Recent advances in boronic acid-based optical chemosensors

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Reversible covalent binding of boronic acids with polyols and Lewis bases has facilitated the development of robust chemosensors for many biologically important species under physiologically or environmentally relevant conditions. This minireview covers selected examples of advances reported in this area from 2014 to 2016. While the discovery of new boron-containing binding motifs and identification of new analytical targets have expanded the utility of boronic acid-based molecular recognition, unconventional sensing strategies such as exploitation of nanoscale self-assembly, multicomponent dynamic covalent assembly, and coupling boronate ester formation with a further chemical reaction have led to significantly improved sensor performance, enabling real-world applications in various areas such as cell biology and asymmetric catalysis.

Introduction

In the pursuit of chemosensors that recognise analytes of biomedical or environmental significance, the dynamic covalent chemistry involving boronic acids has proven to be instrumental, applicable to a wide range of analytes, and capable of functioning in aqueous media. Boronic acids can bind species containing 1,2- or 1,3-cis-diol motifs, forming five- or six-membered cyclic boronate esters. The reaction is pH-dependent, in which diol binding is often found to increase the acidity of boronic acids. This can lead to transformation of the boron centre from the neutral trigonal form to the anionic tetrahedral form within a suitable pH range. This pH sensitive reaction has been frequently utilised for the sensing of saccharides or other biomolecules containing saccharide units. The relative stability of the adduct also allows its utility in multicomponent assembly for fabricating sensor materials. Boronic acids can also function as Lewis acids to bind Lewis bases such as F-, CN-, and amines, enabling sensing applications for these species.

In this minireview, we highlighted selected examples of progress in this area from 2014 to 2016, including sensors for saccharides (or saccharides-containing species) based on the

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boronate ester chemistry, and sensors for Lewis base species that exploit the Lewis acidity of the boron centre. We also included examples of stimuli-responsive materials constructed via multicomponent assembly involving boronate ester linkages that have applications for sensing other species or biological events. Chemodosimeter-type boronic acid probes for reactive oxygen species are out of the scope of this minireview. Note that important advances have been made during this period in terms of fundamental knowledge of noncovalent/covalent interactions involving boronic acids as well as applications of boronic acid chemistry for bioconjugation. These advances can provide implications to guide sensor design, and references to original research papers for this information have also been provided.

Sensors for saccharides or saccharide-containing biomolecules

The development of selective glucose sensors suitable for clinical and biomedical applications is an important goal in the area of chemical sensing based on boronic acids. A major challenge is to invert the intrinsic binding selectivity of boronic acid for fructose over glucose, which results from the higher abundance of the boronic acid accessible form of fructose (β-D-fructofuranose, ca. 25% among all isomers) than that of glucose (α-D-glucofuranose, ca. 0.14% among all isomers). Glucose selectivity is achievable by molecular design due to the ability of α-D-glucofuranose to bind two boronic acid groups, whereas in most cases, fructose only interacts with one boronic acid group. Previous studies have reported the use of diboronic acids that can chelate glucose by forming two boronate ester linkages, thus enhancing glucose affinity. Although the structural design of glucose-selective small molecule sensors has matured, advances in new materials and spectroscopic techniques have facilitated further development to improve sensor robustness for diagnostic purposes. For instance, glucose-selective diboronic acids have been immobilised onto a gold film-over-nanosphere to develop surface-enhanced Raman spectroscopy-based glucose sensors that could distinguish between hypoglycemic, normal, and hyperglycemic ranges. Recent developments, however, have been shifted to an alternative approach that relies on the potential of glucose to selectively induce nanoscale self-assembly of boronic acid-containing amphiphiles or other materials. The molecular design based on the latter approach can be surprisingly simple, as exemplified by some of the recently reported glucose-sensing systems. These systems provide glucose-selective optical responses as a result of induced aggregation, which typically does not occur for fructose (although galactose sometimes also induce aggregation as α-D-galactofuranose can bind two boronic acid groups too). However, the intrinsic glucose/fructose binding selectivity of these systems is usually not as high as that of the rigid, preorganised diboronic acid-based glucose receptors. Another potential problem with the aggregation approach is the compromised reversibility as the aggregates formed with glucose might not instantly dissociate in response to lowered glucose concentrations.

