipase inhibition by formation of a tetrahedral boronate adduct with an active site serine hydroxyl [48].

HIV transmission. Vaginal fluid has a precoital pH that is acidic, ranging from pH ≈4–5. Semen is capable of neutralizing the vaginal fluid due to its alkaline nature, high buffering capacity, and larger volume [52–54]. The transmission of HIV starts through transport of virions from the seminal fluid to the mucosal surfaces in the vagina. The virions can then transverse the vaginal epithelium to enter the sub-epithelial tissue where the CD4 + T-cells, macrophages, and dendritic cells are infected [55]. Targets for active agents in microbicides include the mucosa, tissue or cell/virus surfaces and interruption of the replication cycle within the cell [55].

Kiser and coworkers synthesized polymers capable of exploiting the well-known complexation behavior between phenylboronic acid moieties and diols to form hydrogel networks in physiological pH ranges. Boronic acid-containing polymers were shown to form reversible covalent interactions with salicylhydroxamic acid (SHA) moieties on another polymer. Typically phenylboronic acids form stable complexes with diols in neutral or alkaline environments [10,12–14]; however, SHA has been shown to also form stable complexes with phenylboronic acid at mildly acidic pHs [56,57]. When two random copolymers of 2-hydroxypropylmethacrylamide (HPMA) or acrylic acid (AA) and 10 mol% *N*-[3-(2-methylacryloylamino) propyl]-4-amidophenylboronic acid (APMAmPBA) and HPMA or AA and 10 mol% 4-[(2-methylacryloylamino)-methyl]-salicylhydroxamic acid (MAAmSHA) were mixed, the phenylboronic acid and SHA moieties associated to form bonds that were reversible and formed a dynamically crosslinked hydrogel network (Fig. 2) [58].

The hydrogels demonstrated a responsive viscoelastic behavior with enough fluidity for application, yet at the higher pH that results after insemination, became a highly crosslinked network that entraps HIV-1 virions to prevent penetration of the mucosa. This physical barrier can potentially halt the first steps of HIV infection. Therefore, these hydrogels may serve as pH-sensitive vaginal microbicides, though other possible applications as lysosomal and gastric drug delivery systems exist [58].

The viscoelastic behavior of these gels could be controlled by varying the comonomer polymerized with the boronic acid or SHA monomer [58]. When the polymer backbone was composed of HPMA with APMAmPBA or MAAmSHA, the gel exhibited a viscous behavior and slowly flowed under gravity due to the boronic acid-SHA equilibrium lying toward the unbound state with only a few groups complexed to form a viscoelastic network. When the pH was raised to 7.6, the equilibrium shifted primarily to the bound state leading to a more highly crosslinked network. However, if AA was used as the comonomer, the gels at pH 7.6 exhibited a behavior similar to HPMA gels at pH 4.2 due to the Donnan effect [58,59]. Kiser et al. also examined copolymers with 2-acrylamido-2-methyl-1-propanesulfonic acid [60]. The negatively charged backbone allowed for reversible crosslinks to form at neutral pH, which was not typically observed in similar systems with an uncharged backbone.

In addition to fundamental studies on the viscoelastic behavior of the aforementioned boronic acid-polymeric gels, Kiser et al. examined the diffusion of Gag-Cherry labeled HIV-1 virions at various pHs to access the possibility of the poly(HPMA-*co*-APMAmPBA) and poly(HPMA-*co*-MAAmSHA) hydrogels to retain HIV virions of approximately 110–128 nm [52]. At pH 4.3, the virions were able to diffuse rapidly through the network. In general, with increasing pH, the movement of the virion particles through the hydrogel decreased. Interestingly, at pH 4.5, the HIV-1 virions had even lower diffusion coefficients than smaller (100 nm) polystyrene beads, which was attributed to the ability of the phenylboronic acid moieties to bind terminal sialic acid residues on glycosylated regions of the HIV-1 envelope protein gp120 [52].

Another possible mechanism of HIV microbicides is to inhibit entry of the virus into cells. The gp120 envelope proteins are largely responsible for entry of HIV-1 into the CD4+ cells. Balzarini proposed that carbohydrate-binding agents that target the glycans on gp120 could show a marked enhancement of HIV neutralization [61]. Hall et al. demonstrated the ability of polymers containing multiple benzoboroxole moieties to bind glycopyranosides that were similar to sugar moieties on gp120 [62]. Kiser and coworkers synthesized high molecular weight copolymers of HPMA and 5-methacrylamido-2-hydroxymethylphenylboronic acid with 25, 50, and 75 mol-% benzoboroxole groups (Fig. 3A) [63]. All three polymers demonstrated the ability to inhibit HIV entry for the strains tested, with the activity increasing with the number of benzoboroxole sites [4,63]. Hypothetically, the benzoboroxole sites on the polymer are capable of complexing with the mannose residues on gp120, rendering the HIV-1 inactive before reaching the CD4+ cells and halting HIV transmission (Fig. 3B, C) [63].

4. Saccharide sensing and controlled release/delivery

Diabetes mellitus, commonly referred to as diabetes, is a chronic disease in which the body does not manufacture or use insulin effectively. The World Health Organization (WHO) estimates that 180 million people are afflicted with diabetes, with that number being expected to double by the year 2030. Blood glucose control is typically accomplished via insulin therapy, a practice which has

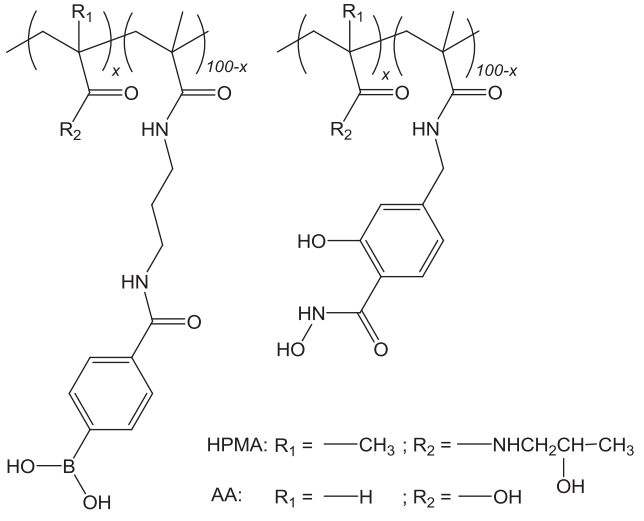


Fig. 2. Water-soluble polymers with phenylboronic acid and salicylhydroxamic acid (SHA) moieties with 2-hydroxypropylmethacrylamide (HPMA) or acrylic acid (AA) polymer backbones.

