JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Article

pubs.acs.org/JACS

Chemical Sensing of Polyols with Shapeshifting Boronic Acids As a Self-Contained Sensor Array

Johannes F. Teichert, Dmitry Mazunin, and Jeffrey W. Bode*

Department of Chemistry and Applied Biosciences, Laboratorium für Organische Chemie, ETH Zürich, Wolfgang Pauli Strasse 10, 8093 Zürich, Switzerland

Supporting Information

ABSTRACT: Boronic acid-substituted shapeshifting bullvalenes bearing a ^{13}C label are employed as sensor arrays for polyhydroxylated compounds, such as carbohydrates, flavanols, and sialic acids. The dynamic nature of the bullvalene core allows for covalent binding to a wide variety of analytes, allowing for specific analyte detection by a single NMR measurement. The resulting ^{13}C NMR patterns permit an inference to the identity of a particular analyte bound. Conversion of the ^{13}C NMR to an easy-to-read barcode provides a convenient method to catalog polyol analytes. The synthesis and study of a structurally related static sensor, which is not suitable for analyte recognition, underscores the advantages of the shapeshifting nature of the sensor.

INTRODUCTION

Noninvasive sensing of metabolites is an important research area,[1] mostly driven by the desire to use metabolic imaging for disease detection and diagnosis.[2] A variety of read-out techniques have been investigated for noninvasive metabolic imaging including positron emission tomography (PET), magnetic resonance imaging (MRI), near IR spectroscopy, fluorescence, and polarimetry.[2a] In the context of metabolite detection, chemical sensing has been utilized to a much lesser extent. Boronic acids have been put forward as key chemical sensing units for carbohydrate detection, including blood glucose monitoring devices.[3] For these reasons, chemical sensing of polyhydroxylated compounds with boronic acid-based sensors has been well studied, and a large variety biologically relevant analytes, such as carbohydrates, have been studied.[4]

To date, the majority of boronic acid sensing systems rely on fluorescence quenching for reporting a binding event.[5] This has limitations in *in vivo* applications with regards to tissue optics.[5c−e] In contrast, nuclear magnetic resonance (NMR) offers a noninvasive imaging technique[6] and can be used for high resolution imaging in an *in vivo* setting. For example, ^{13}C NMR has found application as read-out technique for *in vivo* applications in medical imaging, and ^{19}F NMR has been applied to the difficult problem of detecting ligand binding by a noninvasive method.[7] We reasoned that a boronic acid-based chemical sensor, with the potential for noninvasive polyol sensing,[3] paired with ^{13}C NMR as read-out technique would manifest a new approach for a polyol sensing system.

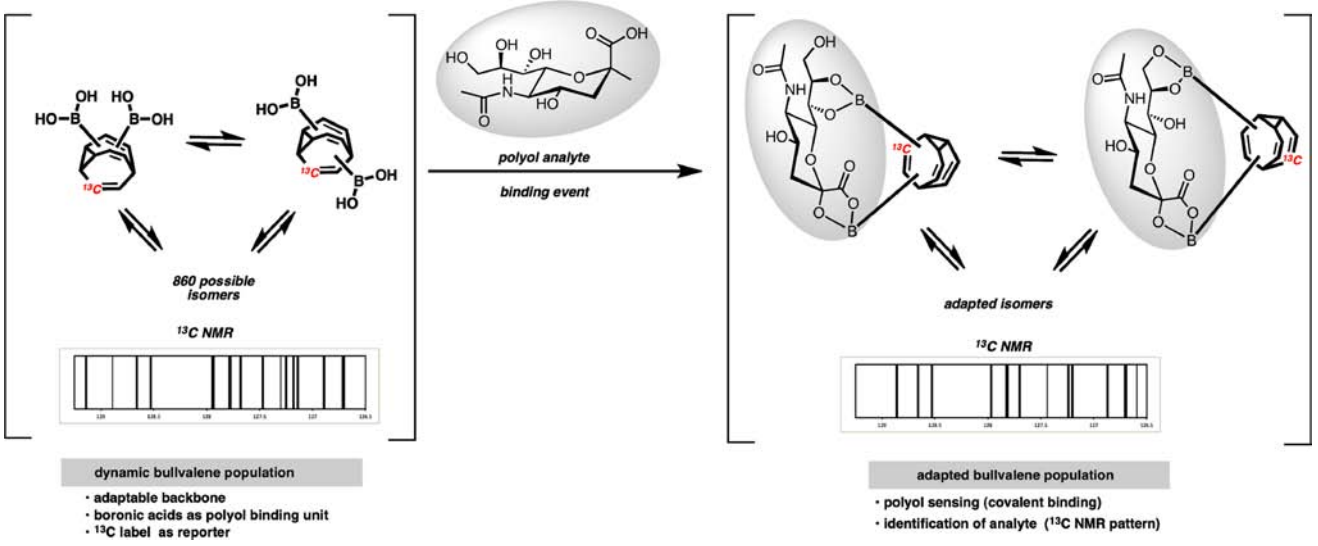
Boronic acid-based sensors of polyols display selective binding behavior to analytes depending on the structure and properties of their "backbone",[4b,5a] i.e., the part of the molecule that links the boronic acid moieties.[8] Careful design of the backbone can lead to specific and high affinity binding for a particular analyte.[4] In cases where selective recognition of one particular compound is enhanced, the analyte scope is reduced. This is a general property of chemical sensors; one that necessitates extensive design and optimization for each different analyte—a time-consuming and often unpredictable processes.[9] To overcome this limitation, sensor arrays have been introduced to improve analyte scope in chemical sensing.[10] In these systems, the read-out is composed of the combined signals of an ensemble of individual sensors, and this collective signal is characteristic for a particular analyte. Therefore, sensor arrays offer the selectivity for an analyte of interest while keeping the general scope of detectable compounds wide. This principle has successfully been applied to boronic acid-based sensors of carbohydrates[11] and polyols.[5f,g]

We have recently introduced a new approach to sensor arrays[12] based on ^{13}C-labeled shapeshifting bullvalenes.[12,13] Substituted bullvalenes rapidly undergo structural remodeling through Cope rearrangements,[14] resulting in a dynamic combinatorial mixture of hundreds or thousands of discrete structural isomers. When equipped with appropriate binding moieties,[13,14e,15] these molecules can function as a self-contained sensor array to recognize and report the binding of analytes using only one initial structure as the starting point. Binding to an analyte results in a shift of the equilibrium population of the bullvalene isomers,[12,13] which can be detected by ^{13}C NMR (Scheme 1).[12] The advantage of this approach is a single synthetic route leading to a multitude of structurally related sensors, eliminating the need for multiple syntheses of the components of a sensor array. In prior work, we have investigated ^{13}C-labeled bullvalenes with porphyrin ligands that bind to fullerenes through noncovalent interactions,[12] leading

Received: May 23, 2013
Published: June 26, 2013

dx.doi.org/10.1021/ja404981q | J. Am. Chem. Soc. 2013, 135, 11314−11321

Scheme 1. Proposed Polyol Binding with Shapeshifting Bullvalene Bis-Boronic Acid



to small but perceptable changes in the ^{13}C NMR spectrum. We anticipated that analyte binding through covalent bonding would lead to a more distinct bullvalene isomer distribution on the NMR time scale and therefore to more pronounced changes in the ^{13}C NMR spectrum itself. In this manuscript, we report the successful development of a dynamic, boronic acid-based sensor array for diverse polyols that gives distinct, reproducible signals by a single ^{13}C NMR experiment.

