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Isolation, Solubility, and Characterization of D-Mannitol Esters of 4-Methoxybenzeneboronic Acid

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ABSTRACT

The purpose of this study was to determine the aqueous solubility of a model phenyl boronic acid, 4-methoxybenzeneboronic acid, as a function of pH both in the absence and in the presence of varying D-mannitol concentration. Solid isolated D-mannitol esters were characterized by differential scanning calorimetry, thermogravimetric analysis, powder X-ray diffraction, and single-crystal X-ray studies, and the boronic acid-to-D-mannitol ratio was quantified by HPLC. Hydrolysis of the monoester was studied using UV spectral differences between the monoester and the parent boronic acid. Two D-mannitol esters of 4-methoxybenzeneboronic acid were isolated. The triboronate ester was very insoluble whereas a symmetrical monoboronate monohydrate was also less soluble than the parent. Both esters were crystalline. The monoboronate monohydrate was, however, more soluble than the parent at alkaline pH values due to its lower p*K*a value (6.53) compared to the parent acid (9.41). Hydrolysis of the monoboronate was extremely fast when even small amount of water was added to dry acetonitrile solutions of the ester. The hydrolysis was buffer concentration dependent and apparent pH sensitive with hydrolysis accelerated by acid. Implications affecting the formulation of future boronic acid drugs are discussed.

Introduction

The objective of this study was to determine the aqueous solubility of the model Lewis boronic acid, 4-methoxybenzeneboronic acid (4-MBBA, Fig. 1), as a function of pH and in the presence of varying D-mannitol (Fig. 1b) concentrations. D-Mannitol can form reversible esters with boronic acids (see Figs. 1c-1e for some possible esters). The kinetics of hydrolysis of the monoester was also determined because there was minimal literature on this subject.

An aromatic boronic acid was chosen for study on account of its greater chemical stability from oxidative breakdown compared to alkyl boronates.[1-5] An earlier study characterized the physical properties of 4-MBBA itself and its corresponding anhydride or boroxine.[6]

During the formulation of the alkyl boronic acid drug, bortezomib, the presence of D-mannitol was shown to increase bortezomib solubility due to ester formation.[7-10] A drop in the apparent p*K*a value of boronic acids on ester formation with various 1,2-diols has also been noted.[1,11-14]

Formation of esters of alkyl and aryl boronic acids with 1,2-diols including polyols with more than one 1,2-diol pair has mainly been studied with the 1,2-diols being present in excess over the boronic acid. Under these conditions, 1:1 or monoesters have been implied or observed.[11] Formation of higher order boronic acid and boric acid esters with 1,2-diol polyols has been mentioned in the literature but minimally studied and confirmed.[1,15,16]

Few studies have explored the role that ester formation plays in altering the physicochemical properties including aqueous solubility of alkyl and aryl boronic acids.[1,11] An increase in solubility of the D-mannitol ester of 2 boronic acids has been reported in formulation studies.[1,7-10,17] However, predicting the solubility of new chemical entities is not possible because one is not capable of predicting the solid-state characteristics *a priori* of any new entity formed.[18-23]

The solubility of 4-MBBA in the presence of low and high molar ratio of D-mannitol to boronic acid as a function of pH may have implications for the formulation of future boronic acid drugs in the presence of 1,2-diols.

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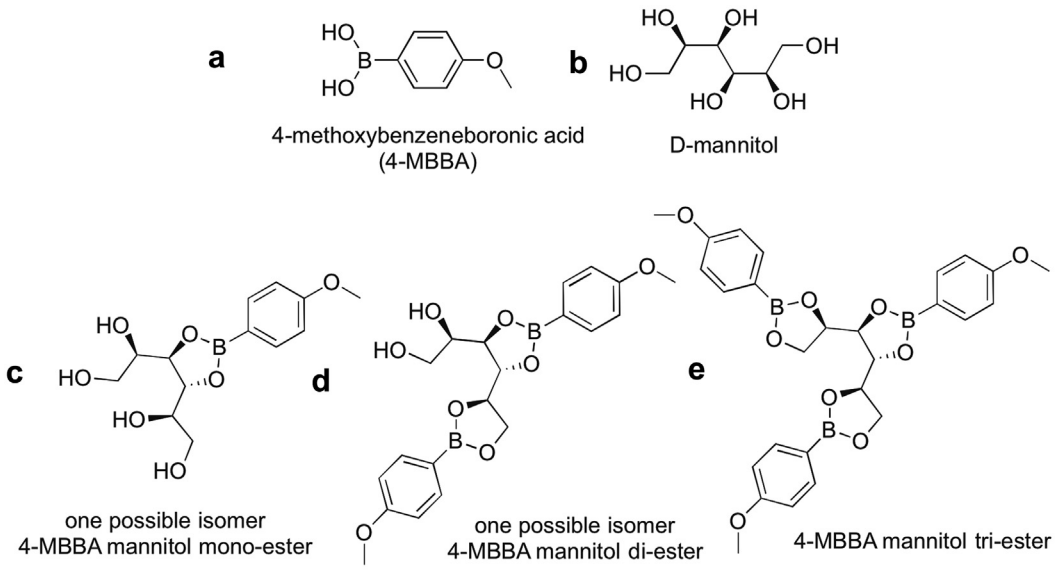

Figure 1. Chemical structures of 4-MBBA (a), D-mannitol (b), and 3 possible D-mannitol esters of 4-MBBA, the monoester (c, 1 of 3 possible isomers), the diester (d, 1 of 2 possible isomers), and the triester (e).