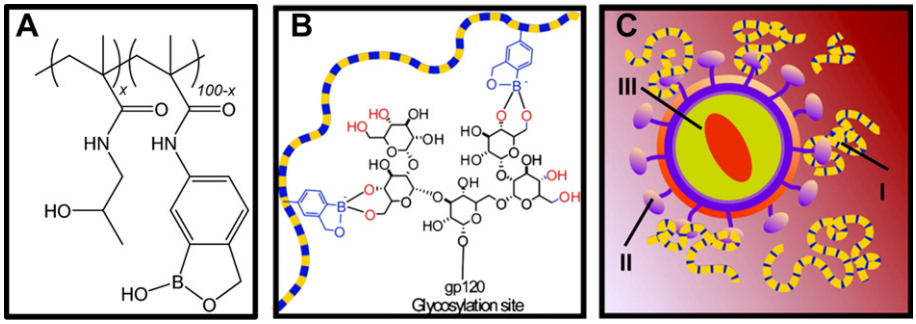


Fig. 3. (A) Poly(2-hydroxypropylmethacrylamide) (PHPMA)-*co*-poly(5-methacrylamido-2-hydroxymethylphenylboronic acid. (B) Proposed scheme of polymer-bound *o*-hydroxymethylphenylboronic acid complexed with the high mannose region of gp120. (C) Graphical depiction of the polymer (I) interacting with gp120 (II) of HIV-1 (III) [63]. Fig. 3B and C reprinted with permission from Mol. Pharmaceutics, 7, Jay, J.I., Lai, B.E., Myszka, D.G., Mahalingam, A., Langheinrich, K., Katz, D.F., Kiser, P.F., "Multivalent benzoboroxole functionalized polymers as gp120 glycan targeted microbicide entry inhibitors", 116–129. Copyright (2010) American Chemical Society.

been used since at least 1921. Because insulin must be subcutaneously injected several times per day and blood sugar values must be checked regularly, patient compliance is often low. One mechanism to increase patient compliance is the development of improved glucose monitoring systems and self-regulated insulin delivery systems.

There are numerous examples of saccharide sensors [64–66] and insulin release systems [67–79] that rely on lectins (*e.g.*, Concanavalin A) or glucose oxidase. While these methods are highly specific to glucose [64], the reliance on protein-based components may limit applications under non-biological conditions or over longer time spans due to the potential of denaturation [16,80]. Therefore, there is significant interest in the development of glucose sensing and insulin delivery systems based on purely synthetic components. Because of their ability to covalently bind with diols (*i.e.,* sugars), boronic acid-containing polymers have shown particular promise in this respect [80].

4.1. Saccharide sensing

There are several examples of boronic acid-containing sensors and receptors [81–84]. Typically, the sensing moiety is immobilized on a support that facilitates end-use applications [82]. Saccharide sensing with boronic acid-based systems generally relies on either optical property changes or conductivity changes upon binding of a sugar with a boronic acid moiety [81].

4.1.1. Optical sensors

Several methods of glucose sensing with boronic acids rely on a change in absorption upon binding with saccharides [85–89]. Shinkai et al. synthesized poly(L- and D-lysine)s modified with phenylboronic acid residues [85–87]. Upon complexation of the boronic acid groups with saccharides, the resulting anionic boronate esters led to electrostatic interaction with a cationic cyanine dye, leading the dye absorption spectrum to shift to shorter wavelengths (Fig. 4a). Wolfbeis and coworkers copolymerized aniline and 3-aminophenylboronic acid to obtain a sugar-binding polymer film (Fig. 4b) [89]. Changes in the absorption spectra were attributed to either steric effects that resulted from the insertion of the saccharide altering the interactions between the boronic acid and Lewis basic nitrogen atoms or the loss of interlayer hydrogen bonding that occurred when the boronic acid groups were converted to boronate esters. Other examples of boronic acid polymers serving as optical saccharide sensors have relied on interruption of azobenzene-boronic acid side chain complexes upon sugar-binding (Scheme 3 and Fig. 4c) [88,90].

A number of fluorescence-based saccharide sensors have been reported [91–95]. Wang and coworkers employed conventional

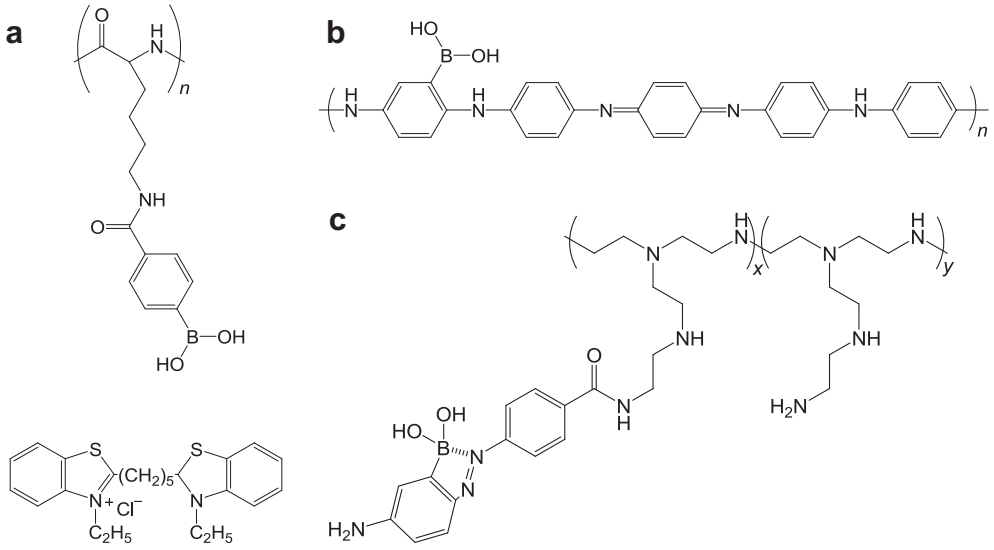
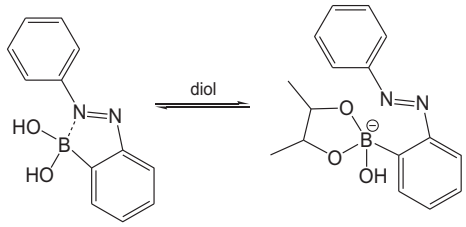


Fig. 4. Boronic acid polymers used for saccharide sensing via changes in absorption.