Hayashita and coworkers employed electrostatic assembly between phenylboronic acid azoprobe 1 and polyamidoamine (PAMAM) dendrimer for saccharide sensing. At pH 7, a mixture of 1 and PAMAM displayed quenching of the azobenzene absorption in response to saccharide binding, with the extent of quenching in the order of glucose > fructose > galactose. Transmission electron microscopy (TEM) and dynamic light scattering (DLS) studies revealed that glucose induced the aggregation of the 1/PAMAM complex to form particles with an average diameter around 150 nm; this is presumably because glucose crosslinked the 1/PAMAM complex via binding two boronic acids. However, TEM and DLS experiments showed no aggregation induction by fructose, and therefore, the extent of absorption quenching induced by fructose (due to fructose-induced binding of 1 to PAMAM) was less.

Amphiphilic compound 2 developed by Hayashita and coworkers is another example in which glucose-induced aggregation was observed. Compound 2 existed as micellar aggregates at 20 μM in alkaline solutions. Disassembly of the micelles to monomeric forms of 2 occurred upon fructose binding, whereas glucose binding induced further assembly to form larger aggregates with the diameter around 300 nm. Because of different assembly states, fructose and glucose generated different types of responses in the UV-vis absorption of the azobenzene chromophore.
Jiang and coworkers exploited the concept of dynamic covalent chemistry and supramolecular aggregation to obtain a selective glucose sensing ensemble that operates simply by mixing commercially available reagents (Fig. 1). In this case, the amphiphilic boronic acid was assembled in situ via reversible imine bond formation between 4-formylphenylboronic acid and octylamine. Mixing of the aldehyde component, the amine component, and glucose in alkaline solutions resulted in the formation of vesicular aggregates composed of glucose/complexes with an average diameter of ca. 700 nm. The supramolecular aggregation process resulted in opaque solutions and can be followed by light scattering or using the hydrophobic fluorescent probe Nile red. Galactose induced aggregation to a lesser extent, whereas no amphiphile aggregation took place with fructose. Interestingly, the extent of imine bond formation was found to depend on the presence of different saccharides. Imine formation was 7% with the aldehyde, and the amine components, each present at 3 mM in a buffer (pH 10.5) in the absence of saccharides, underwent only a minor increase to 12% in the presence of 5 mM of fructose, whereas dramatically increased to 38% with 5 mM of glucose and to 26% with 5 mM of galactose. This effect was attributed to stabilisation of the imine bond within the amphiphile aggregates, which were only formed in the presence of glucose and galactose under the experimental conditions. Despite the drawbacks that high component concentrations and a long response time of 30 min were required, the system demonstrated a promising analytical strategy of an in situ sensor assembly using multiple dynamic covalent bonds.

As demonstrated in the abovementioned examples, fructose normally binds as a monovalent ligand and induces dissociation of the self-assembled boronic acid aggregates due to its hydrophilicity. Note that induction of aggregation with fructose has been recently reported. Xing and coworkers synthesized pyrene-functionalised diboronic acid sensors 4 and 5 that respond to saccharides via changes in both monomer (381 nm) and excimer (510–530 nm) emissions. At pH 10, the induction of aggregation (probed via increased excimer emission) of both sensors was found for saccharides including glucose, fructose, xylose, galactose, and mannose, whereas ribose only induced aggregation of 5. The fructose-induced aggregation occurred at low fructose concentrations (below 100 μM) and the aggregates gradually dissociated at higher fructose concentrations. It was proposed that at low concentrations, fructose bound the sensors via the β-D-pyranose form that could complex two boronic acid groups, thus inducing aggregation; however, at high concentrations, binding of the monodentate β-D-pyranose form dominated. The monomer and excimer emission bands of the two sensors were utilized as a four-channel sensor array that could differentiate among six saccharides, giving 100% classification correctness at the fixed saccharide concentration of 100 μM or 83.3% correctness at the saccharide concentrations ranging from 20 to 100 μM.