To achieve this we designed a ^{13}C-labeled shapeshifting bullvalene appended with boronic acid binding units as a dynamic sensor array for polyols (Figure 1). The shapeshifting

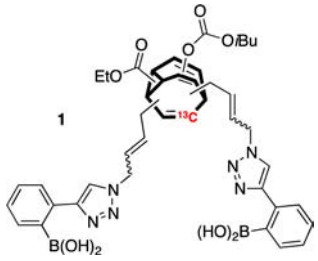


Figure 1. ^{13}C-labeled bullvalene-based polyol sensor **1**.

core would simultaneously deliver two advantages. First, it would keep the system structurally flexible and adaptable to a wide variety of analytes. Second, it would act as the actual reporting unit by signaling a binding event while at the same time transmitting information about the actual analyte bound through the adapted isomer distribution. By establishing a catalogue of the patterns generated upon binding to a known analyte, this system can provide information about the identity of analytes. NMR, as a noninvasive technique for the read-out of sensor arrays,[17] bears potential for polyol sensing for an *in vivo* setting and has been employed as read-out technique to study the binding of boronic acid-based polyol sensors.[16,17c,18]

RESULTS AND DISCUSSION

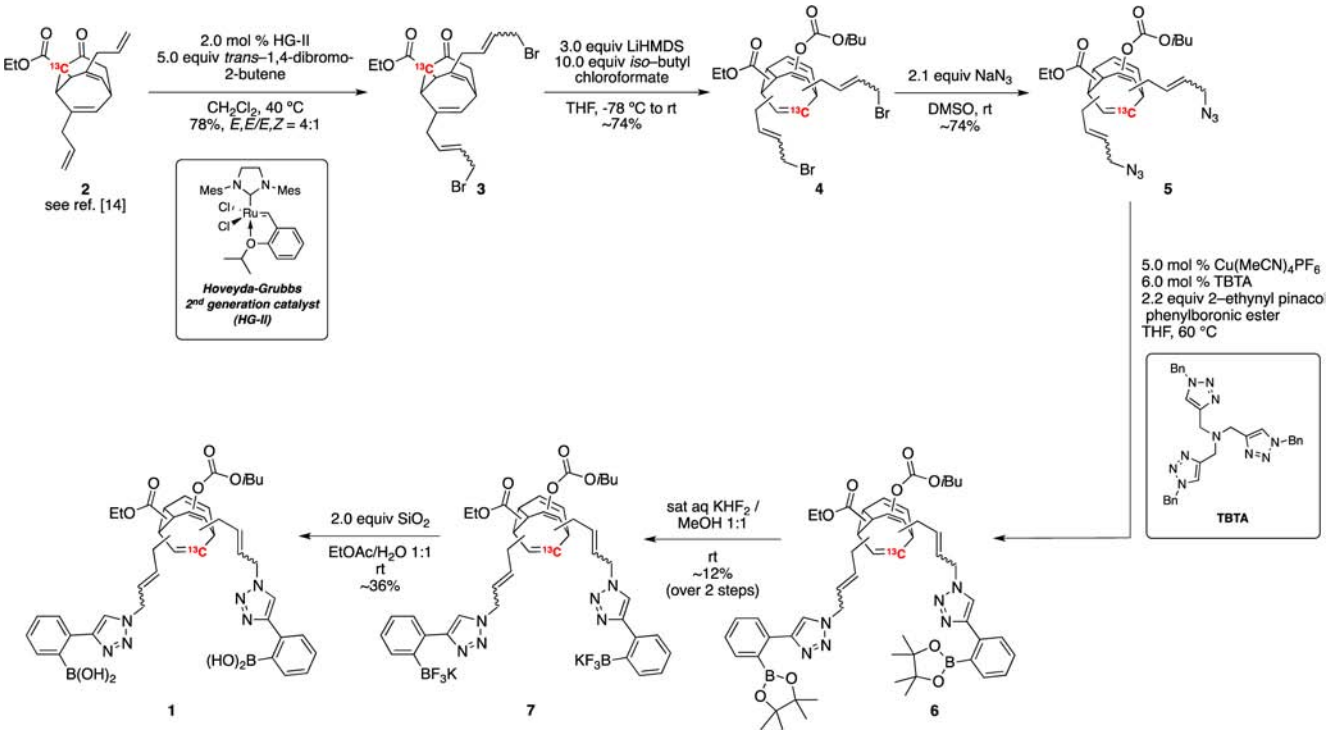
Synthesis of Dynamic Bis-Boronic Acid Bullvalene 1. The design of the binding moieties for shapeshifting polyol sensor **1** was inspired by a report on boronic acid carbohydrate sensors constructed by Cu-catalyzed alkyne−azide cycloaddition (CuAAC).[19] We therefore chose to introduce the boronic acid units by CuAAC and synthesized dynamic bis-azide **5** from ^{13}C-labeled bis-allyl bullvalone **2**[12] in a three-step sequence: cross-metathesis with *trans*-1,4-dibromo-2-butene to give bullvalone **3**, followed by conversion to the corresponding dynamic bullvalene **4**, and transformation to **5** by double nucleophilic substitution of the allylic bromides (see Scheme 2). We found that executing the CuAAC in the presence of TBTA ligand[20] successfully suppressed the otherwise rapid protodeboronation of bis-boronic ester **6**, a common problem for CuAAC reactions with boron-containing compounds.[4d] Bis-boronic ester **6** could be transformed to the corresponding dynamic bis-boronic acid **1** in a two-step sequence involving transformation[21] to the corresponding bis-potassium trifluoroborate **7** followed by hydrolysis[22] to yield dynamic bis-boronic acid sensor **1**.

Synthesis of Static Bis-Boronic Acid Sensor 14. As a negative control with a static backbone incapable of undergoing Cope rearrangements, we synthesized the structurally related ^{13}C-labeled tetrahydrofuran bis-boronic acid **14** from diol **8**[12] (Scheme 3). As reported earlier by our group, diol **8** can be converted to the corresponding tetrahydrofuran **9**.[13b,15a] Originally an unwanted side-reaction, we exploited the resulting compounds as static analogs of bullvalenes in which the ^{13}C label and substituted groups are locked into discrete positions. Transformation of the ketone to the vinyl carbonate **10** yielded bis-allyl tetrahydrofuran, which could successfully be converted to static bis-boronic acid **14** in a similar reaction sequence (**11**−**14**) as in the route toward dynamic bullvalenes (**5** to **1**, see Scheme 2).

