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LETTERS

Saccharide Accelerated Hydrolysis of Boronic acid Imines

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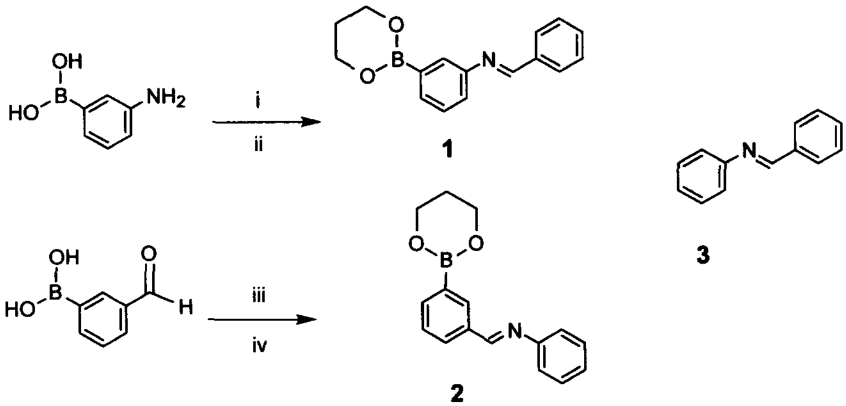
Abstract: Saccharides accelerate the rate of hydrolysis of imines **1** and **2** at pH 7.77. In contrast, the rate of hydrolysis of imine **3** is unaffected by added saccharides. © 1999 Elsevier Science Ltd. All rights reserved.

In an effort to understand the mechanism of enzyme reactions, simple models that show binding prior to chemical reaction steps are required. Synthetic systems based on noncovalent interactions have been extensively studied.[1] The development of boronic acid receptors for saccharides, utilising the covalent interaction of boronic acids with saccharides, has shown this to be a useful binding force in aqueous solution. The interaction of boronic acids with saccharides has been used to develop sensory systems[2] and transport systems for saccharides.[3] The interaction between boronic acid and saccharides has also been used to modify enzyme activity.[4] The increased Lewis acidity of boronic acids on saccharide binding controls both the enzyme inhibition and fluorescence of these systems.

With this work we decided to investigate how the Lewis acidity of boronic acids influences the hydrolysis of simple imines. Boronic acid imines **1** and **2** were prepared as outlined in **Scheme 1**. Imine **3** was purchased from Aldrich and used without further purification.



Scheme 1. *Reagents (Yields)*:- i, 1,3-propanediol, trimethyl orthoformate, 2h, rt, (93%); ii, benzaldehyde, trimethyl orthoformate, 60h, rt, (88%); iii, 1,3-propanediol, trimethyl orthoformate, 2h, rt, (quant); iv, aniline, trimethyl orthoformate, 60h, rt, (quant).

The rates of hydrolysis of imines **1**,**2** and **3** at pH 7.77 in 33% (w/w) methanol-water buffer[5] were followed by disappearance of the imine absorption band at 320 nm. This wavelength was chosen in each case because it is the absorption maximum of the imine and the hydrolysis products do not absorb significantly at this wavelength.

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The rate constants are *pseudo*-first order and were obtained by curve fitting the disappearance of the imine absorption band. The first order analysis was valid for the whole course of the hydrolysis with $r^2 \approx 1$. The rate of hydrolysis of **1** and **2** is accelerated by added saccharide, whereas the rate of hydrolysis of **3** is not affected by added saccharide. The concentration dependence of the hydrolysis of **1** and **2** with D-fructose shows saturation at $\geq$ 0.01M and half activities of 0.0035M (**Figure 1**). The rate constant of hydrolysis of **1** with other monosaccharides at a concentration of 0.01M are given in **Table 1**. **Table 1** also contains the stability constants for saccharide phenylboronic acid complexes.[6] From **Table 1** it can be seen that the rate of imine hydrolysis correlates with the stability of the saccharide-phenyl boronic acid complexes. D-Fructose forms the most stable complex and is the system hydrolysed the fastest. D-Glucose forms the least stable complex and is hydrolysed the slowest.