Apart from amphiphilic organic small molecules, the glucose-induced aggregation strategy is also applicable to inorganic nanomaterials for glucose sensing. Qiu and coworkers fabricated boron-doped graphene quantum dots (BGQDs) that function as highly potent glucose sensors at physiological pH (Fig. 2). Treatment of graphene sheets with B2O3 vapour followed by cutting the formed boron-doped graphene via a hydrothermal approach produced water-dispersible BGQDs with the diameters of 2–4 nm. The BGQDs contained exposed boronic acid groups, allowing their interaction with saccharides. At pH 7.4 and pH 10.0, glucose triggered the aggregation

Fig. 1. Multicomponent dynamic covalent assembly among 4-formylphenylboronic acid, octylamine, and glucose, leading to the formation supramolecular aggregates. The aggregation process did not occur with fructose. Adapted with permission from Chem. Commun., 2016, 52, 6981–6984.

Fig. 2. Schematic showing the glucose-induced aggregation of boron-doped graphene quantum dots, leading to photoluminescence enhancement. Reproduced with permission from Anal. Chem., 2014, 86, 4423–4430.
of the BGQDs into wire-like chains, as shown by microscopic imaging. The glucose-induced aggregation led to the enhancement of visible photoluminescence and light scattering from BGQDs, allowing glucose determination in the range of 0.1–10 mM by following either signal. These responses did not occur for fructose, galactose or mannose.

In addition to the induction of supramolecular aggregation, the crosslinking ability of glucose can give rise to shrinkage of boronic acid-containing polymeric materials, which allows the design of highly selective glucose sensors, as demonstrated by a recent example reported by Wu and coworkers. Two boronic acid-containing microgels with covalently-immobilized graphene sheets (GSs) were prepared: GS@poly(4-VPBA) based on poly(4-vinylphenylboronic acid) and GS@pPBAs that contains poly-(N-isopropylacrylamide) as an additional matrix component (Fig. 3). The boronic acid groups in the microgels completely ionised at pH 7.4, with their high acidity presumably originating from complexation of graphene with electron-rich boronate ions. Both microgels selectively shrunk in response to glucose due to additional crosslinks afforded by the formation of glucose-bisboronate esters. The volume phase transition induced by glucose further led to an increase in the graphene photoluminescence. The materials were successfully applied to glucose determination in blood serum samples.

Saccharide interaction with boronic acids can proceed via the formation of two or three B–O–C ester bonds at the boron centre. Oesch and Luedtke developed the push–pull fluorophores 6 and 7 that can optically discriminate between saccharides that bind boronic acids via two hydroxyl groups and those that bind via three hydroxyl groups.6 6 and 7 respond to saccharide binding via modulation of the twisted intramolecular charge transfer (TICT) emission. Compound 6 showed quenching of the emission from the locally excited, non-TICT state (330 nm) upon ionisation of the boron centre in the absence of saccharides. At pH 7.4, saccharides that bind as a diol, such as ribose and glucose, quenched the fluorescence of 6 and 7 due to ionisation of the boron centre induced by saccharide binding. Importantly, saccharides that form three B–O–C ester bonds with a boron centre, including fructose and galactose, produced a completely different spectral response in terms of a red-shifted emission around 360 nm, which was assigned to TICT emission. This finding provides a new approach to increasing the discriminating ability of boronic acid sensors for saccharide analytes.

Different from small molecule supramolecular hosts that rely on rational structure design to selectively bind the guest of interest, molecular imprinted polymers (MIPs) provide an alternative means to selective guest binding, achieved by guest-templated formation of the polymer matrix to create a binding cavity complementary to the targeted guest. The use of boronate-affinity molecular imprinting, i.e. incorporating boronic acid groups as the binding sites in MIP, has gained significant popularity in developing materials that selectively bind both small molecules and large biomolecules. This approach may be advantageous compared to non-covalent MIPs in terms of enhancing the binding affinity, weakening of non-specific binding, and facilitating guest removal using acidic solutions due to the dissociation of boronate esters under acidic conditions. Tang and coworkers demonstrated the utility of the boronate-affinity molecular imprinting approach to the development of nanocrystal-based sensors for glycoprotein (Fig. 4). They prepared CdTe nanocrystals with a boronate-functionalised MIP-shell by coating the CdTe nanocrystals with a polymerisable surfactant octadecyl-p-vinylbenzyltrimethyl-ammonium chloride; this was followed by copolymerisation with N-isopropylacrylamide (NIPAAm) and 4-vinylphenylboronic acid (VPBA) in the presence of a glycoprotein template (horse-radish peroxidase, HRP, was used). This MIP nanosensor could reversibly bind and release HRP, by switching the solution pH between 9 and 6, allowing effective removal of the HRP template by washing with an acidic solution. The sensor showed a selec-

