Preliminary Communication

Brighid B. Pappin, Stephan M. Levonis[a], Peter C. Healy, Milton J. Kiefel, Michela I. Simone and Todd A. Houston*

Crystallization-induced amide bond formation creates a boron-centered spirocyclic system

DOI 10.1515/hc-2017-0023
Received February 1, 2017; accepted February 20, 2017; previously published online May 19, 2017

Abstract: The 5-nitrosalicylate ester of 2-acetamidophenylboronic acid ($C_{15}H_{10}BN_2O_6$) is formed under crystallization conditions from the 5-nitrosalicylate ester of 2-aminophenylboronic acid. The boron at the center of this structure exists as a tetrahedral complex produced by a dative bond with the amide carbonyl. The perpendicular shape produces an unusual packing structure including a bifurcated hydrogen bond between the amide hydrogen and carbonyl groups on two neighboring molecules. We propose that this reaction occurs due to increased Lewis acidity of the nitrosalicylate ester of 2-aminophenylboronic acid.

Keywords: amidation; boronate ester; crystal structure; dative bond; Lewis acid.

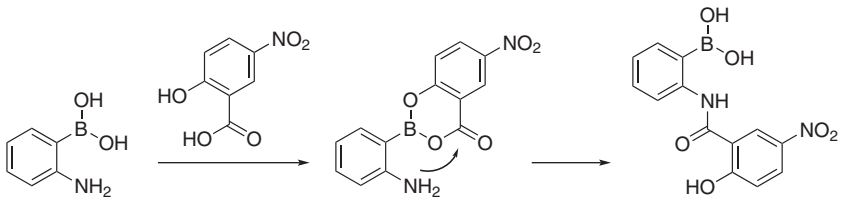
Boron acids are useful catalysts for many transformations including amidation and esterification reactions [1–3]. In the first known example where 2-aminophenylboronic acid was used in amidation, it was shown by Groziak in 1994 that this compound could form a formamide by refluxing in formic acid [4]. It is unclear whether the boronic acid plays a role in catalyzing the amidation as the reaction can occur thermally at temperatures greater than 100°C [5]. Previously, we have demonstrated that boric acid is an effective catalyst for esterification of α-hydroxycarboxylic [6, 7], malonic [8] or salicylic acids [9]. By chelating the carboxylate and the alcohol (or second carboxylate), boron activates the carbonyl group toward esterification [10]. We reasoned that such chelation would allow for direct, facile amide bond formation between 2-aminophenylboronic acid and α-hydroxycarboxylic acids or salicylic acids (Scheme 1). Boron ester formation would place the activated carbonyl six atoms away from the amine.

Heating a mixture of 2-aminophenylboronic acid and 5-nitrosalicylic acid in acetonitrile at 50°C resulted in formation of **1** as a light brown precipitate rather than the desired amide. Attempted crystallization of **1** from EtOAc/hexane produced the unexpected crystalline product **2** (Scheme 2). This amidation reaction with ethyl acetate does not occur when 2-aminophenylboronic acid alone is heated in this solvent system suggesting the nitrosalicylate ester plays a role in this reaction.

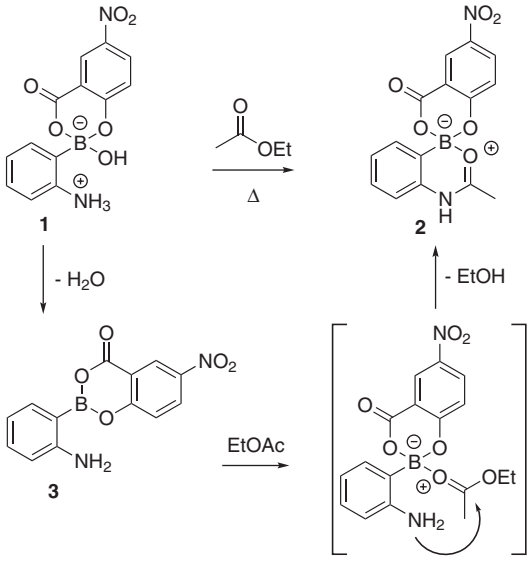
We propose that **1** likely undergoes dehydration to form a free amine and neutral boronate ester **3** that can subsequently activate the ester carbonyl as shown in the bracket. The nitrosalicylate ester of the boronate would make the boron more Lewis acidic than its parent boronic acid allowing it to better activate the carbonyl group of ethyl acetate [11, 12]. Compound **2** does not accumulate in solution and thus its formation appears to be a result of the crystallization process. The ORTEP diagram for the X-ray crystal structure of **2** is shown below in Figure 1.