Scheme 3. Proposed mechanism for the sugar-induced spectral change [90]. Reprinted from Colloids Surf., B, 79, Okasaka, Y., Kitano, H., "Direct spectroscopic observation of binding of sugars to polymers having phenylboronic acids substituted with an *ortho*-phenylazo group", 434–439, Copyright (2010), with permission from Elsevier.

radical polymerization and atom transfer radical polymerization (ATRP) to prepare fluorescent imprinted polymers that contained boronic acid groups [91]. The resulting polymers showed an increase in fluorescence intensity upon the addition of D-fructose. This method of preparing sensors has been extended to other sugars and catecholamines. Singaram et al. adopted a slightly different approach for the design of fluorescence-based sensors by synthesizing a two-component system that allowed continuous blood glucose monitoring [92,96]. A hydrogel based on a cationic boronic acid-based quencher monomer and an anionic pyrene-based crosslinker was prepared by radical polymerization in the presence of 2-hydroxyethyl methacrylate and poly(ethyleneglycol dimethacrylate). The electrostatic interaction of the anionic dye and the cationic receptor resulted in quenching of the pyrene fluorescence. However, upon addition of glucose, the shift to anionic, tetrahedral boronic ester groups led to increased fluorescence due to attenuation of the electrostatic attraction between the cationic receptor/quencher and the anionic dye (Scheme 4). Because this approach was based on fully reversible electrostatic interactions, the system proved capable of continuous glucose detection. As opposed to solution-based systems, these sensing components were immobilized into thin-film poly(2-hydroxyethyl methacrylate) hydrogels suggesting their potential for *in vivo* continuous glucose detection [92,97].

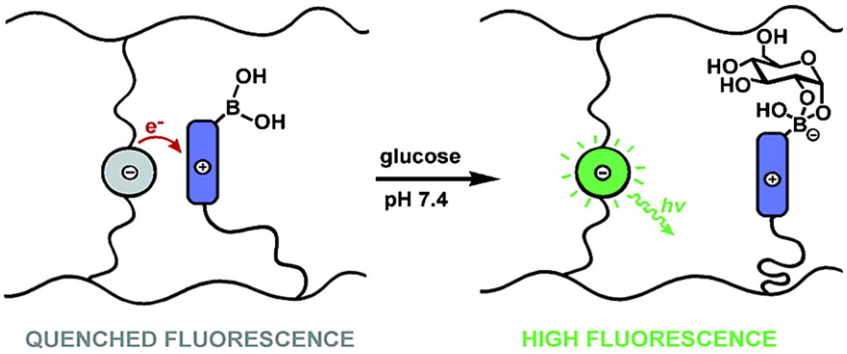
In a similar manner, Yam et al. synthesized polyacrylamide-*co*-poly(3-acrylamidophenylboronic acid) (PAPBA) copolymers and exploited the shift of the boronic acid moieties to the anionic, tetrahedral form upon binding with glucose to result in the aggregation of positively charged pyrene derivatives which led to a strong excimer emission [93]. Tao et al. synthesized a copolymer containing pyrene and boronic acid units, from 3-acrylamidophenylboronic acids (APBA) [94]. The saccharide-induced conformational change of the copolymer could be monitored via fluorescent spectroscopy.

Appleton and Gibson synthesized boronic acid-containing photoinduced electron transfer (PET) materials [98]. Polymers with amine, fluorophore, and boronic acid moieties in each repeat unit exhibited increased fluorescence in the presence of saccharides (Fig. 5a). It is believed that the saccharide binding to the boronic acid moieties enhanced the Lewis acid-Lewis base interactions between the amine and the boronic acid, which decreased the interaction of the lone pair on the amine nitrogen with the fluorophore, thereby leading to a decrease in PET and an increase in fluorescence emission. Interestingly, these polymers exhibited high specificity for glucose. James et al. reported a similar approach of saccharide sensing based on PET [99]. A small molecule amine that contained two boronic acid units and a pyrene fluorophore with a maleic anhydride copolymer backbone allowed the preparation of a variety of sensors in a modular manner (Fig. 5b).

Other methods of saccharide detection have relied on swelling of boronic acid-containing hydrogels upon glucose binding due to the increase in osmotic potential that occurs when the neutral boronic acid groups are converted to anionic boronate esters [100–108]. Asher et al. have conducted extensive research involving crystalline colloidal arrays (CCAs) embedded into a network containing phenylboronic acid units [100–104]. Because the diffraction behavior of the CCAs depend on the hydrogel volume, glucose concentration could be directly inferred from the change in diffraction wavelength (Scheme 5). Interestingly, these materials have been examined for use as ocular inserts for the monitoring of blood glucose values [101]. In a similar manner, Lowe and coworkers synthesized holographic biocompatible hydrogels using either APBA or 2-acrylamido-5-fluorophenylboronic acid [105,106]. Glucose-induced swelling of the hydrogel led to a concentration dependent red shift. Zenkl et al. synthesized crosslinked nanospheres of APBA and *N*-isopropylacrylamide (NIPAM) that contained a fluorescence resonance energy transfer donor and acceptor [107]. Swelling of the nanoparticles resulted in separation of the donor/acceptor pair which caused a decrease in the energy transfer rate.

4.1.2. Conductivity sensors

Other saccharide sensing systems have relied on a change in conductivity that occurs during the interaction of boronic acid moieties with saccharides [109–114]. Okano and coworkers prepared a copolymer of *N*,*N*-dimethylacrylamide (DMA), 3-methacrylamidophenylboronic acid (MAPBA), 3-dimethylaminopropyl acrylamide (DMAPAA), and *n*-butyl methacrylate that formed complexes when mixed with poly(vinyl alcohol) [109]. When coated on a platinum electrode, the resulting gel membranes swelled upon introduction of a saccharide. The swelling resulted in an increase in ion diffusion and thus a current



Scheme 4. Proposed electrostatic interaction between fluorescent anionic dye and a cationic, boronic acid/ester receptor in the presence and absence of glucose [96]. Reprinted with permission from Langmuir, 22, Gamsey, S., Suri, J.T., Wessling, R.A., Singaram, B., "Continuous glucose detection using boronic acid-substituted viologens in fluorescent hydrogels: Linker effects and extension to fiber optics", 9067–9074. Copyright (2006) American Chemical Society.