![Fig. 3 Synthesis of glucose-responsive microgels GS@poly(4-VPBA) and GS@pPBAs. Abbreviations: 4-VPBA, poly(4-vinylphenylboronic acid); MBAAm, N,N'-methylenebis(acrylamide); and NIPAM, N-isopropylacrylamide. Reproduced with permission from Macromolecules, 2014, 47, 6055–6066.](image1)

![Fig. 4 Synthesis of CdTe nanocrystals coated with a glycoprotein-imprinted polymer. Adapted with permission from Angew. Chem., Int. Ed., 2014, 53, 12489–12493.](image2)
tive fluorescence quenching response to HRP at micromolar concentrations without interference from other proteins; thus, it could be applied to HRP sensing in human urine samples.

Zhao and coworkers demonstrated cross-linked micelles as ideal candidates for the implementation of the boronate-affinity MIP concept to develop selective sensors for monosaccharides in aqueous solutions (Fig. 5). The template glucose, galactose, or mannose was converted to diboronate esters functionalised with vinyl groups, which were then implanted into the micelles via copolymerization with methacrylate groups within the micelle core. The molecularly imprinted micelles obtained after template removal were found to bind its template selectively over other monosaccharides, with millimolar affinity at pH 7.4, determined by isothermal calorimetric binding studies. On further functionalization with fluorogenic or chromogenic reporter groups, these systems could be adapted to produce water-soluble nanosensors selective for any saccharide of interest.

New organoboron compounds that are structurally different from traditional boronic acids have been developed for the labeling or sensing of saccharides. Brothers and coworkers reported the direct conjugation of glucose to the core of boron-dipyromethene (BODIPY) dye via the formation of two B–O–C bonds. The BODIPY–glucose conjugates were prepared by treating chlorine-substituted BODIPY with glucose in acetonitrile, giving a 1 : 1 α-glucosfuranose/BODIPY complex 8, a 1 : 2 α-glucosfuranose/BODIPY complex 9, and, surprisingly, a 1 : 2 α-glucoseptanose/BODIPY complex 10. The products are hydrolytically stable and therefore this reaction is not amenable to sensing applications. The use of the boron atom within the core of a fluorophore as a binding site represents a new approach for saccharide labeling, different from other approaches as saccharide receptors with binding sites are more remote from the fluorophore. More recently, the use of this approach for reversible binding and sensing of saccharides was achieved by Egawa and coworkers. They synthesised a red fluorescent sensor 11 that contains a boronate moiety within a xanthene skeleton. The binding of fructose and catechol in a buffer (pH 7.4) led to a red shift in absorption and changes in the fluorescence spectra. These spectral responses were rationalised by DFT calculations, revealing that the HOMO–LUMO gap of 11 was reduced upon binding to polyols. Catechol additionally caused fluorescence quenching of 11 due to photoinduced electron transfer from catechol to 11. Because of the high acidity of the boron centre, saccharide sensing was pH-independent in the pH range from 5.5 to 11. The study demonstrated the feasibility to achieve saccharide-induced spectral responses by embedding the boron atom within a π-conjugation chromophore.

While boronic acid-based fluorescent or colorimetric sensors are, in general, unselective or have limited selectivity, sensors that provide $^{19}$F NMR outputs can overcome this limitation, owing to the discriminating ability of $^{19}$F NMR signals that are sensitive to subtle structural changes. Schiller and coworkers developed a group of fluorinated boronic acids 12, 13, and 14 as a sensor array that can discriminate among nine polyol analytes. Due to the slow equilibrium exchange of boronic acid–polyol binding on the NMR timescale, each analyte generated a unique set of $^{19}$F signals from the three sensors, which was used as a 2D barcode for the identification of the analyte without the requirement for multivariate analysis.