Experimental Materials and Methods

Materials

All chemicals were analytical grade or ACS reagents and used without further purification unless otherwise noted. Sodium acetate 99%, sodium chloride BioXtra ≥99.5%, acetic acid ACS reagent (≥99.7%), and HCl 37% ACS reagent were commercially sourced from Sigma-Aldrich (St. Louis, MO) and used without further purification. Sodium hydroxide (NaOH) pellets, $NaH_2PO_4 \cdot H_2O$, and Na_2HPO_4 anhydrous certified ACS, acetonitrile (ACN), methanol (HPLC grade), and D-mannitol (USP powder) were purchased from Fisher Scientific Company (Fair Lawn, NJ). The boronic acid, 4-MBBA (98%), was purchased from Lancaster Synthesis Ltd. (Windham, NH). Water (H_2O, distilled deionized water) was filtered through 2 Cole-Parmer (Vernon Hills, IL) ion X changer cartridges and distilled unless otherwise noted.

Methods

pH-Solubility Determination

An excess of 4-MBBA (40 mg) was added to 1 mL of acidic or basic solutions and titrated to the desired pH using 200 mM HCl and NaOH without and with 20, 100, and 500 mM of added D-mannitol. Each sample was left in a shaking water bath at 25°C, over 2 days, sufficient to reach equilibrium conditions based on prior validation studies. The third-day aliquots of 800 μL were taken, placed in 1.5-mL polypropylene microcentrifuge tubes, and centrifuged at 13,000 rpm for 10 min at 25°C, using an Eppendorf centrifuge 5417R instrument (Brinkmann Instruments, Inc., Westbury, NY). The supernatant was then filtered through a CR 13-mm Acrodisc syringe filter with 0.2-μm polyterafluorethylene membrane (PALL® Life Sciences, Ann Arbor, MI), validated to not absorb or adsorb 4-MBBA. The pH of these solutions was monitored with a Fisher Scientific Accumet pH meter model 925 combined with a Thermo Scientific Orion 8103BN ROSS Combination Semi-micro pH Electrode (Laboratory Equipment Division, Water Analysis Instruments, Chelmsford, MA). Each filtered aliquot was then diluted 100:1 with the HPLC mobile phase described below (10 μL of sample into 990 μL of mobile phase). Each sample was then analyzed by HPLC as described in the following High Performance Liquid Chromatography section.

Solubility Versus D-Mannitol Concentration at pH 3

Phase solubility analysis was performed at pH 3 (HCl 10^{-3} M) with an excess of 4-MBBA (98.7 mM and 296.1 mM) and with a saturated solution of 4-MBBA, that is, with no solid 4-MBBA present (34.3 ± 0.6 mM, 5.2 ± 0.1 mg/mL). To these samples, weighed solid D-mannitol was added to give final D-mannitol concentrations of 0-500 mM. Each sample was equilibrated in a shaking water bath at 25°C, over 2 days (validated by studies to give equilibrium conditions longer than 2 days), and then the supernatant analyzed by HPLC as described below.

High-Performance Liquid Chromatography

Samples were analyzed by the following HPLC method. A Shimadzu SIL 10-A system including an SIL-10A autoinjector, an SPD-10A UV-VIS detector, an SCL-10A system controller, LC-10AT pumps, and Class-VP version 4.10 software was purchased from Shimadzu Scientific Instruments (Columbia, MD). Analytes were separated on a Phenomenex HyperClone 5μ octadecyl-silica column (C-18, 150 × 4.60 mm, 5-μm particle size) purchased from Phenomenex Inc. (Torrance, CA).

The mobile phase consisted of 60% water with 0.1% acetic acid and 40% methanol run at 1mL/min. The column oven temperature was set at 40°C. 4-MBBA was detected at 235 nm and quantitated from a linear relationship between the peak area and concentration. The total acquisition time was 10 min.

Generation of Solid Materials

Solid materials were generated from the phase solubility analysis at pH 3 with a saturated solution of 4-MBBA and added D-mannitol concentrations of 15-500 mM. The triboronate ester solid material was generated from the phase solubility analysis at pH 3 with a suspension of 4-MBBA (296.1 mM) and added D-mannitol concentration of 100 mM and analyzed by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), powder X-ray diffraction