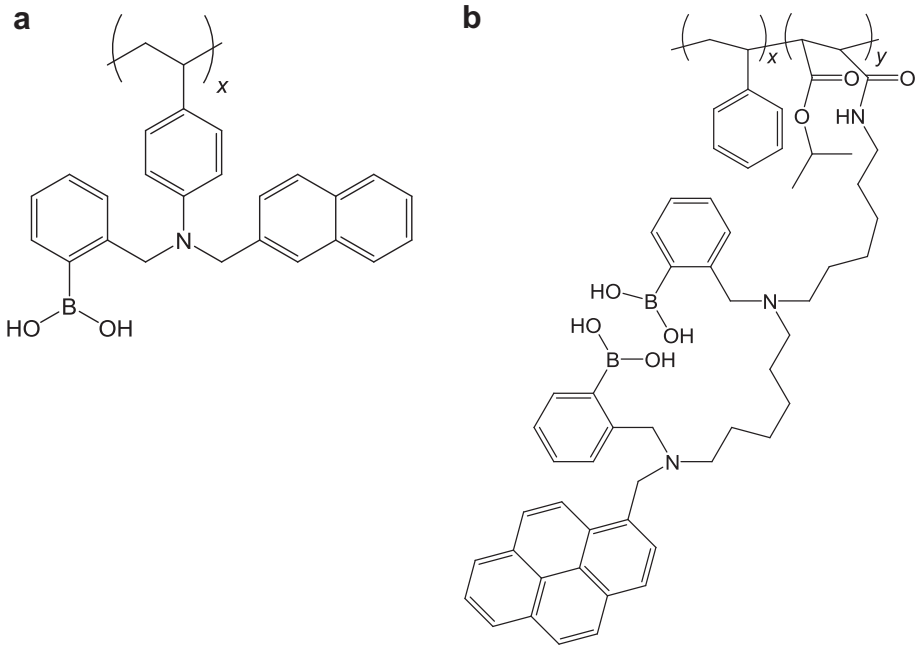


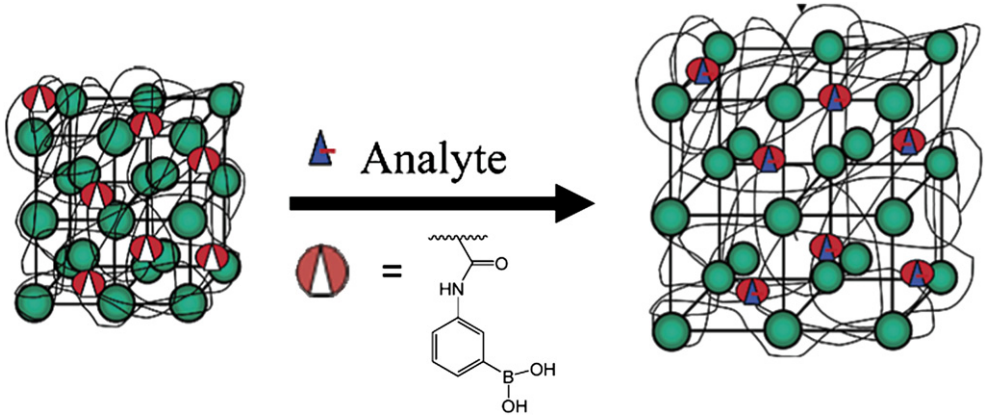
Fig. 5. Boronic acid polymers for saccharide sensing via photoinduced electron transfer (PET) [98,99].

change. Michaels and coworkers also reported a conduction-based glucose detection system based on boronic acid moieties immobilized in a hydrogel [110]. Freund et al. synthesized a poly(aniline boronic acid) (PABA)-based system capable of continuous saccharide monitoring in the physiological relevant range of 4–6 mM [111,112]. Oxidative polymerization with the horseradish peroxidase enzyme in the presence of an anionic polyelectrolyte template has been used to prepare self-doped copolymers of poly(aniline-*co*-3-aminobenzeneboronic acid) that were capable of optical and electrochemical detection of saccharides with improved sensitivity as compared to chemically synthesized counterparts [113].

4.2. Controlled release and drug delivery

Reliable knowledge of blood sugar concentrations is indeed a key component to the management of diabetes. However, treatment of the disease typically requires insulin delivery. Boronic acid polymers have proven useful in this respect as well, with most delivery strategies relying on the change in hydrophilicity brought on by conversion of neutral boronic acid moieties to anionic boronate esters upon reaction with a diol (*i.e.*, glucose) [14]. As the concentration of a compatible diol is increased, the ratio of the anionic boronate (**2**) and boronate ester (**3**) to neutral boronic acid (**1**) increases, and the hydrophilicity of the system is enhanced (Scheme 1) [12].

Many of the boronic acid-based polymers for insulin delivery are hydrogels that either swell or collapse in response to the hydrophilicity increase in the presence of glucose. A number of the systems are based on APBA [9,15,115–128]. PAPBA (co)polymers can be readily prepared by the postpolymerization modification of a precursor polymer, typically PAA with a boronic acid amine. Alternatively, direct polymerization of APBA or the polymerization of its diol ester followed by deprotection has been reported (*vide*



Scheme 5. Swelling of crystalline colloidal arrays in response to carbohydrates [100]. Adapted with permission from J. Am. Chem. Soc., 125, Asher, S.A., Alexeev, V.L., Goponenko, A.V., Sharma, A.C., Lednev, I.K., Wilcox, C.S., Finegold, D.N., "Photonic crystal carbohydrate sensors: Low ionic strength sugar sensing", 3322–3329. Copyright (2003) American Chemical Society.

infra). The postpolymerization functionalization strategy of PAA has been described in several reports for the preparation of boronic acid-containing gels or microgels [9,117,124,125,127]. In several cases, the inclusion of a cationic comonomer, such as *N*,*N*-dimethylamino ethylacrylate (DMAEA) allowed the net surface charge of microgels to be switched from cationic to anionic at critical glucose concentrations (Fig. 6) [124,125]. Swelling induced by the change in charge balance allowed delivery of insulin. Instead of modification of PAA, Strongin et al. synthesized sugar-responsive hydrogels via the modification of commercially available poly(methyl methacrylate) with 3-aminophenylboronic acid moieties and demonstrated the possibility of release from the swollen hydrogels [118].