Fig. 5  Synthesis of molecularly imprinted micelles for saccharide recognition. Reproduced with permission from J. Am. Chem. Soc., 2016, 138, 9759–9762.
Liu and coworkers demonstrated that the array-based discriminative sensing of saccharide analytes is possible using only one boronic acid sensor.35 Relying on the sensitivity of boronic acid–saccharide interaction to solution pH, they developed a new concept termed pH-featured encoding to extract more signals from a single boronic acid sensor that are required for pattern recognition (Fig. 6). A simple phenylboronic acid moiety was immobilised onto a filter paper and treated with a solution containing the saccharide analyte and alizarin red S (ARS). The extent of ARS fluorescence quenching reflected the binding affinity of the tested saccharide for the boronic acid moiety, which depend on the solution pH. The fluorescence signal was obtained at three solution pH values (7.4, 8.5, and 9.4). Therefore, each analyte generated three signals in this virtual lectin array. Principal component analysis allowed discrimination among nine monosaccharides, showing the effectiveness of this simple analytical method.

Chang and coworkers have recently developed boronic acid-based sensors for adenosine triphosphate (ATP)36 and nicotinamide adenine dinucleotide (NADH).37 In these sensors, analyte binding reaction was coupled with further chemical reactions, leading to dramatic changes in the absorption and fluorescence properties of the sensors (Fig. 7). The ATP sensor 15 could bind ATP via a combination of boronate ester formation, π–π stacking, and ion pairing. The binding of ATP triggered reversible ring-opening and resultant fluorescence enhancement of 15. Because of the three-point binding specific for ATP, interference from other phosphate-containing biomolecules was minimal. Sensor 15 could be selectively localised in the mitochondria and used to monitor the change in mitochondrial ATP levels during biological processes. The NADH sensor 16 contains boronic acid conjugated to a reducible fluorophore resazurin. The resazurin unit was reduced by NADH once boronic acid bound the ribose unit of NADH and thus brought the electron donor to the proximity of the resazurin unit, facilitating the hydride transfer reaction. This led to fluorescence enhancement response, selective for NADH over other biomolecules at physiological pH. Sensor 16 was applicable to imaging the ATP levels in live cells although the potential issue of irreversibility might impede its applicability to continuous monitoring. In these two examples, the boronic acid–analyte interaction either drove the equilibrium (15) or enhanced the rate (16) of the reaction occurring at the fluorophore. The potent sensing performance of these sensors has clearly benefited from the incorporation of a chemical reaction that occurs specifically in the presence of the analytical target.

**Sensors for anions**

Boronic acids have been used for sensing basic anions such as $\text{F}^-$ and $\text{CN}^-$ that can coordinate to the Lewis acid boron centre.6 The boronic acid–$\text{F}^-$ interaction is strong in an organic solvent but dramatically weakens in aqueous media. Therefore, these sensors can barely detect aqueous $\text{F}^-$ below 1 mM.38 To address this limitation, Jiang and coworkers used supramolecular polymers formed by amphiphilic boronate esters to stabilise the boron–$\text{F}^-$ adduct.39 At pH 2, simultaneous binding of $\text{F}^-$ and 4-carboxycatechol triggered the transition of sensor 17 from monomeric forms to supramolecular polymers, leading to the emergence of excimer emission from the pyrene fluorophore (Fig. 8). This allowed $\text{F}^-$ binding with mM affinity and direct sensing at parts per million (ppm).
levels in aqueous solutions. The high sensitivity compared to that of other boronic acids likely originates from (i) stabilisation of the boron–F– adduct in supramolecular aggregates that provided a water-excluding microenvironment and (ii) enhanced Lewis acidity of the boron centre upon binding of the catechol component. The hypothesis was supported by a comparison with reference systems.

While the Lewis-type boronic acid–anion interaction is well-known, Martínez-Aguirre and Yatsimirsky showed that boronic acids can additionally bind anions with the two hydroxyl groups at the boron atom serving as hydrogen bond donors. Via the combination of 11B and 1H NMR studies, the authors found that in DMSO and acetonitrile, simple boronic acids functioned as hydrogen bond donors for Cl–, Br–, HSO4–, and AcO– (see Fig. 9 for an interaction with AcO–), whereas binding of F– and H2PO4– proceeded via Lewis-type interactions. It was also demonstrated that 3-nitrophenylboronic acid showed a red-shifted UV-vis absorption maximum upon binding of AcO– via a hydrogen bond in acetonitrile and DMSO. However, this type of interaction cannot tolerate aqueous media and thus further improvements are required to make it practically useful for the optical sensing of aqueous anions.

