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Sugar complexation to silicone boronic acids†

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A new class of surface-active compounds based on the combination of silicones and boronic acids is described. The properties of the compounds can be tuned by manipulation of both the hydrophobic (silicone size and 3D structure) and hydrophilic components (by binding different saccharides to the boronic acid). Stabilization of the four-coordinate boron structure is provided by Tris buffer that also maintains neutral pH to suppress silicone hydrolysis.

Silicones are both highly mobile (Tg < 123 °C)[1] and hydrophobic entities (surface energy 23 mN m^{-1})[2] and, as a consequence, are widely used – depending on formulation – as both foaming and defoaming agents.[3,4] When combined with hydrophilic entities,[5] particularly poly(ethylene glycol) and other polyether oligomers, they exhibit surface activities that cannot be matched by either fluorocarbon- or hydrocarbon-based surfactants. Silicone surfactants are used in applications ranging from polyurethane foam stabilization[3] to delivery of agricultural bioactives.[6]

It would be of interest to develop responsive surfactants, whose properties could be manipulated by external stimuli including pH, temperature, *etc.* Silicones are exceptionally stable near neutrality, but are subject to hydrolytic cleavage and depolymerization away from pH 7.[7] Amino- or carboxylic acid-modified silicones are readily available, but are not normally used as surfactants due to the associated pH sensitivity. As part of an examination of other potentially responsive organic functional groups, we chose to establish if boronic acids could be incorporated on a silicone backbone and used to mediate surface activity of the silicone.

Boronic acids ($RB(OH)_2$, BA) provide a highly flexible functionality that can be manipulated using a number of well-studied procedures. Not only can they be used in carbon–carbon bond forming reactions such as the Suzuki–Miyaura cross-coupling,[8] but the boronic acid hydroxyl groups provide pH-sensitive binding sites for appropriate diol-containing substrates.

The stability of boronate complexes is affected by the pH of the solution and the presence of any Lewis base. For example, the equilibrium between tri- **1** and tetracoordinate **2** boron compound favours the latter when Lewis bases are present, including hydroxide at higher pH.[9] The equilibrium is also affected by the R group on the boronic acid: arylboronic acids are more acidic than alkylboronic acids; and bulky substituents surrounding boron can cause a decrease in acidity due to restricted access of water to the p-orbital on boron.[10]

Many applications of boronic acids rely on binding selectivity for specific 1,2- or 1,3-diol sites **3**, which are particularly prevalent on saccharides (Fig. 1). This specificity has led to the use of boronic acids as tunable sensors for saccharides: the structure of a given BA will determine to which sugar it will preferentially bind. Based on selective binding several *in vivo* applications for BAs, such as drug delivery devices[11] and artificial lectin (sugar binding protein) mimics,[12] have been proposed. Key to the utility of boronic acids in such applications is the very large range of binding constants – over three orders of magnitude – for sugars with different diol stereostructures.[13,14] Stability of the cyclic products is enhanced when good Lewis bases are present **4**.

Silicone-modified boronic acids should be interesting, tuneable surfactants. If the presence of the hydrophobic silicone does not significantly affect the sugar binding properties of the boronic acid, it should be possible to modify the surface activity by controlling the size (length of linear polydimethylsiloxane chains) and 3D structure (the presence of branching in the silicone moiety) of the silicone hydrophobe, and also the hydrophilicity of the boron head group by manipulating the type and size of hydrophilic sugar to which the boron is temporarily grafted. We report the first synthesis of silicone

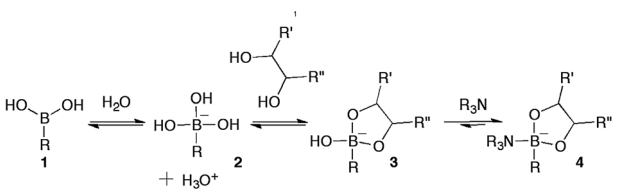

Fig. 1 Boronate-diol binding equilibria.[15]

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† Electronic supplementary information (ESI) available: NMR of **7** before and after hydrolysis to **13** in the absence and presence of Tris; full experimental protocols and characterization for compounds **7–12** (Table 1); hydrolysis and sugar binding protocols; and complex viscosity from rheolgoical data for **17** and **18**. DOI: 10.1039/c2cc37438b

boronic acids (SBAs) and provide preliminary data demonstrating their ability to differentially bind saccharides.

