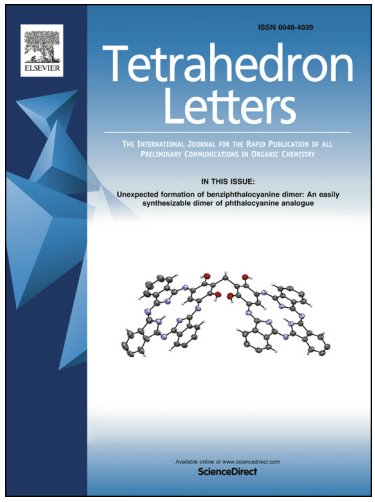

Tris(2-carboxyethyl)phosphine Promotes Hydrolysis of Iminoboronates

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Graphical Abstract

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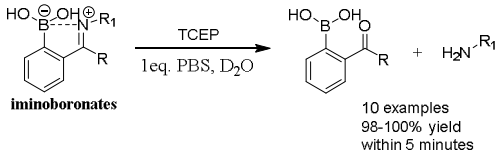

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Tris(2-carboxyethyl)phosphine Promotes Hydrolysis of Iminoboronates

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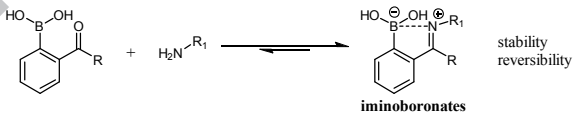
ABSTRACT

Iminoboronates are stable and formed fast. Their B-N bonds could be reverted by some endogenous biological molecules. The reversible characteristic attracts significant attention in biological and chemical fields. Although synthesis of iminoboronates is well-studied, less efforts have been devoted to disconnecting the units. Here, a series of selected compounds were screened to evaluate their hydrolytic capability of iminoboronates by ^{1}H NMR or ^{11}B NMR detection. Tris(2-carboxyethyl)phosphine (TCEP), was emerged as an excellent reagent, which decomposed most iminoboronates in short time with high yields. In addition, TCEP is also able to hydrolyze hydrazones and oximes with moderate yields.

1. Introduction

Iminoboronate conjugations are stable and could be reverted by some endogenous biological molecules. Such decent characteristics have garnered significant attentions in chemical and biological fields. Iminoboronates are simply formed through the reaction with 2-formylbenzeneboronic acid or 2-acetylbenzeneboronic acid to an amine group (Scheme 1).[1] Due to the unique B–N bond properties,[2] iminoboronates have been extensively exploited to efficiently modify proteins at the amine groups, [3-7] and assist the formation of thiazolidinone on the amino thiol, [8-10] oxime and hydrazone condensations, [11-13] which are applied to bio-orthogonal reactions.[14] Iminoboronate as a useful tool in the enantiomeric field has also been studied. [15, 16]

Many applications do not only require stable linker for coupling molecular units, but also efficient disconnection to revert the modification on the target molecules. [17, 18] Although iminoboronates demonstrate great stability, it could be cleaved by some endogenous molecules, such as glutathione (GSH) (**1a**), dopamine (**1b**) and fructose (**1c**) (Figure 1).[3] Saccharide and dopamine facilitate the hydrolysis of boronic acid imines probably due to their binding to boric acid moiety and formation of boronate esters. [3, 19-22] Nevertheless, all the methods could not decompose the iminoboronate completely and 7% of iminoboronate are still uncleaved after 1 day under the best performed reagent, GSH, in the previous study.[3] In the reversible reaction, the efficiencies of both the connection and disconnection processes are vital for the reaction yields. In this work, we screened a series of compounds and their mixtures with fructose to evaluate their hydrolytic capabilities compared to GSH. Tris (2-carboxyethyl) phosphine (TCEP), was emerged as an excellent reagent, which decomposed many iminoboronates in short time with remarkable yields.



Scheme 1 The formation of iminoboronates

2. Results and discussion

GSH showed the best performance to hydrolyze the iminoboronates according to the references[3]. Its strong nucleophilicity was presumed to play an important role in iminoboronate disconnection. Following this hypothesis, a series of mercaptophenyl nucleophilic compounds were selected to investigate their potential in the hydrolysis of iminoboronate. Taking GSH as reference, the nucleophilic compounds included 4-mercaptobenzoic acid (**1d**), 4-mercaptophenylacetic acid (**1e**) and 4-mercaptophenol (**1f**) as well as TCEP (**1g**) (Figure 1), a versatile and useful phosphorus nucleophile with broad application in reduction of disulfide bonds through nucleophilic substitution (SN2) reactions.[23, 24] Furthermore, to evaluate the effect of saccharide, mixtures of nucleophilic reagent and fructose were also employed to cleave the iminoboronates.