Pyrophosphate, an important anionic species involved in biological (de)phosphorylation reactions, was recently shown to interact with highly acidic boronic acids in aqueous solutions with strong affinity and specificity (Fig. 10), as reported by Matsumoto and coworkers. The binding affinity of 3-pyridineboronic acid with pyrophosphate was determined to be 950 M–1 at pH 5 by 11B NMR titrations, with a reduction of binding observed with further increases in solution pH. The interaction was proposed to involve the formation of cyclic adducts containing two or three B–O–P ester bonds (Fig. 10). Surprisingly, interactions of 3-pyridineboronic acid with other phosphate-containing molecules, including monophosphate, triphosphate, and deoxyadenosine diphosphate (dADP), were negligible despite the latter two substrates appearing to possess the motifs required for this type of interaction. This was attributed to steric hindrance. The discovery of this new interaction motif could lead to the development of highly specific and reversible sensors for pyrophosphate or diphosphate-containing biomolecules based on boronic acids.

Chirality sensors

Optical sensors that can distinguish between a pair of enantiomers of the analyte and thus generate optical responses dependent on the enantiomeric excess (ee) of the analytes have potential application as analytical tools to determine the enantioselectivity of the asymmetric synthesis. These sensors could be used for high throughput screening of asymmetric catalysis if the sensor–analyte interaction proceeds sufficiently fast and can avoid interference from impurities present in the reaction mixtures. Boronic acids appear to be ideal for this purpose as the covalent binding rapidly occurs and is selective for compounds containing certain functional groups. Jiang and coworkers attached boronic acid groups to a perylene bisimide (PBI) chromophore to develop the chirality sensors 18 and 19 for α-hydroxy carboxylates based on induced helical dye aggregation in aqueous solutions. Upon binding of α-hydroxy carboxylates to the boronic acid groups, 18 and 19 formed columnar aggregates with helically arranged PBIs, whose helical sense was dictated by the molecular chirality of the α-hydroxy carboxylate analytes. The aggregates showed induced circular dichroism (CD) signals from the PBI chromophore that indicated the ee of the analytes. Moreover, the interaction of 18 and 19 with α-hydroxy carboxylate analytes was found to enhance the extent of dye aggregation, resulting in suppressed UV-vis absorption of the PBI chromophore that can be used for determining the analyte concentrations. While most sensor-analyte systems displayed a CD intensity linear with respect to the ee of the analyte, in a few systems, non-linear CD-ee relationship was observed (Fig. 11). In a later study, Chen, Jiang and Anslyn examined the accuracy for ee determination using different systems that show a linear CD-ee curve (19/lactate), a majority-rules-type response with the curve showing a steeper slope at low ee (20/tartrate), and an unusual anti-majority-type response with the curve showing a steeper slope at high ee (19/malate, Fig. 11). It was found that for anti-majority, 19-malate system shows a higher accuracy (average absolute error 0.2% ee) for determination of high
ee (90% to 100% ee); the ee region is most important to be analysed for optimisation of asymmetric reactions. The exploitation of this non-linear response is an attractive means to improve the sensitivity of chirality sensors at high ee region, but mechanistic insights are required to allow rational design of the working systems. In a separate report, Jiang and co-workers used a mixture of sensor 18 and an aldehyde-functionalised PBI sensor 20 for binding and (chirality) sensing of DOPA via a combination of boronate ester linkage and an imine bond (Fig. 12).46 Interestingly, the two sensor components showed cooperative binding to DOPA presumably due to the aggregation of the PBI chromophore that brings the boronic acid and aldehyde groups to proximity, allowing simultaneous formation of the two dynamic covalent bonds. Apart from PBI aggregates, Jiang and coworkers also reported the use of Ag⁺ coordination polymers containing boronic acid groups as chirality sensors for glucose.47