4-Vinylphenylboronic acid (styrylboronic acid) **5** is a convenient starting material to which silicones can be grafted using the efficient hydrosilylation process.[16] Initial attempts to directly perform hydrosilylation on vinyl-substituted boronic acids, including **5**, were unfortunately only sporadically successful. Active hydrogen compounds including carboxylic acids and alcohols are known to react with Si–H groups to form H_2 and siloxanes in a process that can compete with the desired addition to alkenes, which is likely the origin of the inconsistent results.[17] It was necessary, therefore, to protect the B–OH groups. Although several protecting groups were examined many, including catecholates,[18] proved to be too stable to subsequent reactions: the conditions necessary for catecholate hydrolysis, for example, led to silicone redistribution/depolymerization.[7]

Therefore, a high yielding two-step synthesis was developed that required little purification and for which by-products were not observed (Fig. 2). Dimethyl-L-tartrate boronic ester **6** was formed from the reaction of **5** with dimethyl tartrate. Simple dehydration using molecular sieves afforded **6** in near-quantitative yield, and required no purification prior to use in the subsequent reaction. The second step utilized platinum-catalyzed hydrosilylation of the protected acid **6** using Karstedt's catalyst at room temperature (Table 1). Compounds **7**, **8**, and **10–12** demonstrate the ability to vary the size of polydimethylsiloxane hydrophobes, while compound **9** has a different connectivity (branched 3D structure) between the hydrophobe and boronic acid moieties. The silicone-boronate compounds were isolated in good to excellent yield as a mixture of regioisomers that were inseparable by silica chromatography: their relative concentrations could be determined by ^{1}H NMR. Such regioisomeric mixtures during hydrosilylation are particularly problematic with aryl-substituted olefins.[16]

Prior to examining the ability of the silicone boronic acids to complex with sugars, the protecting tartrate had to be removed.

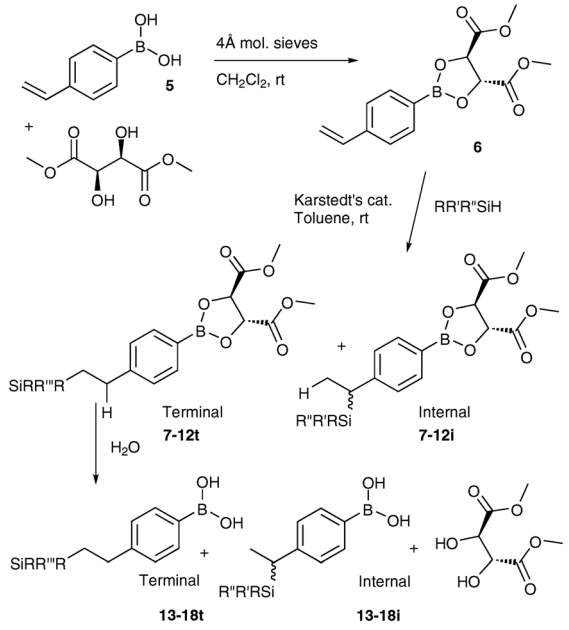
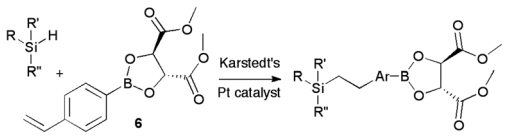
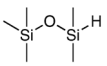
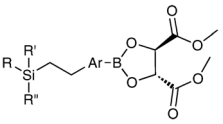
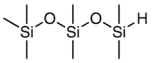
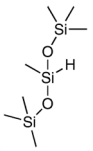
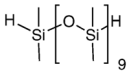
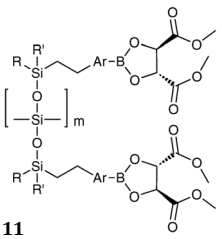
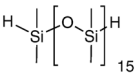
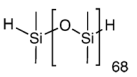


Fig. 2 Tartrate protection of 4-vinylphenylboronic acid and synthesis of silicone-boronic esters **7–12** (for RR′R″, see Table 1).

Table 1 Preparation of silicone boronate esters



H-functional siloxane RR′R″SiH	Yield (%)	Ratio T : I (term : int)	Product[a]
Monofunctional linear			**7**
	87	10 : 7	
	59	10 : 7	**8**
Branched			
	61	5 : 2	**9**
Difunctional (α,ω)			**10**
	54	2 : 1	
	81	5 : 4	**11**
	76	5 : 4	**12**

[a] Shown for terminal regioisomer. The boronic acid products after hydrolysis (Fig. 2) are compounds **13**, **14**, **15**, **16**, **17** and **18**.

Actually, it was necessary to maintain an anhydrous environment during the hydrosilylation to form compounds **7–12** because the tartrate boronic ester was very susceptible to hydrolysis (Fig. 2). Silicone-boronic acids were liberated from their tartrate protecting groups to give **13t,i–18t,i** simply by treatment with PBS buffer within the pH range of 4.5 to 9.0. This was readily determined by observing changes in the chemical shift of diagnostic signals within the ^{1}H NMR spectra (for compound **7**, see ESI†).