Compound **2** demonstrates some interesting supramolecular features in its crystal lattice (Figure 2). The main hydrogen bond supporting the packing structure is a bifurcated hydrogen bond between the hydrogen on the nitrogen in the amide (N^1) and two neighboring carbonyl oxygen (O^4) from two other molecules. This hydrogen bond brings together two planar systems and two perpendicular systems together. The boron complex has put torsional strain on some bond lengths in the molecule, but the bond length of the B^1–C^1 of 1.58 Å is consistent with typical values in the literature [13]. Coordination of an amide oxygen to create a spirocyclic center at boron via a five-membered ring has also been observed [14]; however,

[a]Current address: Faculty of Health Sciences and Medicine, Bond University, Robina, QLD 4226, Australia
***Corresponding author: Todd A. Houston,** Institute for Glycomics and School of Natural Sciences, Griffith University, Gold Coast, QLD 4222, Australia, e-mail: t.houston@griffith.edu.au
Brighid B. Pappin and Stephan M. Levonis: Institute for Glycomics, Griffith University, Gold Coast, QLD 4222, Australia
Peter C. Healy: School of Natural Sciences, Griffith University, Nathan, QLD 4111, Australia
Milton J. Kiefel: Institute for Glycomics and School of Natural Sciences, Griffith University, Gold Coast, QLD 4222, Australia
Michela I. Simone: Discipline of Chemistry, Priority Research Centre for Chemical Biology and Clinical Pharmacology, University of Newcastle, Callaghan, NSW 2308, Australia



Scheme 1 Proposed direct amide formation between 2-aminophenylboronic acid and 5-nitrosalicylic acid.



Scheme 2 Postulated mechanism for amidation reaction of **1**.

the extended supramolecular topology of compound **2** appears unique.

Formation of compound **2** occurs via amidation of **1** with ethyl acetate during the crystallization process. It is unclear at present whether amide bond formation is induced by the rich hydrogen bonding network within the crystal lattice, or whether compound **2** has a strong propensity to crystallize once formed. Nonetheless, we are exploring the proposed Lewis acid activation toward nucleophilic attack by the adjacent amine in other systems and will report on success in this arena in due course.

Experimental

4′-Hydroxy-3-methyl-6′-nitro-4′*H*-spiro[benzo[*c*][1,5,2]oxazaborinine-1,2′-benzo[*d*][1,3,2]dioxaborinin]-1-uide (2)

To a stirring solution of 2-aminophenylboronic acid (50.0 mg, 0.37 mmol) in acetonitrile (3.65 mL) was added 5-nitrosalicylic acid (66.9 mg, 0.37 mmol). The mixture was allowed to react at 323 K for 1 h and then the precipitated product **1** as a light brown powder was collected via vacuum filtration (109.2 mg, 99%). ^{11}B NMR (DMSO-d_6): δ 5.59 with BF_3-OEt_2/$CDCl_3$ as standard. ESI-MS(-). Calcd for $C_{13}H_{10}BN_2O_6^-$, $(M\text{-}H)^-$: *m/z* 301.06. Found: *m/z* 301.1. Crystallization occurred via a slow evaporation process