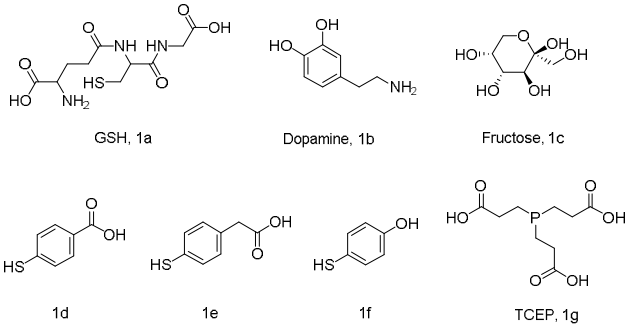
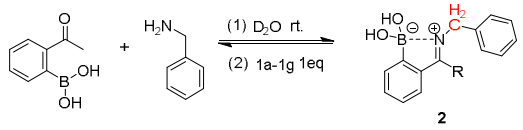


Figure 1 The reported (**1a-1c**) and screened reagents (**1d-1g**) to facilitate the hydrolysis of iminoboronates

The iminoboronate **2** prepared from 2-acetylbenzeneboronic acid and benzylamine was engaged as a model substrate for hydrolysis analysis (Scheme 2). The synthesis of iminoboronate **2** was performed in phosphate-buffered saline (PBS, 50 mM, pH 7.4) at room temperature for 5 minutes with quantitative yield. In ^{1}H-NMR spectra, the clean conversion was observed and the chemical shift of CH_2 of benzyl was altered from 3.70 ppm (H_b) to 4.87 ppm (H_a) obviously (Figure 2). Based on these results, the efficiency to hydrolyze iminoboronate **2** of compound **1a-1g** was evaluated by ^{1}H NMR.



Scheme 2 The formation and reversible hydrolysis of iminoboronate **2**

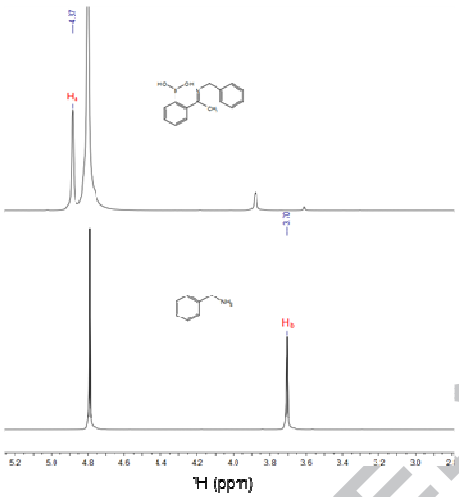
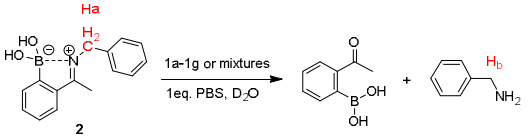


Figure 2 ^{1}H-NMR data indicating the clean conjugation to form iminoboronate **2**

The reversible hydrolysis of iminoboronate **2** (0.05 mmol) by **1a-1g** compounds were carried out in PBS buffer (0.6 mL) with 5% D_2O for locking and shimming in NMR. After reaction for 5-30 miniutes, ^{1}H NMR was recorded directly. The ratio of H_a to H_b signal intensity was used to evaluate the hydrolytic conversion (Figure 3). The data showed that under the acidic condition (HCl, pH=3), the iminoboronate was not dissociated at all. GSH (**1a**) and dopamine (**1b**) decomposed the iminoboronate **2** with more than 75% yield, and a small amount of substrate remained, which was similar as the results in literature.[3] All the mercaptophenyl nucleophiles **1d-1f** hydrolyzed the iminoboronate **2** with a low to moderate yield (38%-50%). A composition of a nucleophilic agent (**1a**, **1d**, **1e** or **1f**) and fructose at a 1:1 ratio improved the hydrolytic efficiency compared to individual compound itself. However, the improvement was limited. Surprisingly, TCEP (**1g**) was emerged as an excellent reagent, which decomposed iminoboronate **2** completely in 5 minutes in the initial trail (Figure 3, Table 1).