The resulting free boronic acids were relatively insoluble in water, which is not surprising given the hydrophobicity associated with silicones: even with the small disiloxane, the hydrophobic group trumped the hydrophilic boronic acid. However, this behaviour could be altered by altering the character of the boronic acid.

The preference for boronic acid binding to fructose over glucose was first observed by Lorand and Edwards[19] and has since become accepted as a common property of many boronic acids.[13] The ability of free boronic acid **13i,t** to bind fructose or glucose, respectively, in D_2O was examined using ^{1}H NMR spectroscopy. The chemical shifts of relatively isolated aromatic

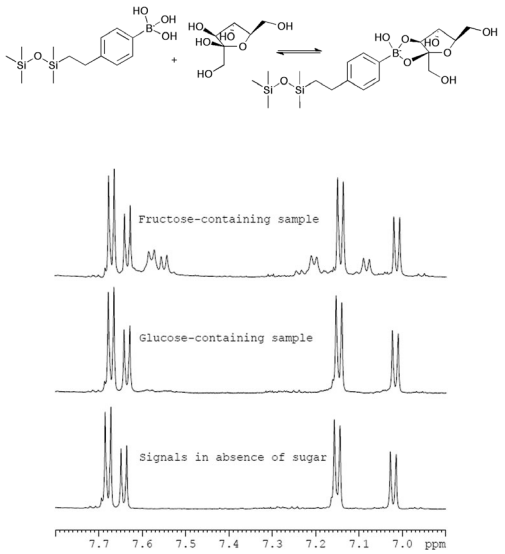


Fig. 3 Selective sugar binding of **7** with fructose in PBS pH 7.4/DMSO-d_6.

proton peaks were monitored for changes due to binding at boronic acid. In particular, the signals near 7.6 and 7.1 ppm (Fig. 3) were diagnostic for changes in the environment near boron. There was no change in the spectrum for silicone-boronic acid exposed to glucose in solution, however, upon exposure to fructose a new set of peaks was observed. Integration of these peaks with respect to the unbound compound signals demonstrated that approximately one-third of the silicone-boronic acid in solution was bound to fructose: as would be expected for boronic acids, no binding to glucose was observed. The fructose complex of **13i,t** exhibited enhanced water solubility: the solubility nearly doubled compared to the free boronic acid (ESI†); however, it was not possible to measure a critical micelle concentration for any of the compounds. Larger silicones such as **11** could be compatibilized with water by complexation with fructose. Thus, as with other boronic acids, the binding of SBAs to saccharides was dependent on diol structural characteristics.[13,20]

The equilibrium of free **2** and bound **3** boronic acids is highly dependent on the pH of solution and the presence of Lewis bases. Neutral conditions were used as much as possible to avoid silicone hydrolysis, particularly of the branched trisiloxane compound **15**.[2] Fortunately, Lewis bases that favour formation and also stabilize against hydrolysis the tetracoordinate complex **4** (Fig. 1) are readily available. An examination of a series of buffers showed that tris(hydroxymethyl)amine (Tris) was particularly efficacious in this regard. As the concentration of Tris was increased from 0–28 mM, the fraction of tetracoordinate boronate complexed to fructose (but not glucose) increased, as demonstrated by enhanced solubility under these conditions (ESI†). That is, the hydrophilicity of the boronic acid head group could be increased both by complexing with saccharides and an appropriate Lewis base such as Tris, which also stabilized the product against hydrolysis. SBAs were less soluble in water alone.

Additional evidence for unusual physical properties of SBAs comes from rheological studies. The kinematic viscosities of starting silicone oils, of 2.8 and 97 mPa s (~liquid honey), respectively, and their boronic acid products **11** and **12**, were low. Upon hydrolysis, dramatic changes occurred leading to increases in viscosity of several orders of magnitude (for complex viscosities of **17** and **18**, see ESI†). Normally, the viscosities of homologous polymers track with chain length. In this case, however, the density of boronic acid groups is more important, as shown by the higher viscosity exhibited by the silicone with shorter chain lengths. We propose that segregation of boronic acids from silicones act as physical crosslinks leading to the significant change in viscosity.

Boronic acids offer a series of interesting properties based on their ability to reversibly and selectively bind diols, particularly those affiliated with saccharides. New silicone surfactants based on boronic acids have been prepared using a straightforward synthetic strategy. The hydrophilic boronic acid termini allow for these surface-active materials to bind selectively to *cis*-diols of biologically interesting molecules, changing their surface activity. The self-affinity of boronic acids in a silicone environment suggests their broader use to structure silicone networks.

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