Direct copolymerization of APBA with other hydrophilic or stimuli-sensitive monomers is another strategy to prepare hydrogels capable of releasing insulin in response to increased sugar concentrations. In particular, gels composed of APBA and NIPAM have been heavily considered, as a result of the synergistic combination of sugar and temperature sensitivity [15,119–121]. In addition to increased negative charge in the presence of sugar leading to osmotic swelling, gels containing NIPAM demonstrated volume phase transition temperatures dependent on the number of boronic acid moieties. Ravaine et al. demonstrated the ability of such gels to encapsulate insulin and release it in a relatively linear manner in response to increased concentrations of glucose [120]. Xie and coworkers reported a similar system but with poly(NIPAM-*co*-APBA) side chains grafted to the poly(NIPAM-*co*-APBA) hydrogels [122]. The more highly branched systems were found to have particularly fast glucose responses.

In addition to a charge-driven increase in osmotic pressure, an alternative strategy of sugar-induced release of hydrogel-encapsulated compounds capitalizes on competitive cleavage of boronic ester crosslinks by transesterification with saccharides. For example, copolymers containing APBA have been crosslinked by complexation with compounds that contain more than one diol functionality. These multi-diol crosslinkers can be small molecules (*e.g.,* diglucosylhexanediamine [123]) or polymers (*e.g.,* poly(vinyl alcohol) [115,116]). Gels formed in this manner contain boronic ester crosslinks that can be cleaved by transesterification with monofunctional diols (*i.e.*, sugars). This approach has been employed to prepare sugar-responsive nanoparticles with narrow size distributions [126]. Upon exposure to glucose, complexes formed between the boronic acid polymer and the multi-diol crosslinker were displaced due to preferential binding to glucose molecules. The resulting decrease in cross-linking density allowed swelling and subsequent controlled release from the hydrogels or nanogels. Okano and coworkers reported a slightly different competition-based approach involving hydrogel beads that contained boronic acid units complexed to gluconic acid-modified insulin (G-Ins) [129–132]. The addition of free glucose led to displacement and linear release of G-Ins.

Dissociation of boronic acid-containing interpolyelectrolyte complexes is another mechanism for sugar-responsive delivery of potential therapeutics. De Smedt and coworkers utilized 4-sodium polystyrene sulfonate (NaPSS) and a random copolymer of APBA and DMAEA to form hollow polyelectrolyte capsules by a layer-by-layer approach [128]. Electrostatic interactions between the alternating layers of negatively charged sulfonate groups in the NaPSS and positively charged ammonium moieties in poly(APBA-*co*-DMAEA) allowed polyelectrolyte capsules to be formed at neutral pH. When the pH was raised to 9 and glucose was added to the system, a critical number of the boronic acid units became negatively charged, disrupting the electrostatic balance. The interruption of the multilayers led to dissociation of the capsules (Fig. 7).

Most of the materials described above demonstrate maximum glucose-sensitivity at pH ≈ 9–10. In an effort to synthesize gels that respond at physiologically relevant pH, Kataoka et al. recently introduced a novel boronic acid monomer, 4-(1,6-dioxo-2,5-diaza-7-oxamyl)phenylboronic acid (DDOPBA), with a pK_a of approximately 7.8 [133–135]. Gels were synthesized with DDOPBA and a thermoresponsive polymer, poly(*N*-isopropylmethacrylamide), that exhibited a phase transition temperature of approximately 40 °C. The gels underwent volume changes under physiological conditions in response to changes in glucose concentrations within the range of typical sugar levels.

In order to fully exploit the unique properties of boronic acid polymers in delivery applications, it is important to prepare well-defined copolymers with predictable molecular weights, narrow molecular distributions, and retained chain end functionalities, the latter of which is particularly important for the preparation of block copolymers capable of self-assembly into nanoscale delivery vehicles, such as micelles, vesicles, etc [136,137]. Controlled/"living" radical polymerization (CRP) methods, such as ATRP [138–140] and reversible addition-fragmentation chain transfer (RAFT) polymerization [141–145], offer control over these areas and have been used to prepare organoboron-containing polymers [32,146–164]. Jäkle and coworkers synthesized poly(4-vinylphenylboronic acid)-*b*-polystyrene (PVPBA-*b*-PS) block copolymers by ATRP. A block containing a silylated styrenic precursor was borylated and subsequently hydrolyzed to yield the boronic acid functionality [149,155].

Our group has exploited RAFT polymerization to synthesize a variety of well-defined boronic acid block copolymer via two general routes (Scheme 6) [150,158–160]. One approach relies on the polymerization of pinacol esters of boronic acid monomers followed by a mild deprotection procedure via hydrolysis and transesterification with solid-supported boronic acid groups [158]. The second approach involved direct synthesis of well-defined boronic acid (co)polymers by controlled polymerization of free, unprotected boronic acid monomers [159,160]. The latter approach was made possible by the robust functional group tolerance of RAFT and has the benefit of eliminating a deprotection step.

Block copolymers with DMA prepared by either route were fully water-soluble above the pK_a of the boronic acid moieties

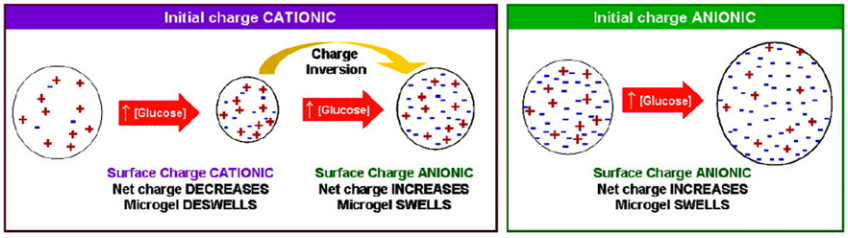


Fig. 6. Microgel behavior with initial cationic charge and initial anionic charge after the addition of glucose [125]. Reprinted with permission from Biomacromolecules, 9, Hoare, T., Pelton, R., "Charge-switching, amphoteric glucose-responsive microgels with physiological swelling activity", 733–740. Copyright (2008) American Chemical Society.