Anzenbacher and coworkers developed a fluorescence assay for determining ee of chiral primary amines based a multi-component dynamic covalent assembly (Fig. 13).48 The assembly between 2-formylnaphthaleneboronic acid, 1,1′-bi-2-naphthol (BINOL), and a chiral amine giving diastereomeric complexes has been previously reported as a CD protocol for sensing ee of chiral amines.49 The diastereomers formed, however, do not differ in fluorescence properties. In the current study, more bulky diol components, including 22 and 23, were used in place of BINOL. The diastereomeric complexes formed with a pair of amine enantiomers now show a substantially different fluorescence quantum yield and polarization, allowing determination of the chiral amine component by fluorescence spectroscopy in propionitrile. In the initial paper, this method was satisfactorily applied to relatively bulky amines, such as α-methylbenzylamine, but failed for smaller amines, such as 2-aminobutane, because the diastereomers formed with small amines showed almost the same fluorescence property.48 To overcome this drawback, the authors used water and citric acid to destabilise the assembly, which increased the difference in the stability constant between a pair of diastereomers to the extent that the chiral amine enantiomers can be resolved by fluorescence measurements.48b

Compound 24 synthesized by Tang and coworkers is also capable of discriminating between a pair of chiral Lewis base enantiomers.50 This compound was designed as an intrinsically chiral AIEgen that is non-fluorescent when fully solubilised but becomes fluorescent when it forms aggregates and in the solid-state, a phenomenon known as aggregation-induced emission (AIE).51 Compound 24 could bind Lewis bases, such as alcohols and amines, to its boron centre (Fig. 14), leading to cleavage of the labile B-N bond and a blue shift in the absorption spectrum because of an increased HOMO–LUMO energy gap upon ring-opening. In 1,2-dichloroethane where aggregation did not occur, 24 was found to bind menthol in an enantioselective manner, with (+)-menthol showing a high affinity for 24 (0.012 M⁻¹) than the (−)-enantiomer (7 × 10⁻⁵ M⁻¹). The binding affinity of a chiral amine α-methylbenzylamine was higher but the enantioselectivity was weaker (2.31 M⁻¹ for the R-enantiomer and 1.57 M⁻¹ for the S-enantiomer). Note that the above-mentioned sensing relied on the UV-vis absorption response in the non-aggregate state, and the AIE property of 24 has not been exploited, which might lead to improved sensitivity for ee determination.
Wolf and coworkers attached a urea and a boronic acid motif to a stereodynamic aryl-acetylene-aryl scaffold to develop the chirality sensor 25 for α- and β-hydroxy carboxylates functioning in acetonitrile (Fig. 15). Without guest binding, the acetylene linker can freely rotate; thus, the sensor is achiral and CD-silent. The binding of α- and β-hydroxy carboxylate guests via a combination of hydrogen bonds and a dative B–O bond locks the conformation of 25, leading to an asymmetric structure and therefore the generation of CD signals applicable to ee determination. In addition, the sensor could be used for determination of guest concentration via responses in the UV-vis spectra in an ee-independent manner. Impressively, 25 was applied to the determination of the reaction yield and product ee in an α-keto acid reduction reaction, giving results (errors within a few percentage) satisfactory for high throughput screening without the need of product purification. This CD protocol was shown to be advantageous over traditional chromatographic methods for determining ee of hydroxyl acids that require product purification and further derivatisation.

Other sensing applications

The reversible yet relatively strong boronate ester formation is not only useful for the direct binding of analytical targets but also applicable as an interaction to join different components in the construction of stimuli-responsive polymeric materials. Stenzel and coworkers synthesized a series of polymers containing terminal dopamine groups, which were found to bind boronic acids depending on pH and the polymer molecular weight. A block copolymer composed of oligo(ethylene glycol)methyl ether methacrylate and tert-butyl acrylate, incorporating green fluorescein tags, formed micelles in aqueous solutions and was conjugated to a yellow-fluorescent acridine boronic acid 26 (Fig. 16). Confocal fluorescence microscopy studies carried out using a cancer cell line indicated that the resultant boronate micelles could be stably internalized by the cells and localized in the lysosomes over 24 h. After the cells were treated with an anti-cancer drug, oxaliplatin, the yellow fluorescence from 26 was found to be scattered all over the cytosol, whereas the green fluorescence from the fluorescein-containing micelles remained localized in the lysosomes, indicating the dissociation of 26 from the micelles. The control experiments are consistent with the hypothesis that increased levels of H2O2 (that oxidized the dopamine group) and/or Ca2+ ions (that chelated to the dopamine group), a result of drug-induced apoptosis, are responsible for the boronate ester cleavage and consequent release of 26 to the cytosol. This boronate-functionalised polymer can thus be applied to visualize the onset of apoptosis.