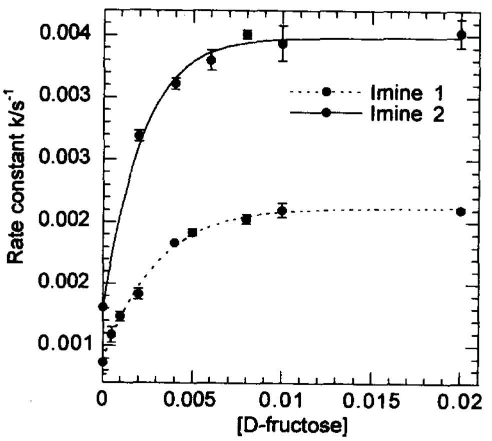


Figure 1. Rate constant for hydrolysis *versus* [D-fructose] profile at 20°C; 5x10^{-5}M of imine **1** and **2** in 33% (w/w) methanol-water buffered at pH 7.77

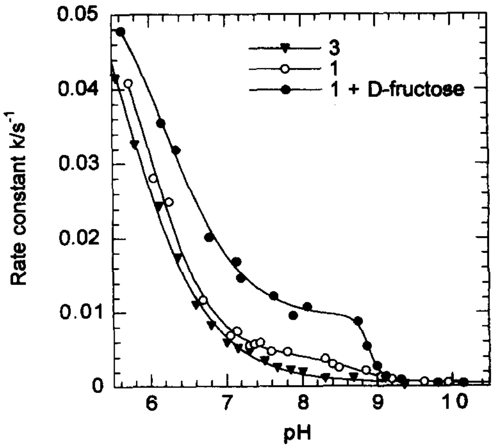


Figure 2. Rate constant for hydrolysis *versus* pH profile of (○) imine **1**, (●) imine **1** with 0.01M D-fructose, (▼) imine **3** at 20°C; 5x10^{-5}M in water; 0.05M NaCl osmotic buffer.

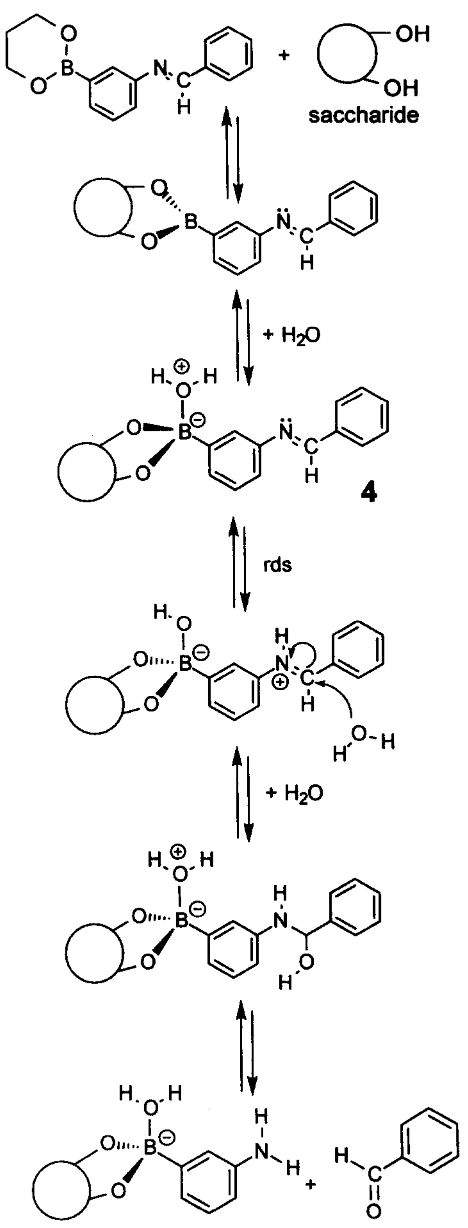
Table 1. Kinetic data for the hydrolysis of boronic acid imine **1**[a] in pH 7.77 buffer.