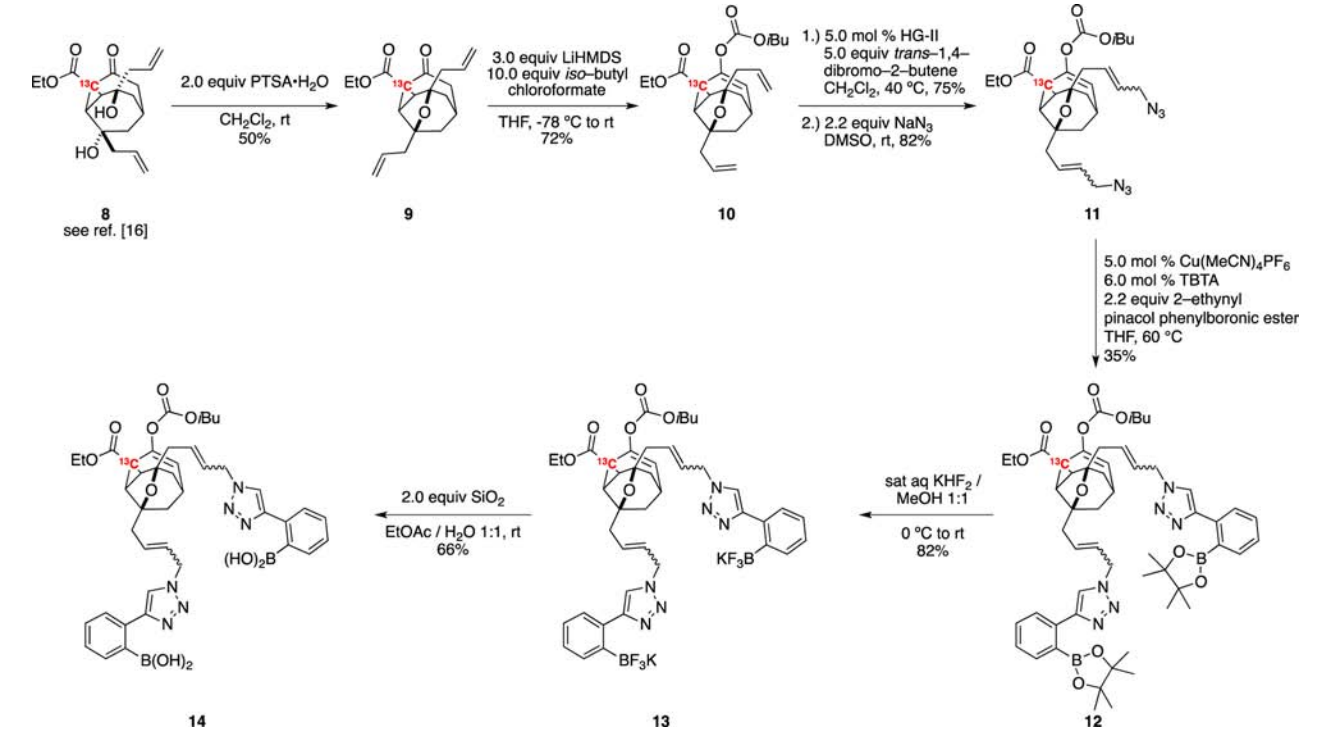
Sensing Experiments. In a representative sensing experiment, **1** was mixed with a polyol analyte in DMSO/phosphate buffer solution (pH = 7.2) at ambient temperature and allowed to equilibrate for 1 h.[23] The ^{13}C NMR spectrum of the mixture was recorded and compared to the reference NMR spectrum of **1** alone under otherwise identical conditions. The differences in peak intensities, chemical shift, and number of peaks in the region of the olefinic bullvalene carbon resonances (130−126 ppm), which have previously been identified as diagnostic,[12] display the adapted equilibrium population of **1** in the presence

dx.doi.org/10.1021/ja404981q | J. Am. Chem. Soc. 2013, 135, 11314−11321

Scheme 2. Synthesis of Shapeshifting Polyol Sensor 1



Scheme 3. Synthesis of Static Bis-Boronic Acid Sensor 14



of an analyte (see Scheme 1). The ^{13}C NMR spectra therefore constitute the actual read-out of the sensor.

Reduction of Complexity and Generation of Barcodes. For ease of recognition and facile comparison of the resulting patterns, ^{13}C NMR signals are displayed as a "barcode" (see Figure 2). To reproducibly generate a barcode from the ^{13}C NMR spectrum, the complexity was first reduced by binning, a technique that has been used for pattern recognition for the study of metabolites in body fluids by NMR.[24] The spectrum is displayed as the integral of peak intensities of equally sized partitions of the ^{13}C NMR spectrum (0.03 ppm in our case). The chemical shifts and peak heights of the resulting "binned" spectrum are extracted and converted to a barcode; the peak height in the spectrum is reflected by a corresponding larger line thickness in the respective barcode[25] (Figure 2).

dx.doi.org/10.1021/ja404981q | J. Am. Chem. Soc. 2013, 135, 11314–11321

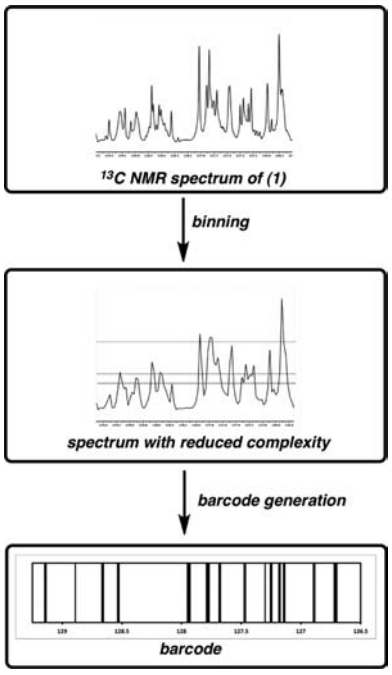


Figure 2. Conversion of ^{13}C NMR spectrum to a barcode (binned spectrum: lowest dashed line: lower cutoff for barcodes; middle dashed line: cutoff from normal to thick lines in barcodes; top dashed line: cutoff for thickest lines in barcodes).

Sensing Results with Dynamic Sensor 1. The results of the sensing experiments of substituted bullvalene **1** with a variety of naturally occurring or biologically relevant polyols as analytes are presented in Tables 1 and 2. The characteristic line pattern, consisting of the respective chemical shift and intensities in the barcodes varies with the analytes investigated, allowing for the successful recognition of these compounds with **1**. As expected, the sensing of a variety of compound classes is feasible, owing to the adaptable nature of the flexible and dynamic bullvalene backbone of the sensor.

The barcode patterns for naturally occurring polyphenols (Table 1, entries 2–6) including chlorogenic acid (**15**), ellagic acid (**16**) and tannic acid (**17**) are distinct from the reference barcode of the bullvalene sensor **1** (entry 1) and therefore allow for recognition of these substances. The resulting barcodes differ from the reference of **1** alone in number of lines and their shift as well as their thicknesses. Therefore, all representation modes of the resulting barcodes can be exploited to display the differences after substrate binding.

The same holds true for barcode patterns obtained for flavanols[11f,g,26] epigallocatechin gallate (EGCG) (**18**) and epicatechin gallate (**19**) (entries 5 and 6). These are naturally occurring ingredients of green tea, with a wide variety of biological acitivities.[27] Even though the structure of analytes **18** and **19** differs only by the presence or absence of one phenolic OH group, these subtle variations are reflected in the respective barcodes. As expected, the barcodes appear similar but show small differences in the number of lines. This case of sensing structurally closely related analytes represents a limitation of sensing with dynamic bullvalene bis-boronic acids. Differences in the chemical structures are reflected in the barcodes, but naturally, these differences are small and therefore difficult to read-out and detect as significant. In the case of polyphenol Alizarin Red S (ARS) (**20**) as substrate (entry 7), two ^{13}C-signals of the analyte appear in the diagnostic chemical shift region of bullvalene sensor **1**.[23] Therefore, as too many sensor signals are concealed by the signals of the analyte, no clear distinction of the barcode can be made.