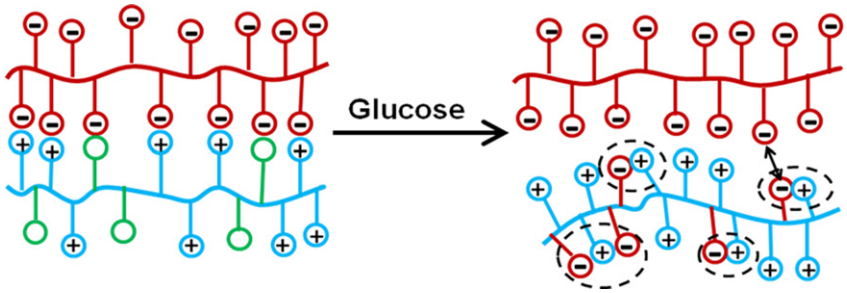


Fig. 7. Disruption of polyelectrolyte layers upon addition of glucose [128]. Adapted with permission from Langmuir, 22, De Geest, B.G., Jonas, A.M., Demeester, J., De Smedt, S.C., "Glucose-responsive polyelectrolyte capsules", 5070–5074. Copyright (2006) American Chemical Society.

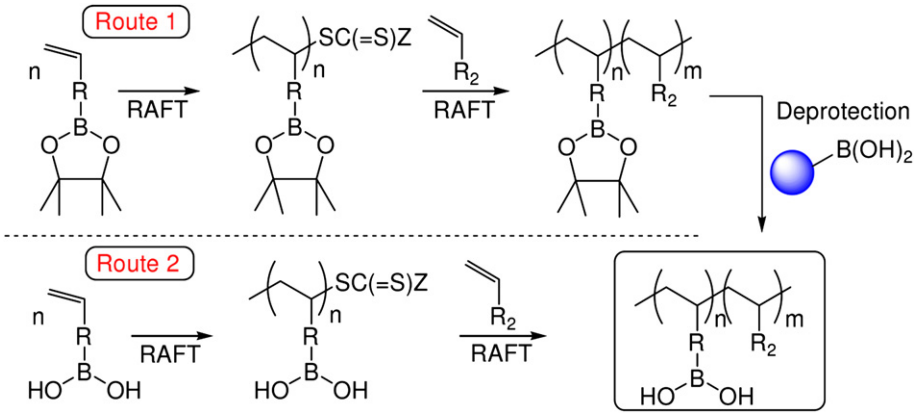
[159]. However, the block copolymers self-assembled to form micelles with boronic acid cores at reduced pH. When the pH was raised above the pK_a or glucose was introduced, the micelles dissociated. When the hydrophilic DMA block was replaced with temperature-responsive poly(*N*-isopropylacrylamide) (PNIPAM) [165], triply-responsive block copolymers that respond to changes in pH, glucose concentration, and temperature were obtained (Fig. 8) [160].

Shi et al. and Ji et al. used ATRP to prepare poly(ethylene glycol) (PEG)-containing boronic acid block copolymers that were sugar-sensitive [161,162] and capable of insulin release [161]. Recently, van Hest et al. reported the synthesis of a block copolymer with 4-dimethylaminomethylstyrene-3-pinacol boronate and PEG via RAFT using a PEG macroCTA [163]. The boronate ester moieties were deprotected in situ leaving a block copolymer with Wulff-type boronic acid moieties with lower pK_a values due to the interaction between B and N atoms that stabilized the boronate ester at lower pH values [166,167]. The resulting block copolymers were capable of dissociation in response to saccharides in a phosphate buffer at the physiologically relevant pH of 7.4 (Fig. 9).

5. Dopamine sensing

Dopamine (Fig. 10) is a catecholamine neurotransmitter involved in the reward and pleasure centers of the brain. Dopamine also plays a role in the regulation of movement, and abnormal dopamine levels are linked to neurological disorders such as schizophrenia, Huntington's disease, and Parkinson's disease. To assess *in vivo* dopamine levels, sensors must be fast, sensitive, and selective [168]. Dopamine concentrations can be 0.01–1 μM in healthy individuals and even lower in patients with Parkinson's disease [168–171]. A possible method of dopamine detection relies on facile oxidization to dopamine-*o*-quinone with conventional electrodes [168,171]. However, the presence of other easily oxidized compounds, such as ascorbic acid, often present in higher concentrations in brain fluid samples further complicates accurate measurements [168,171]. This has resulted in the use of boronic acids and their unique ability to complex with diols to increase the selectivity of electrodes for measuring dopamine concentrations.

PABA (Fig. 4b) can be used in the synthesis of electrodes for improved dopamine detection [172–176]. Interdigitated microarray [172] and glassy carbon electrodes [173] have been modified with PABA. In these cases, dopamine bonding to boronic acid moieties on the polyaniline resulted in reduced electrical conductivity. The sensors worked fairly selectively even in the presence of ascorbic acid. Nonetheless, the polyaniline backbone continued to promote some degree of oxidation of ascorbic acid [173]. However, incorporation of Nafion into the PABA film significantly suppressed the ascorbic acid response, allowing further increased selective determination of dopamine [171,177]. Nafion electrostatically repels the ascorbic acid [171] and cation exchange leads to uptake of positively charged dopamine [177]. In another study, gold electrodes were modified with PABA and single-walled carbon nanotubes wrapped with single-stranded DNA (ss-DNA/SWNT) [174–176]. The sensitivity to dopamine increased four orders of magnitude as compared to electrodes modified with PABA only, an observation attributed to the ss-DNA/SWNT serving as a template during the polymerization and therefore increasing the quality of the PABA film (Fig. 11) [171,175,176].



Scheme 6. Synthesis of boronic ester-containing block copolymers via RAFT followed by deprotection (Route 1) and direct RAFT polymerization of an unprotected monomer to yield boronic acid-containing block copolymers (Route 2) [16]. Reprinted from Prog. Polym. Sci., 35, Roy, D., Cambre, J. N., Sumerlin, B. S., "Future perspectives and recent advances in stimuli-responsive materials", 278–301, Copyright (2010), with permission from Elsevier.

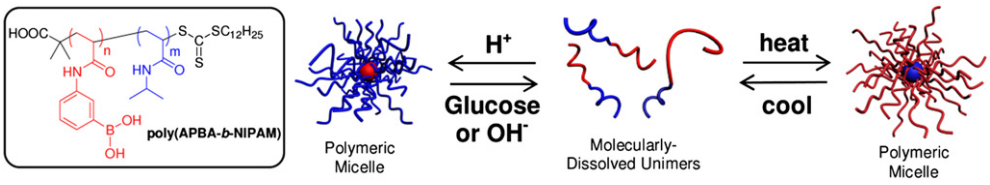


Fig. 8. PAPBA-*b*-PNIPAM self-assembly/dissociation in response to changes in pH, glucose concentration, and temperature [160]. – Reproduced by permission of The Royal Society of Chemistry.