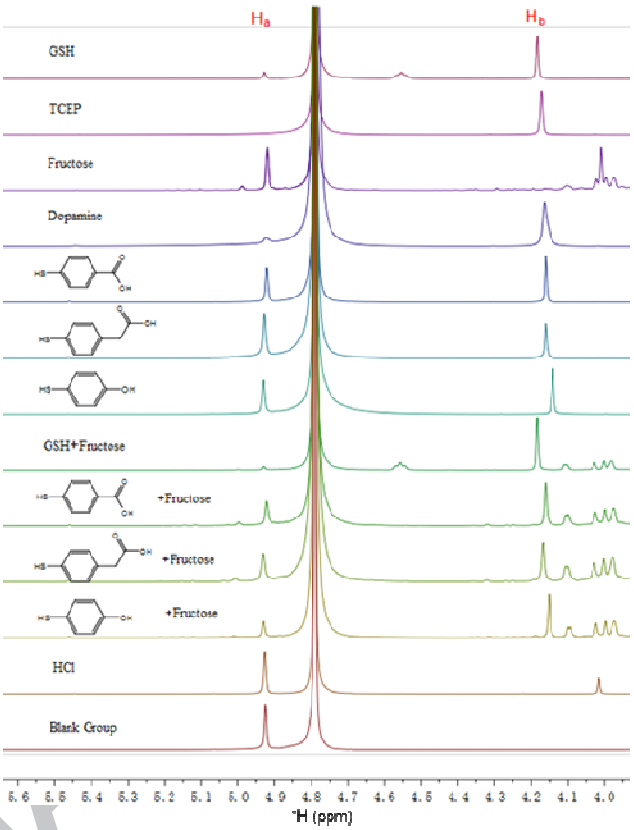


Figure 3 The hydrolytic efficiency of different reagents to iminoboronate **2** were evaluated by ^{1}H-NMR

Table 1. The hydrolytic efficiency of different reagents

Entry	Reagents	Yield %[a]
1	GSH (**1a**)	79
2	Dopamine (**1b**)	76
3	Fructose (**1c**)	17
4	HS–COOH (**1d**)	49
5	HS–CH_2COOH (**1e**)	38
6	HS–OH (**1f**)	50
7	TCEP (**1g**)	100
8	**1a** + Fructose	85
9	**1d** + Fructose	52
10	**1e** + Fructose	43
11	**1f** + Fructose	67
12	HCl pH 3	0

a. The yield was determined by ^{1}H-NMR: $AH_b / (AH_a + AH_b) \times 100\%$; AH_a and AH_b represent the relative peak area.

As ^{11}B is sensitive to its chemical environment and rare in common chemicals, it is especially useful for evaluating the reaction efficiency in complicated mixtures. We recorded the ^{11}B NMR spectra to show the hydrolytic efficiency of the selective nucleophiles (**1e**), TCEP (**1g**), and GSH. Iminoboronate **2** displays a peak around 7.2 ppm. Addition of TCEP (**1g**) to iminoboronate **2** resulted that the signal at 7.2 ppm disappeared

entirely and new peak at 29.7 ppm appeared which were exactly consistent with the signals of 2-acetylbenzeneboronic acid, peak at 19.3 ppm corresponded to $B(OH)_3$[9] (Figure 4). In the same condition, for GSH and compound **1e**, signals at 7.2 ppm were still left. All the results further supported that TCEP was a potentially effective agent to decompose iminoboronates.

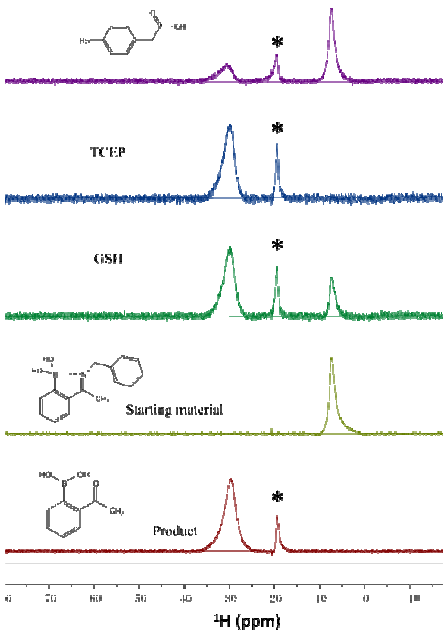


Figure 4 The hydrolytic efficiency of different reagents to iminoboronate **2** was detected by ^{11}B NMR. * indicates $B(OH)_3$.