Sialic acids play a paramount role in cellular recognition processes,[28] which renders them attractive targets for recognition studies,[29] as one could employ successful sensors as potential biomarkers. *N*-acetylneuraminic acid (sialic acid) (**21**) and the corresponding 2-*O*-Me-*N*-acetylneuraminic acid (**22**) (Table 2, entries 2 and 3) differ only by the substituent on the 2-OH position, a relatively minor structural difference, as with **18** and **19**. In this case the read-out of the sensor was influenced in a much more pronounced manner. The barcode for *N*-acetylneuraminic acid (**21**) (Table 2, entry 2) shows clear, discernible differences in terms of line shift and their pattern in comparison to the unbound sensor **1**; the 2-methyl-substituted derivative **22** shows no difference in the barcode (Table 2, entry 3) compared to **1**. We conclude from this result that **22** does not bind strongly to **1** due to the absence of the free 2-OH group and therefore does not alter the equilibrium population of **1** enough to obtain a discriminable read-out. This observation is in line with the proposition of the binding mode of other boronic acid sensors to sialic acid (**21**),[29b,c] suggesting that the formation of a five-membered ring of the 1-CO_2H and the 2-OH with boronic acid sensor **1** is crucial for binding. The formation of a similar structure is not possible with the substituted OH in **22** (see Figure 3).

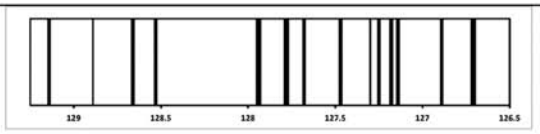
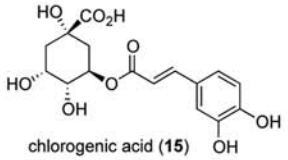
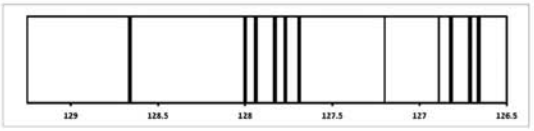
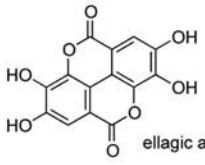
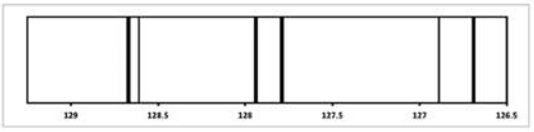
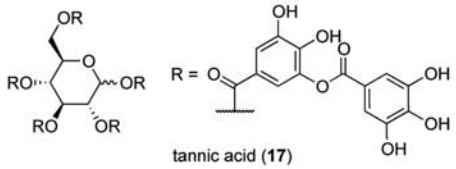
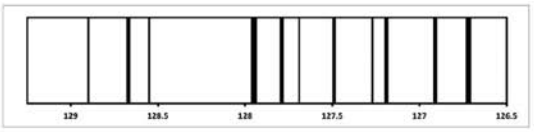
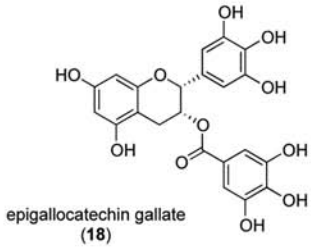
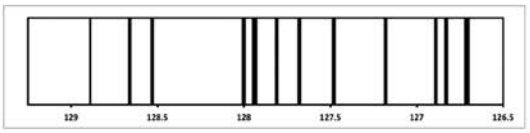
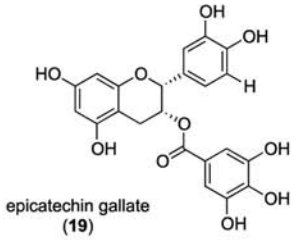
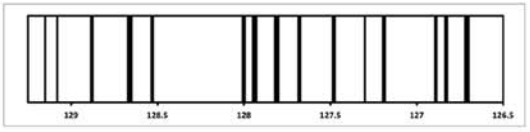
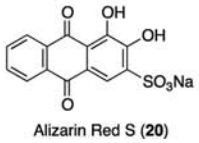
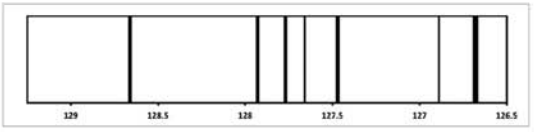
Other mono- and a disaccharides have also been investigated as analytes for bullvalene sensor array **1**, thereby probing the use of our system for potential carbohydrate sensing. Whereby the barcode for D-fructose (**23**) (Table 2, entry 4) displays small differences compared to the reference spectrum of **1** (Table 2, entry 1), the barcode of sucrose (**24**) (Table 2, entry 5) does not differ from the reference. In analogy to the binding experiments with MeO-sialic acid (**22**) (*vide supra*), we conclude that strong binding between sucrose (**24**) and **1** does not occur, resulting in a nearly unaltered barcode.

We have also investigated the interaction of sensor **1** with mixtures of analytes (Table 2, entries 6 and 7). When a 1:1 mixture of chlorogenic acid (**15**) and sucrose (**24**), a mixture of one strong and one weak binding analyte was measured with **1**, the resulting barcode resembles that of chlorogenic acid (**15**) (compare Table 1, entry 2). This supports our hypothesis that **1** does not strongly bind to sucrose (**24**). When a 1:1 mixture of two tight-binding substrates, chlorogenic acid (**15**) and tannic acid (**17**) were investigated, the resulting barcode (Table 2, entry 7) again resembled that of chlorogenic acid (**15**). This suggests that **1** has higher affinity for chlorogenic acid and is responsible for determining the equilibrium population of **1** in the sensing experiment. The outcomes of sensing experiments with mixtures of analytes lead to the conclusion that a competition of the analytes for the boronic acid binding units of **1** exists, and the respective analyte which exerts the strongest binding to the boronic acid determines the altered equilibrium population of **1** and therefore the resulting barcode. Further studies are needed, as this constitutes a potential advantage over classic sensor arrays.