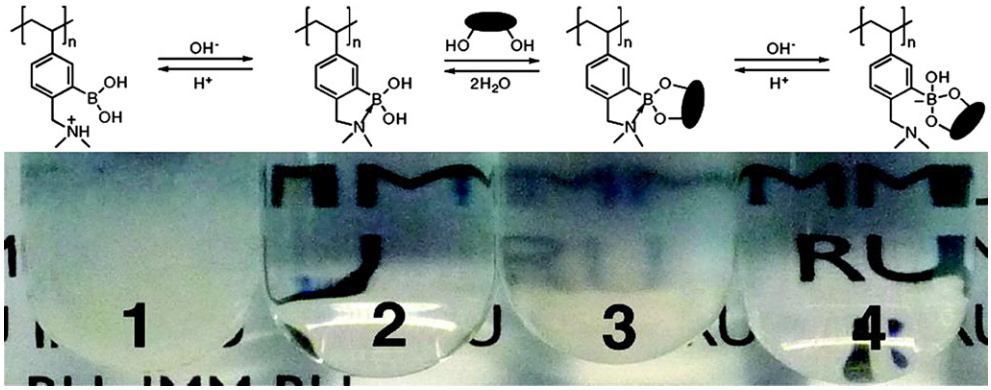


Fig. 9. Wulff-type boronic acid-containing polymers with saccharides in various pH environments. Tube 1: Polymer in phosphate buffer system (PBS) (pH 7.4); Tube 2: Polymer in PBS with D-fructose (50 mM); Tube 3: Polymer in PBS with D-glucose (100 mM); Tube 4: Polymer in TRIS (pH 7.8) with D-glucose (100 mM) [163]. Reprinted with permission from J. Am. Chem. Soc., 131, Kim, K.T.K., Cornelissen, J.J.L.M., Nolte, R.J.M., van Hest, J.C.M., "Polymeric monosaccharide receptors responsive at neutral pH", 13908–13909. Copyright (2009) American Chemical Society.

6. Cell growth surfaces

Typical cell-culture surfaces rely on nonspecific protein absorption [178]. Removal of cell cultures following growth and proliferation typically involves treatment with trypsin, which can result in significant cell damage. An optimal surface would encourage cell adhesion but not require harsh treatment for subsequent cell recovery [178].

Functionalization with boronic acid (co)polymers has proven to be a convenient method to render surfaces useful for cell culturing. For example, Saito and coworkers demonstrated that surfaces functionalized with a terpolymer (PMBV) of 2-methacryloyloxyethyl phosphorylcholine, butyl methacrylate, and 4-vinylphenylboronic acid promoted the adsorption of the glycoprotein fibronectin by boronate ester formation (Fig. 12) [178]. Fibronectin is known to mediate several cellular interactions and plays a vital part in cell adhesion, growth, and differentiation. Thus, surfaces modified in this manner were capable of promoting cell adhesion and proliferation. As opposed to more traditional routes of cell culturing, the adhered cells were readily detached via the addition of D-sorbitol or D-fructose solutions due to competitive binding of the sugars with the boronic acid residues in the polymer. Ivanov et al. prepared surface-initiated poly(*N*,*N*-dimethylacrylamide)-*co*-PAPBA copolymer brushes from siliceous surfaces and studied the effect of the boronic acid moieties on the adherence of agarose particles and yeast cells. Boronate ester formation due to interaction of the polymeric boronic acid units with carbohydrates on the surface of the particles and cells resulted in well-defined monolayer cell absorption at pH 8–9 [179]. Interestingly, surfaces functionalized with the tethered boronic acid copolymers were more effective at encouraging cell adhesion than were surfaces modified with low molecular weight boronic acid compounds. This

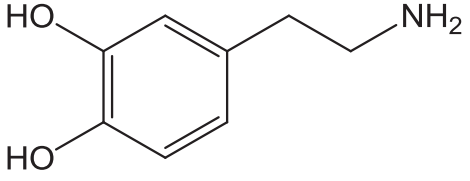


Fig. 10. Structure of the neurotransmitter dopamine.

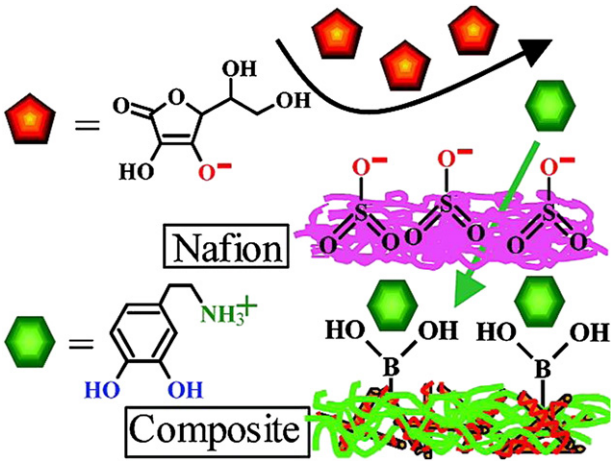


Fig. 11. Boronic acid-polymeric multilayers for the sensing of dopamine. The top Nafion layer electrostatically repels ascorbate from the electrode surface while dopamine penetrates to the bottom layer of the ss-DNA/SWNTs/PAPBA composite to bind with boronic acid groups [171]. Reprinted with permission from Anal. Chem., 79, Ali, S.R., Ma, Y., Parajuli, R.R., Balogun, Y., Lai, W.Y.-C., He, H., "A nonoxidative sensor based on a self-doped polyaniline/carbon nanotube composite for sensitive detection of the neurotransmitter dopamine", 2583–2587. Copyright (2007) American Chemical Society.