Kubo and coworkers used boronate ester linkages to polymerise an AIE-active fluorophore, which led to the development of thermoresponsive emissive nanoparticles (Fig. 17). The nanoparticles were generated by polymerisation between diboronic acid-functionalized tetraphenylethene 27 and pentaerythritol in methanol. While these materials are

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**Fig. 15** Chirality induction of 25 by chiral hydroxyl carboxylate analytes.

**Fig. 14** Interaction of 24 with Lewis bases such as alcohols and amines.

**Fig. 16** Proposed mechanism of apoptosis sensing by 26-conjugated and fluorescein-labelled block copolymer micelles.

**Fig. 17** Synthesis of white-emissive nanoparticles as temperature sensors.
fluorescent in blue light, conjugation of the surface-exposed 1,3-diol motifs with rhodamine-B functionalised boronic acid-containing 28 resulted in white-light emissive materials. These boronate nanoparticles were found to undergo reversible fluorescence quenching with temperature increasing from 25 to 65 °C, which was attributed to flipping of the substituted phenyl rings in 27 following nanoparticle swelling. The thermo-responsive emission property renders these materials as nanothermometers capable of measuring physiological temperature changes in aqueous media.

Based on boronate ester chemistry, Kameta and coworkers functionalised a glycolipid with a pyrene fluorophore and the resultant conjugate 29 showed amino acid-dependent self-assembly behavior and emission property in aqueous solutions, allowing sensing of the concentration or chirality of two hydrophobic amino acids (Fig. 18).35 Compound 29 formed hollow vesicles in aqueous solutions after a film of 29 was dispersed in hot water and cooled down to room temperature. Glucose headgroups were exposed on the outer and inner surfaces of the vesicles due to partial hydrolysis of the boronate ester. Interestingly, the vesicles underwent morphological transformations in the presence of phenylalanine (Phe) and tryptophan (Trp), incorporated into the bilayer membranes. 

The morphology change depended on the chirality of the respective amino acids as D-Phe and D-Trp were both found to transform the blue-emissive vesicles into non-emissive nanorods. Other common amino acids did not induce these structural transformations. The study demonstrated that incorporation of hydrophobic guests via noncovalent interactions can dramatically alter the molecular packing of building blocks in the nanoscale aggregates, providing a promising strategy for sensing analytes that normally weakly interact in aqueous solutions.

Conclusions

In the last three years, significant progress has been made in the area of boronic acid-based sensing, which has been highlighted in this minireview. For example, the toolkit of organoboron-based receptors has been enriched by the discovery of BODIPY32 and boronate33 motifs as polyl binding sites. The accessibility of boronic acid-based molecular recognition has been expanded by the identification of boronic acid-pyrophosphate esterification41 and boronic acid-acetate hydrogen bonding49 interactions. Unconventional sensing methodologies have been explored that have resulted in improved sensitivity, selectivity, and/or simplified sensor preparation. These include exploitation of supramolecular aggregation, multicomponent dynamic covalent assembly, and coupling boronic acid–analyte binding to a further chemical reaction. The emergence of new materials, such as boronate affinity molecularly imprinted micelles,31 and utilisation of less explored spectroscopic techniques, such as 19F NMR,34 have further improved the sensor versatility. It is fascinating to realise that some of the sensors have demonstrated real-world applications such as monitoring the metabolite concentrations in live cells46 and analysing enantioselectivity of asymmetric reactions.52 Note that the performance of many sensors described herein is yet to be improved to confer reversibility, reduce response time, increase biocompatibility, and reduce cross-reactions with non-targeted biomolecules. With advanced knowledge of synthetic organic chemistry, supramolecular chemistry, and material sciences, we expect future developments in this area to generate more reliable analytical tools for clinical purposes as well as biological, pharmacological, and environmental science studies.

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Notes and references