Sensing Experiments with Static Bis-Boronic Acid 14. When sensing experiments were carried out with static bis-boronic acid **14** under otherwise identical conditions, the advantage of the dynamic variant **1** is evident. Since **14** cannot change shape, only one ^{13}C resonance can be observed, therefore the generation of a barcode pattern is not possible. When the ^{13}C NMR resonances of **14** were followed in sensing

dx.doi.org/10.1021/ja404981q | J. Am. Chem. Soc. 2013, 135, 11314–11321

Table 1. Sensing Experiments of 1 with Catechols[a]

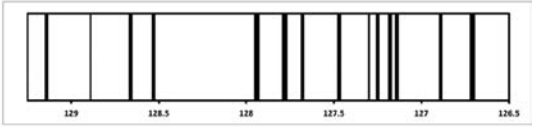
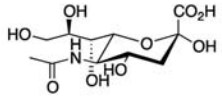
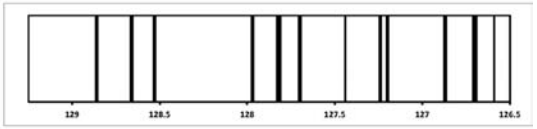
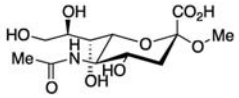
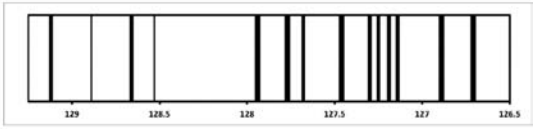
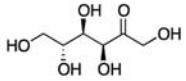
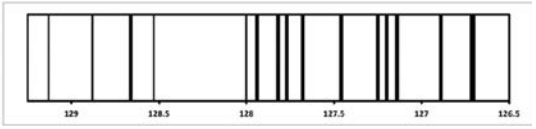
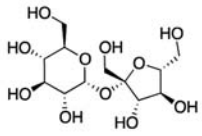
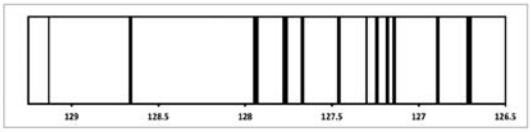
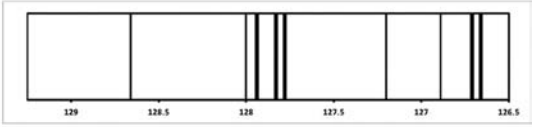
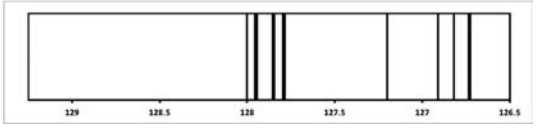
entry	analyte	barcode[b]
1	None (unbound sensor)	
2	 chlorogenic acid (**15**)	
3	 ellagic acid (**16**)	
4	 tannic acid (**17**)	
5[c]	 epigallocatechin gallate (**18**)	
6[d]	 epicatechin gallate (**19**)	
7[e]	 Alizarin Red S (**20**)	

[a]Conditions: 2.5×10^{-6} mol **1** and 5.0×10^{-6} mol of the appropriate analyte were dissolved in 0.6 mL of a 9:1 mixture DMSO-d_6/phosphate buffer (pH = 7.2, 0.05 M) followed by equilibration for 1 h at RT and analysis by ^{13}C NMR spectrum (typically 14500 scans). [b]For generation of barcodes, see Supporting Information. [c]Signals resulting from the ^{13}C NMR resonance at 129.08 ppm, belonging to **18**, were omitted in the barcode. [d]Signals resulting from the ^{13}C NMR resonance at 129.81 ppm, belonging to **19**, were omitted in the barcode. [e]Signals resulting from the ^{13}C NMR resonances at 127.28 ppm and 127.08 ppm, belonging to **20**, were omitted in the barcode.

experiments with analytes **15**, **17**, and **19**, a 0.05−0.01 ppm downfield shift of the ^{13}C signal was observed in all cases (Figure 4).[23] This indicates binding to the respective analyte. In contrast, sucrose (**24**) as analyte induces no significant shift of the ^{13}C resonance ($\Delta\delta$ = 0.006 ppm) and supports the hypothesis that **24** cannot bind to static (**14**) or dynamic (**1**) bis-boronic acids under the given conditions. Interestingly, no significant shift of the ^{13}C NMR resonances upon binding with epigallocatechin gallate (**18**)—a good analyte for the dynamic sensor—was observed. From this result we postulate that the fixed backbone of static bis-boronic acid **14** prevents it from adopting a spatial arrangement of the boronic acids suitable for

dx.doi.org/10.1021/ja404981q | J. Am. Chem. Soc. 2013, 135, 11314−11321

Table 2. Sensing Experiments of 1 with Carbohydrates and Polyol Mixtures[a]

entry	analyte	barcode[b]
1	None (unbound sensor)	
2	 *N*-acetyl neuraminic acid (**21**)	
3	 2-*O*-Me-*N*-acetyl neuraminic acid (**22**)	
4	 D-fructose (**23**)	
5	 sucrose (**24**)	
6[c]	Chlorogenic acid (**15**) and tannic acid (**17**)	
7[d][e]	Clorogenic acid (**15**) and sucrose (**24**)	

[a]Conditions: 2.5×10^{-6} mol **1** and 5.0×10^{-6} mol of the appropriate analyte were dissolved in 0.6 mL of a 9:1 mixture DMSO-d_6/phosphate buffer (pH = 7.2, 0.05 M) followed by equilibration for 1 h at RT and analysis by ^{13}C NMR spectrum (typically 14500 scans). [b]For generation of barcodes, see Supporting Information. [c]5.0×10^{-6} mol of both, **15** and **17** were added under otherwise identical conditions. [d]5.0×10^{-6} mol of both, **15** and **24** were added under otherwise identical conditions. [e]The lower threshold for barcode generation was lowered to 50, see Supporting Information for details.

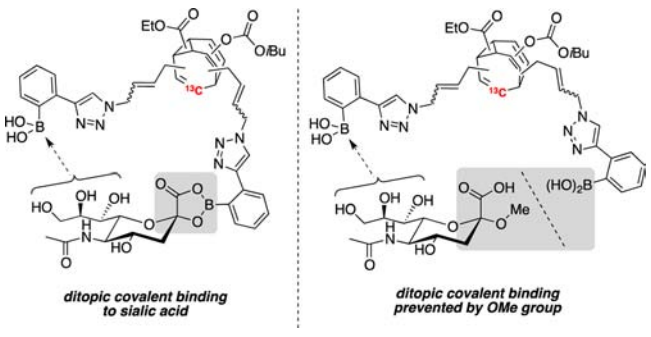


Figure 3. Suggested binding of **1** to sialic acids based on ref 29b.

binding to various, structurally different analytes. It displays the well-known limitations of ditopic nondynamic boronic acid-based sensors. In addition, static sensor **14** can only display whether a binding event with a potential analyte has occurred or not ("yes/no" sensing). The dynamic sensor **1**, on the other hand, can give information on the identity of the bound analyte via an altered peak pattern, in addition to displaying the simple "yes/no" sensing behavior. This particular behavior showcases the general advantage of sensor arrays over classical sensors.