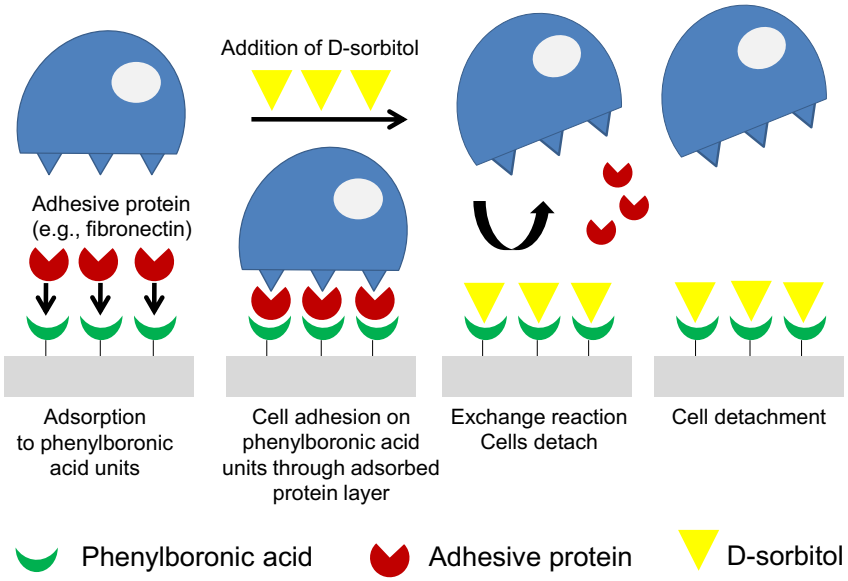


Fig. 12. Concept of a biointerface based on polymeric boronic acids that promotes cell adsorption and subsequent cell release upon the introduction of a competitive small molecule saccharide [178].

basic approach has also proven useful for the adherence, removal, and retention of viability and function of other cells, including mammalian cells [180,181] and lymphocytes [182,183].

Hubbell et al. utilized the interaction between boronic acid residues and carbohydrates on cell surfaces to stabilize and passivate the cells to biological recognition events [184]. A poly(L-lysine) backbone was functionalized to contain PEG and phenylboronic acid side chains. The boronic acid groups allowed the copolymer to be immobilized by complexing to carbohydrates on cell or tissue surfaces, while the PEG component provided steric stabilization. Polymers of this type could be useful to prevent antibody binding to transplanted cells.

7. Boron neutron capture therapy (BNCT)

Irradiation of boron-10 with slow neutrons produces alpha particles and lithium nuclei. Alpha particles are highly damaging to human tissue but are capable of very limited penetration. Therefore, irradiation of boron compounds in tumor cells is a viable means to administer non-invasive and localized radiation therapy. Effective BNCT relies on specific delivery of boron-containing compounds that are rich in ^{10}B to the tumor site. BNCT agents can contain single [28] or multiple borons [28,185–187]. Molecules that have single borons are usually aryl boronic acids due to their oxidative and hydrolytic stability [188,189], though the naturally low concentration of ^{10}B generally requires rather expensive isotopic enrichment in order for boronic acids to be efficient BNCT agents. On the other hand, BNCT agents with multiple borons, typically polyhedral borane anions or carboranes, are much more effective.

Wright et al. employed a commercially available polyacrylamide-based gel with MAPBA groups to prepare gel particle suspensions and colloids for BNCT [190]. Boronic acid groups on the gel surface were allowed to bind oligosaccharide units on avidin, providing sites for the immobilization of biotinylated antitumor antibodies to assist with selective uptake. Jiang and coworkers synthesized dextran-PAPBA nanoparticles with tunable size and compositions [191]. The biocompatible nanoparticles were capable of encapsulating doxorubicin and penetrating cell membranes. These boron-containing nanoparticles were reported to have potential applications in BNCT and chemotherapy for cancer treatment.

Copolymers with either styrenic or acrylamido boronic acid units have also shown potential as BNCT agents [21,192]. Copolymers with 4-vinylphenylboronic acid and maleic anhydrides were partial grafted with α-hydroxy-ω-methoxy-poly(ethylene oxide), and the resulting macrobranched copolymers were complexed with polyethyleneimine [192]. Hydrogen bonding resulted in the formation of supramolecular structures with possible uses for BNCT.

8. Summary

Boronic acid compounds have found utility in a variety of biomedical applications. However, given the rather unique ability of boronic acids to bind to saccharides, the ubiquity of such saccharides in biological systems, and the benefit of exploiting this phenomenon in a multivalent manner, there remains a considerable number of unexplored applications specifically for boronic acid polymers. Indeed, polymeric boronic acids have not been as widely utilized and could provide additional benefits over their small molecule counterparts. While exciting opportunities exist for these polymers, there are several challenges to overcome.

Many of the biological applications of boronic acids rely on interactions with diols (*e.g.*, sugars). However, there are two specific challenges that must be addressed during the design of new boronic acid biomaterials that operate by reacting with diols. Firstly, boronate ester formation occurs most efficiently above the pK_a of the boronic acid. Most phenylboronic acids have pK_a values that are significantly higher than physiological pH. New strategies for preparing polymers with reduced pK_a values have been reported, but more research is needed in this area. Secondly, complexes between boronic acids and diol compounds often exhibit limited specificity. Given the large number of diol compounds present in biological systems, new approaches for increasing specificity could prove useful for both current and future proposed applications. In this respect, much can be learned from the small molecule saccharide sensing literature, where strategies have evolved to

increase selectivity. Additionally, new polymeric materials formed by molecular imprinting or by relying on the increased potential of multivalent interactions of one sugar over another could likely contribute in this area.

Despite these challenges, boronic acid-containing polymers have demonstrated great promise for applications in a variety of biological applications. Given the recent development of new techniques that allow their controlled synthesis, it is likely that boronic acid polymers will demonstrate even greater utility as versatile biomaterials in the near future.

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Abbreviations

AA: acrylic acid
APBA: 3-acrylamidophenylboronic acid
APMAmPBA: N-[3-(2-methylacryloylamino)propyl]-4-amidophenylboronic acid
ATRP: atom transfer radical polymerization
CCA: crystalline colloidal array
DDOPBA: 4-(1,6-dioxo-2,5-diaza-7-oxamyl)phenylboronic acid
DMA: N,N-dimethylacrylamide
DMAEA: N,N-dimethylamino ethylacrylate
DMAPAA: 3-dimethylaminopropyl acrylamide
G-Ins: gluconic acid-modified insulin
HPMA: 2-hydroxypropylmethacrylamide
MAAmSHA: 4-[2-methylacryloylamino)-methyl]-salicylhydroxamic acid
MAPBA: 3-methacrylamidophenylboronic acid
NaPSS: 4-sodium polystyrene sulfonate
NIPAM: N-isopropylacrylamide
PAA: poly(acrylic acid)
PAPBA: poly(3-acrylamidophenylboronic acid)
PABA: poly(aniline boronic acid)
PEG: poly(ethylene glycol)
PET: photoinduced electron transfer
PNIPAM: poly(*N*-isopropylacrylamide)
RAFT: reversible addition-fragmentation chain transfer polymerization
RES: reticuloendothelial system
SHA: salicylhydroxamic acid
ss-DNA/SWNT: ss-DNA-wrapped single-walled carbon nanotube

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