To examine the reaction rate by TCEP, more time points of ^{11}B NMR for hydrolysis were collected (Figure 5). The reaction reached equilibrium so fast that it was difficult to measure the reaction rate directly. We optimized the NMR parameters including tunning, shimming, recycling delay, and scan numbers in order to reduce the dead time caused by NMR operation. The amount of H_2O was in excess compared with the concentration of the iminoboronate, thus we fit these data as a pseudo-first order reaction. The reaction rate was estimated to be in the order of 10^{-2} S^{-1}.

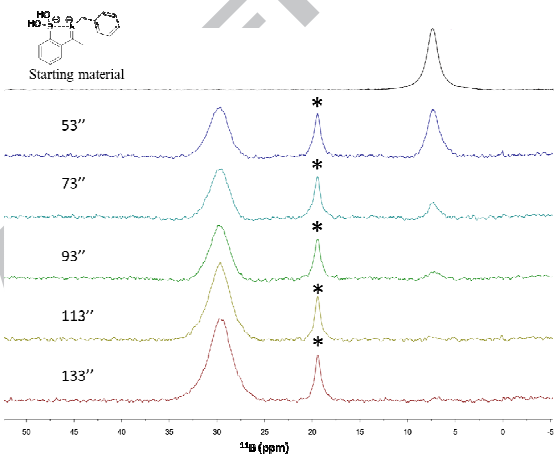
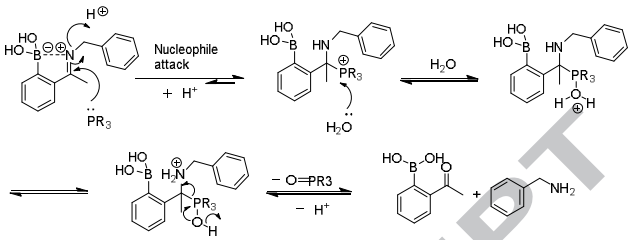


Figure 5 Stacked ^{11}B-NMR spectra of iminoboronates as a function of the hydrolysis time. * indicates $B(OH)_3$.

The proposed mechanism for TCEP-promoted hydrolytic reaction was shown in scheme 3. Nucleophile attack by phosphine appeared to be the rate-determining step. After elimination of the phosphine oxide, the rest procedure was similar to the hydrolysis of imine. Phosphine-containing compound 1,3,5-triaza-7-phosphaadamantane in acidic conditions also decomposed the iminoboronate **2** completely which supported the hypothesis.



Scheme 3 Proposed mechanism

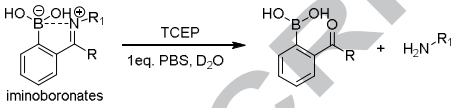
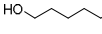


Table 2 Substrates scope for the hydrolysis of iminoboronates with TCEP

Entry	R	R_1-NH_2	Yield %
1			100
2			100
3	CH_3		100
4			24
5			86
6			100
7			100
8			100
9			100
10	H		100
11			99
12			98
13			87

Encouraged by the aforementioned results, we examined the substrate scope of the TCEP-promoted hydrolytic reaction. The conversion was determined by ^{11}B NMR. As shown in Table 2, TCEP decomposed a variety of iminoboronates in satisfactory results (entry1-3, 6-12). TCEP also displayed a certain ability to hydrolyze hydrazones and oximes, which possessed greater intrinsic hydrolytic stability than that of imines (entry 4-5, 13).

3. Conclusion

Iminoboronates have already been used in many biological and chemical fields. Although iminoboronates are stable, it is reversible in certain situations. Such reversible reaction is of great value in drug discovery, drug delivery and self-organizing system.[25] We screened a series of nucleophilic compounds, and mixtures of the compound and saccharide. Their hydrolytic efficiency was analyzed by ^1H-NMR or ^{11}B-NMR detection. Saccharide could assist the nucleophilic compounds and improve the hydrolysis around 10%. Surprisingly, TCEP showed best

hydrolysis capability. It could cleave the iminoboronates completely in 3 min. When we extended the substrates to hydrazones and oximes, which possessed greater intrinsic hydrolytic stability than that of imines, TCEP also displayed a considerable hydrolytic ability. Our results provide a novel strategy in the reversible modification with iminoboronates.

4. Acknowledgements

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