CONCLUSION

In summary, we have developed a new sensor array for polyhydroxylated compounds based on a ^{13}C-labeled shape-shifting bullvalene bis-boronic acid. We demonstrated that the ^{13}C NMR read-out is indicative not only for the binding event with an analyte of interest but also gives structural information of the analyte bound through the corresponding changes in the ^{13}C NMR peak pattern. The patterns were transformed to an easy-to-recognize barcode, rendering identification of an analyte

dx.doi.org/10.1021/ja404981q | J. Am. Chem. Soc. 2013, 135, 11314−11321

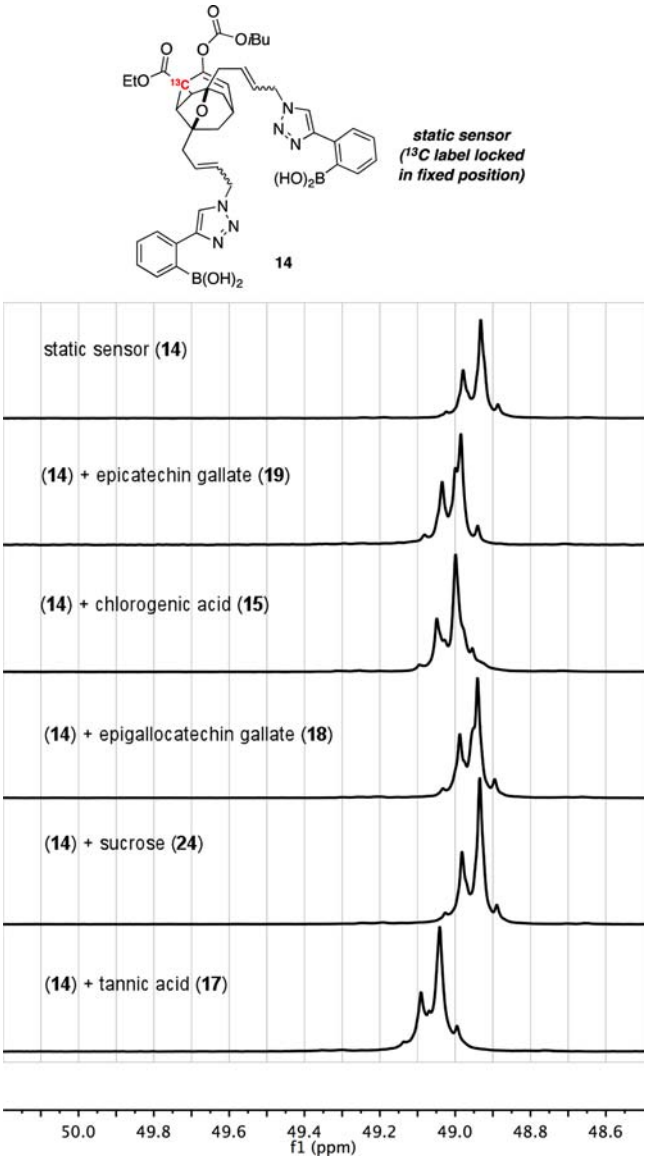


Figure 4. Static bis-boronic acid sensor **14** and ^{13}C NMR spectra of binding experiments.

fast and easy. A variety of biologically relevant analytes, such as sialic acid and its derivatives, were successfully shown to be analytes for this sensor array. Sensing of mixtures of analytes is possible; the strongest binding analyte will dominate the corresponding read-out. As a negative control, a structurally related but nondynamic bis-boronic acid was synthesized and employed as a sensor. The resulting shifts in ^{13}C NMR cannot be employed to generate a pattern for read-out, and it appears that the static backbone prevents this sensor to bind to a wide variety of substrates. These facts underscore the usefulness of shapeshifting bullvalene sensors with flexible and adaptable backbones. We envision that NMR as a noninvasive technique enables this methodology as an *in vivo* sensor to discriminate tissue types in future studies.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, spectroscopic data for all compounds and a template for the generation of barcodes from ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

bode@org.chem.ethz.ch

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partially supported by ETH-Zürich and the ETH Foundation. J.F.T. thanks the German Academy of Sciences Leopoldina for a postdoctoral fellowship. We thank the NMR service of the Laboratorium für Organische Chemie at ETH Zürich (Dr. Marc-Olivier Ebert, Philipp Zumbrunnen, René Arnold) for helpful discussions and technical assistance. Maggie He and Florian Rohrbacher are acknowledged for helpful discussions and technical assistance.

■ REFERENCES

(1) (a) Koschinsky, T.; Heinemann, L. *Diabetes/Metab. Res. Rev.* **2001**, *17* (2), 113−123. (b) Koschwanez, H. E.; Reichert, W. M. *Biomaterials* **2007**, *28* (25), 3687−3703.

(2) (a) Vashist, S. K. *Anal. Chim. Acta* **2012**, *750*, 16−27. (b) Tura, A.; Maran, A.; Pacini, G. *Diabetes Res. Clin. Pract.* **2007**, *77* (1), 16−40. (c) Rohrscheib, M.; Robinson, R.; Eaton, R. P. *Diabetes, Obes. Metab.* **2003**, *5* (5), 280−284.

(3) Hansen, J. S.; Christensen, J. B.; Petersen, J. F.; Hoeg-Jensen, T.; Norrild, J. C. *Sens. Actuators, B* **2012**, *161* (1), 45−79.

(4) (a) James, T. D. Boronic Acid-based Receptors and Sensors for Saccharides. In *Boronic Acids*; Hall, D. G., Ed. Wiley-VCH: Weinheim, 2005; pp 441−479; (b) James, T. D.; Phillips, M. D.; Shinkai, S. *Boronic acids in saccharide recognition*; RSC Publishing: Cambridge, 2006; (c) Yang, W.; Gao, X.; Wang, B. Biological and Medicinal Applications of Boronic Acids. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005; pp 481−512; (d) Dai, C.; Cheng, Y.; Cui, J.; Wang, B. *Molecules* **2010**, *15* (8), 5768−5781. (e) Fossey, J. S.; D'Hooge, F.; van den Elsen, J. M. H.; Morais, M. P. P.; Pascu, S. I.; Bull, S. D.; Marken, F.; Jenkins, A. T. A.; Jiang, Y.-B.; James, T. D. *Chem. Rec.* **2012**, *12* (5), 464−478. (f) James, T. D., Saccharide-selective boronic acid based Photoinduced Electron Transfer (PET) fluorescent sensors. In *Top. Curr. Chem.*, Schrader, T., Ed. Springer: Heidelberg, 2007; Vol. *277*, pp 107−152; (g) James, T. D.; Sandanayake, K.; Shinkai, S. *Angew. Chem., Int. Ed.* **1996**, *35* (17), 1910−1922. (h) James, T. D.; Shinkai, S., Artificial receptors as chemosensors for carbohydrates. In *Top. Curr. Chem.*, Penades, S., Ed. Springer: Heidelberg, 2002; Vol. *218*, pp 159−200; (i) Jin, S.; Cheng, Y.; Reid, S.; Li, M.; Wang, B. *Med. Res. Rev.* **2010**, *30* (2), 171−257. (j) Striegler, S. *Curr. Org. Chem.* **2003**, *7* (1), 81−102. (k) Wang, W.; Gao, X. M.; Wang, B. H. *Curr. Org. Chem.* **2002**, *6* (14), 1285−1317. (l) Hagihara, S.; Tanaka, H.; Matile, S. *J. Am. Chem. Soc.* **2008**, *130* (17), 5656−5657. (m) Hagihara, S.; Tanaka, H.; Matile, S. *Org. Biomol. Chem.* **2008**, *6* (13), 2259−2262.