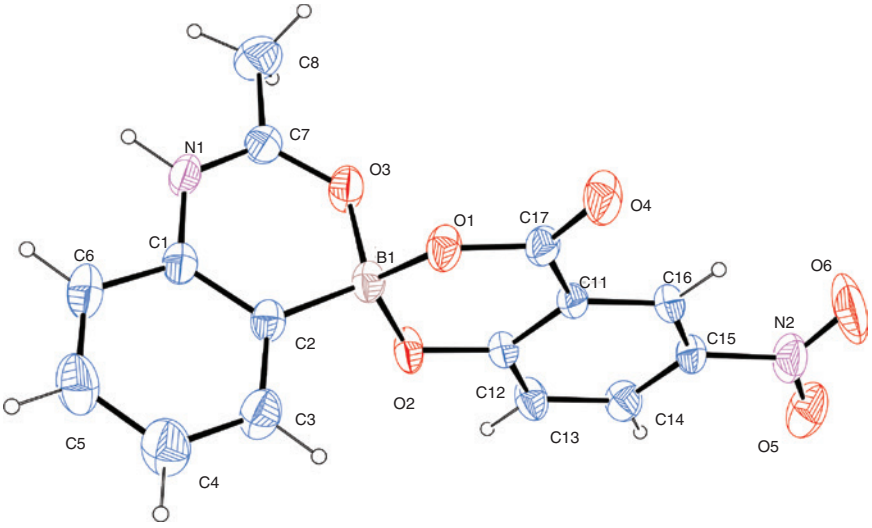


Figure 1 ORTEP diagram of compound **2**.

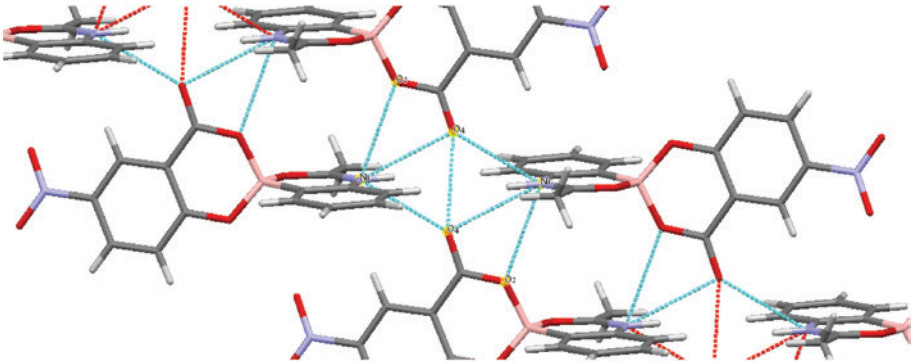


Figure 2 Hydrogen bonding network revealed in X-ray crystal structure of **2**.

at room temperature from hot 1:1 EtOAc/hexane solvent system after purification with activated charcoal. The solution stood for 3 days producing crystals that were clear, small and rectangular in appearance. The crystals were identified as compound **2** by ^{1}H NMR, MS and X-ray crystallography. ^{1}H NMR (DMSO-d_6): δ 2.35 (s, 3H, C**H**$_3$), 7.10 (d, 1H, J = 9.0 Hz, Ar**H**), 7.16 (d, J = 7.0 Hz, 1H, Ar**H**), 7.27 (m, 1H, Ar**H**), 7.42 (m, 2H, Ar**H**), 8.32 (d, 1H, J = 9.0 Hz, Ar**H**), 8.61 (s, 1H, Ar**H**). ESI-MS(-). Calcd for $C_{15}H_{10}BN_2O_6^-$, (M-H)$^-$: m/z 325.06. Found: m/z 324.9.

Crystal data for **2**: $C_{15}H_{11}BN_2O_6$. M = 326.1, monoclinic, space group $P2_1/n$, a = 8.6642(4), b = 11.2685(8), c = 16.0267(10) Å, β = 101.689(6)°, U = 1532.3(2) Å^3, Z = 4, D_c = 1.41 g cm^{-3}, μ = 0.110 mm^{-1}, crystal size: 0.30 Å ~ 0.20 Å ~ 0.20 mm. $T_{min/max}$ = 0.89, 1.00. 6797 reflections collected, 4092 unique (R_{int} = 0.040), R = 0.068 [2187 reflections with $I > 2s(I)$], wRF^2 = 0.130 (all data). Supplementary crystallographic data of **2** is deposited at the Cambridge Crystallography Data Centre (CCDC) as supplementary publication CCDC 1532315. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgments: This paper is dedicated to Professor Binghe Wang of Georgia State University for his important contributions to the study of boronic acids across several fields from catalysis to chemical biology. We thank the Institute for Glycomics and Griffith University for funding.

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