Saccharide[b]	Rate constant /s^{-1} x10^{-4}	Stability constant[c] /M^{-1}
blank	8.54 ± 0.4	-
D-glucose	10.1 ± 0.3	110
D-mannose	10.3 ± 0.4	172
D-galactose	11.9 ± 0.4	276
D-mannitol	18.1 ± 0.5	2275
D-fructose	21.6 ± 0.5	4370

[a]5x10^{-5} M of imine **1**. [b]0.01M of saccharide. [c]From reference 6.

The pH dependent rate profiles for the hydrolysis of imine **1** with and without saccharide (0.01M D-fructose) and **3** are shown in **Figure 2**. From these curves it can be seen that the rate of hydrolysis of imine **1** is coincident with that of imine **3** at high and low pH, but at intermediate pH the rate is faster for imine **1** both with and without saccharide.

Our proposed mechanism for the saccharide-mediated hydrolysis is outlined in **Scheme 2**. We propose that the "bound water" molecule of intermediate **4** acts as a general acid catalyst. The oxygen of a water molecule can act as a Lewis base and bind with the boron centred Lewis acid, this in turn polarises the OH bond making the water a stronger Brönsted acid. It is known that boronic acids become stronger Lewis acids on saccharide binding, therefore, the strength of a "bound water" Brönsted acid should also increase on saccharide binding. The increased strength of the "bound water" Brönsted acid can then accelerate the rate of acid catalysed hydrolysis of **1** and **2**, the imine nitrogen being protonated by the boronic acid bound water via a proton transfer chain of several water molecules. (**Scheme 2**)



Scheme 2. Proposed mechanism for the hydrolysis of imine **1**.

At high pH the boronic acid is ionised to a tetrahedral boronate, and the catalytic species **4** is removed from the system. At high pH imine **1** shows the same rate of hydrolysis (with and without D-fructose) and as imine **3** (**Figure 2**). At low pH the specific acid catalysed hydrolysis of the imines becomes the predominant path of hydrolysis, so the rates of hydrolysis for imine **1** and **3** are again coincident. But, at an intermediate pH the "bound water" can act as a general acid catalyst for the hydrolysis of imine **1**. When saccharides are bound to the boronic acid the boron centre becomes a stronger Lewis acid and so the rate of hydrolysis is enhanced. The observed rate-pH titration for the general acid catalysis gives an indication of the pKa of the boronic acid imine **1**. From **Figure 2** imine **1** in the presence of 0.01M fructose has an apparent pKa of 8.85. This values compares well with the observed pKa of phenylboronic acid which is 8.83.[6] A deuterium isotope study was carried out to determine whether proton transfer is involved in the rate-determining step of the hydrolysis of imine **1** and **2**. The hydrolysis experiments were carried out in unbuffered D_2O (pD 7.25) and H_2O (pH 7.25) and gave a k_H/k_D of 2.2 for **1**, and unbuffered D_2O (pD 7.05) and H_2O (pH 7.05) gave a k_H/k_D of 3.7 for **2**. These results clearly indicate that the rate-determining step involves proton transfer.

Our results with imine **1** and **2** (**Figure 1**) clearly show that the effect observed is not a substituent effect; rate acceleration is observed irrespective of which side of the reaction centre the boronic acid group is placed. This result is not unexpected;

work by Jencks and Cordes has shown that the rate of hydrolysis of imines are only slightly dependant on the nature of polar and electron withdrawing substituents.[7] The electron withdrawing boronic acid substituent may however explain the difference in hydrolysis rates between imine **1** and **2**. The imine nitrogen in **1** will be less basic than the imine nitrogen in **2**; this is a result of an inductive electron withdrawal of the boronic acid group. It is reasonable to expect that a less basic nitrogen will be less easily protonated and hence hydrolysed less readily.

With this work we have shown that boronic acid-water complexes can act as general acid catalysts for the hydrolysis of imines. The strength of the "bound water" general acid catalyst is modulated by the strength of the water-boronic acid interaction, which is in turn controlled by bound saccharide. This study of complexation controlled catalytic activity is an interesting model system which may shed light on more complex catalytic systems.

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