(5) (a) For an excellent discussion of structure/selectivity relationships of bis-boronic acids, see: Cao, H. S.; Heagy, M. D. *J. Fluoresc.* **2004**, *14* (5), 569−584. (b) Pickup, J. C.; Hussain, F.; Evans, N. D.; Rolinski, O. J.; Birch, D. J. S. *Biosens. Bioelectron.* **2005**, *20* (12), 2555−2565. (c) Richards-Kortum, R.; Sevick-Muraca, E. *Annu. Rev. Phys. Chem.* **1996**, *47*, 555−606. (d) Wagnieres, G. A.; Star, W. M.; Wilson, B. C. *Photochem. Photobiol.* **1998**, *68* (5), 603−632. (e) Wouters, F. S.; Verveer, P. J.; Bastiaens, P. I. H. *Trends Cell Biol.* **2001**, *11* (5), 203−211. (f) Ikeda, M.; Fukuda, K.; Tanida, T.; Yoshii, T.; Hamachi, I. *Chem. Commun.* **2012**, *48* (21), 2716−2718. (g) Wiskur, S. L.; Anslyn, E. V. *J. Am. Chem. Soc.* **2001**, *123* (41), 10109−10110.

(6) Liang, Z.-P.; Lauterbur, P. C. *Principles of Magnetic Resonance Imaging: A Signal Processing Perspective*; SPIEE Press: Piscataway, 1999.

(7) (a) Gruetter, R. *Neurochem. Res.* **2002**, *41* (2−3), 143−154. (b) Ross, B.; Lin, A.; Harris, K.; Bhattacharya, P.; Schweinsburg, B. *NMR Biomed.* **2003**, *16* (6−7), 358−369. (c) Takaoka, Y.; Sakamoto, T.; Tsukiji, S.; Narazaki, M.; Matsuda, T.; Tochio, H.; Shirakawa, M.; Hamachi, I. *Nat. Chem.* **2009**, *1* (7), 557−561.

(8) For selected examples, see: (a) James, T. D.; Sandanayake, K.; Iguchi, R.; Shinkai, S. *J. Am. Chem. Soc.* **1995**, *117* (35), 8982−8987. (b) James, T. D.; Sandanayake, K.; Shinkai, S. *Angew. Chem., Int. Ed.* **1994**, *33* (21), 2207−2209. (c) James, T. D.; Sandanayake, K.; Shinkai, S. *Nature* **1995**, *374* (6520), 345−347. (d) James, T. D.; Shinmori, H.; Shinkai, S. *Chem. Commun.* **1997**, *1*, 71−72. (e) Linnane, P.; James, T. D.; Imazu, S.; Shinaki, S. *Tetrahedron Lett.* **1995**, *36* (48), 8833−8834. (f) Murakami, H.; Nagasaki, T.; Hamachi, I.; Shinkai, S. *Tetrahedron Lett.* **1993**, *34* (39), 6273−6276. (g) Zhao, J. Z.; Fyles, T. M.; James, T. D. *Angew. Chem., Int. Ed.* **2004**, *43* (26), 3461−3464.

(9) (a) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40* (3), 486−516. (b) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97* (5), 1713−1734. (c) Lehn, J. M. *Angew. Chem., Int. Ed.* **1990**, *29* (11), 1304−1319. (d) Martinez-Manez, R.; Sancenon, F. *Chem. Rev.* **2003**, *103* (11), 4419−4476. (e) McQuade, D. T.; Pullen, A. E.; Swager, T. M. *Chem. Rev.* **2000**, *100* (7), 2537−2574. (f) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42* (11), 1210−1250. (g) Zeng, F. W.; Zimmerman, S. C. *Chem. Rev.* **1997**, *97* (5), 1681−1712. (h) Schneider, H. J. *Angew. Chem., Int. Ed.* **1991**, *30* (11), 1417−1436. (i) Valeur, B.; Leray, I. *Coord. Chem. Rev.* **2000**, *205*, 3−40.

(10) (a) Otto, S.; Severin, K. Dynamic combinatorial libraries for the development of synthetic receptors and sensors. In *Topics in Current Chemistry*; Schrader, T., Ed.; Springer: Heidelberg, 2007; Vol. *277*, pp 267−288; (b) Albert, K. J.; Lewis, N. S.; Schauer, C. L.; Sotzing, G. A.; Stitzel, S. E.; Vaid, T. P.; Walt, D. R. *Chem. Rev.* **2000**, *100* (7), 2595−2626. (c) Anslyn, E. V. *J. Org. Chem.* **2007**, *72* (3), 687−699. (d) Anzenbacher, P., Jr.; Lubal, P.; Bucek, P.; Palacios, M. A.; Kozelkova, M. E. *Chem. Soc. Rev.* **2010**, *39* (10), 3954−3979. (e) Collins, B. E.; Wright, A. T.; Anslyn, E. V. Combining molecular recognition, optical detection, and chemometric analysis. In *Topics in Current Chemistry*; Schrader, T., Ed.; Springer: Heidelberg, 2007; Vol. *277*, pp 181−218; (f) Lavigne, J. J.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **2001**, *40* (17), 3119−3130. (g) Rochat, S.; Gao, J.; Qian, X.; Zaubitzer, F.; Severin, K. *Chem.—Eur. J.* **2010**, *16* (1), 104−113 and references therein. (h) Umali, A. P.; Anslyn, E. V. *Curr. Op. Chem. Biol.* **2010**, *14* (6), 685−692. (i) Wright, A. T.; Anslyn, E. V. *Chem. Soc. Rev.* **2006**, *35* (1), 14−28. (j) Herrmann, A. *Chem.—Eur. J.* **2012**, *18* (28), 8568−8577. (k) Janowski, V.; Severin, K. *Chem. Commun.* **2011**, *47* (30), 8521−8523. (l) Jagt, R. B. C.; Gomez-Biagi, R. F.; Nitz, M. *Angew. Chem., Int. Ed.* **2009**, *48* (11), 1995−1997. (m) Mueller-Graff, P.-K.; Szelke, H.; Severin, K.; Kraemer, R. *Org. Biomol. Chem.* **2010**, *8* (10), 2327−2331. (n) Niu, W.; Kong, H.; Wang, H.; Zhang, Y.; Zhang, S.; Zhang, X. *Anal. Bioanal. Chem.* **2012**, *402* (1), 389−395. (o) Zaubitzer, F.; Buryak, A.; Severin, K. *Chem.—Eur. J.* **2006**, *12* (14), 3928−3934.

(11) (a) Edwards, N. Y.; Sager, T. W.; McDevitt, J. T.; Anslyn, E. V. *J. Am. Chem. Soc.* **2007**, *129* (44), 13575−13583. (b) Ghosh, K. K.; Yap, E.; Kim, H.; Lee, J.-S.; Chang, Y.-T. *Chem. Commun.* **2011**, *47* (13), 4001−4003. (c) Lim, S. H.; Musto, C. J.; Park, E.; Zhong, W.; Suslick, K. S. *Org. Lett.* **2008**, *10* (20), 4405−4408. (d) Schiller, A.; Wessling, R. A.; Singaram, B. *Angew. Chem., Int. Ed.* **2007**, *46* (34), 6457−6459. (e) Shabbir, S. H.; Joyce, L. A.; da Cruz, G. M.; Lynch, V. M.; Sorey, S.; Anslyn, E. V. *J. Am. Chem. Soc.* **2009**, *131* (36), 13125−13131. (f) Zhang, X.; Anslyn, E. V.; Qian, X. *Supramol. Chem.* **2012**, *24* (7), 520−525. (g) Zhang, X.; You, L.; Anslyn, E. V.; Qian, X. *Chem.—Eur. J.* **2012**, *18* (4), 1102−1110.

(12) Larson, K. K.; He, M.; Teichert, J. F.; Naganawa, A.; Bode, J. W. *Chem. Sci.* **2012**, *3* (6), 1825−1828.

(13) (a) Lippert, A. R.; Keleshian, V. L.; Bode, J. W. *Org. Biomol. Chem.* **2009**, *7* (8), 1529−1532. (b) Lippert, A. R.; Naganawa, A.; Keleshian, V. L.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, *132* (44), 15790−15799.

(14) (a) Doering, W. v. E.; Ferrier, B. M.; Fossel, E. T.; Hartenstein, J. H.; Jones, M.; Klumpp, G.; Rubin, R. M.; Saunders, M. *Tetrahedron* **1967**, *23* (10), 3943−3963. (b) Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1963**, *19* (5), 715−720. (c) Oth, J. F. M.; Müllen, K.; Gilles, J. M.; Schröder, G. *Helv. Chim. Acta* **1974**, *57* (5), 1415−1433. (d) Schröder, G.; Oth, J. F. M.; Merenyi, R. *Angew. Chem., Int. Ed.* **1965**, *4* (9), 752−761. (e) He, M.; Bode, J. W. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108* (36), 14752−14756.

(15) (a) Lippert, A. R.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128* (46), 14738−14739. (b) He, M.; Bode, J. W. *Org. Biomol. Chem.* **2013**, *11* (8), 1306−1317.

(16) (a) Nicholls, M. P.; Paul, P. K. C. *Org. Biomol. Chem.* **2004**, *2* (10), 1434−1441. (b) Rohovec, J.; Maschmeyer, T.; Aime, S.; Peters, J. A. *Chem.—Eur. J.* **2003**, *9* (10), 2193−2199. (c) Van den Berg, R.; Peters, J. A.; Van Bekkum, H. *Carbohydr. Res.* **1994**, *253*, 1−12.

(17) (a) Han, S. I.; Garcia, S.; Lowery, T. J.; Ruiz, E. J.; Seeley, J. A.; Chavez, L.; King, D. S.; Wemmer, D. E.; Pines, A. *Anal. Chem.* **2005**, *77* (13), 4008−4012. (b) Jindal, A. K.; Merritt, M. E.; Suh, E. H.; Malloy, C. R.; Sherry, A. D.; Kovacs, Z. *J. Am. Chem. Soc.* **2010**, *132* (6), 1784−1785. (c) Kitamura, M.; Suzuki, T.; Abe, R.; Ueno, T.; Aoki, S. *Inorg. Chem.* **2011**, *50* (22), 11568−11580. (d) You, L.; Berman, J. S.; Anslyn, E. V. *Nat. Chem.* **2011**, *3* (12), 943−948.

(18) (a) Egawa, Y.; Tanaka, Y.; Gotoh, R.; Niina, S.; Kojima, Y.; Shimomura, N.; Nakagawa, H.; Seki, T.; Anzai, J.-i. *Chem. Lett.* **2010**, *39* (11), 1188−1189. (b) Heinrichs, G.; Schellentraeger, M.; Kubik, S. *Eur. J. Org. Chem.* **2006**, *18*, 4177−4186. (c) Maue, M.; Schrader, T. *Angew. Chem., Int. Ed.* **2005**, *44* (15), 2265−2270. (d) Oi, T.; Takeda, T.; Kakihana, H. *Bull. Chem. Soc. Jpn.* **1992**, *65* (7), 1903−1909. (e) Sartain, F. K.; Yang, X.; Lowe, C. R. *Chem.—Eur. J.* **2008**, *14* (13), 4060−4067. (f) Uggla, R.; Sundberg, M. R.; Nevalainen, V. *Tetrahedron: Asymmetry* **1996**, *7* (6), 1741−1748. (g) Van Duin, M.; Peters, J. A.; Kieboom, A. P. G.; Van Bekkum, H. *Tetrahedron* **1984**, *40* (15), 2901−2911. (h) Van Duin, M.; Peters, J. A.; Kieboom, A. P. G.; Van Bekkum, H. *Tetrahedron* **1985**, *41* (16), 3411−3421. (i) Wiskur, S. L.; Lavigne, J. J.; Ait-Haddou, H.; Lynch, V.; Chiu, Y. H.; Canary, J. W.; Anslyn, E. V. *Org. Lett.* **2001**, *3* (9), 1311−1314.

(19) Scrafton, D. K.; Taylor, J. E.; Mahon, M. F.; Fossey, J. S.; James, T. D. *J. Org. Chem.* **2008**, *73* (7), 2871−2874.

(20) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6* (17), 2853−2855.

(21) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60* (10), 3020−3027.

(22) Molander, G. A.; Cavalcanti, L. N.; Canturk, B.; Pan, P.-S.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74* (19), 7364−7369.

(23) See Supporting Information for details.

(24) (a) Craig, A.; Cloareo, O.; Holmes, E.; Nicholson, J. K.; Lindon, J. C. *Anal. Chem.* **2006**, *78* (7), 2262−2267. (b) Nicholson, J. K.; Connelly, J.; Lindon, J. C.; Holmes, E. *Nat. Rev. Drug Discovery* **2002**, *1* (2), 153−161. (c) Spraul, M.; Neidig, P.; Klauck, U.; Kessler, P.; Holmes, E.; Nicholson, J. K.; Sweatman, B. C.; Salman, S. R.; Farrant, R. D.; Rahr, E.; Beddell, C. R.; Lindon, J. C. *J. Pharm. Biomed. Anal.* **1994**, *12* (10), 1215−1225.

(25) See Supporting Information for details.

(26) For examples of boronic acid sensors for flavanols, ginsenosides and the related flavanoids, see: (a) Hennig, A.; Hagihara, S.; Matile, S. *Chirality* **2009**, *21* (9), 826−835. (b) Hargrove, A. E.; Reyes, R. N.; Riddington, I.; Anslyn, E. V.; Sessler, J. L. *Org. Lett.* **2010**, *12* (21), 4804−4807.

(27) Nagle, D. G.; Ferreira, D.; Zhou, Y.-D. *Phytochemistry* **2006**, *67* (17), 1849−1855 and references therein.

(28) Angata, T.; Varki, A. *Chem. Rev.* **2002**, *102* (2), 439−469.

(29) For examples of sialic acid sensing with boronic acids, see: (a) Crich, S. G.; Alberti, D.; Szabo, I.; Aime, S.; Djanashvili, K. *Angew. Chem., Int. Ed.* **2013**, *52* (4), 1161−1164. (b) Levonis, S. M.; Kiefel, M. J.; Houston, T. A. *Chem. Commun.* **2009**, *17*, 2278−2280. (c) Levonis, S. M.; Kiefel, M. J.; Houston, T. A. *Aust. J. Chem.* **2011**, *64* (11), 1454−1457. (d) Yamamoto, M.; Takeuchi, M.; Shinkai, S. *Tetrahedron* **1998**, *54* (13), 3125−3140. (e) Otsuka, H.; Uchimura, E.; Koshino, H.; Okano, T.; Kataoka, K. *J. Am. Chem. Soc.* **2003**, *125* (12), 3493−3502.