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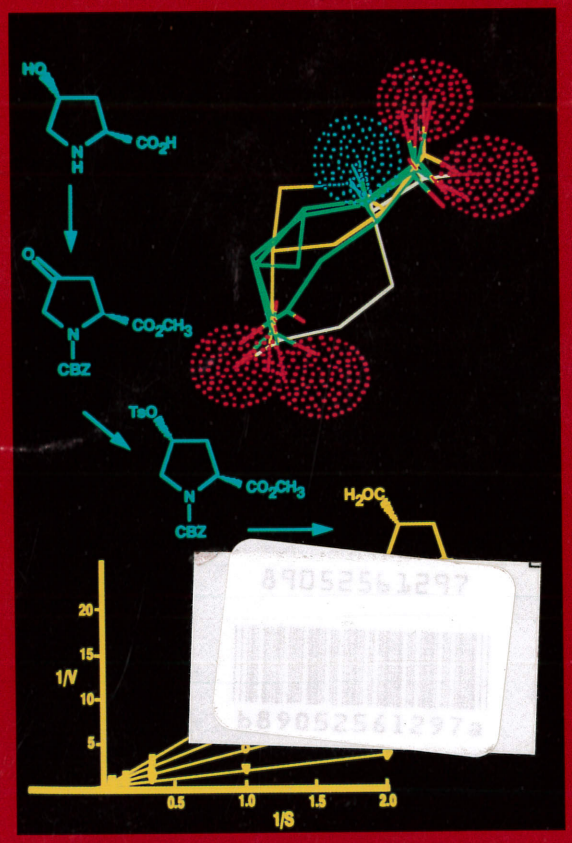

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DIPHENYLBORINIC ACID IS A STRONG INHIBITOR OF SERINE PROTEASES≠

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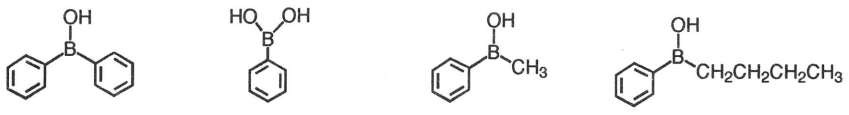
Abstract. Diphenylborinic acid, a commercially available and reasonably air stable compound, was found to be a strong competitive inhibitor of three serine proteases. Compared to phenylboronic acid, it was a thirty-fold better inhibitor of α-chymotrypsin, a fifteen-fold better inhibitor of subtilisin BPN', and a sixty-fold better inhibitor of bovine trypsin. The pK_a and inhibitory ability of methylphenylborinic acid was also determined.

Boronic acids have been studied as competitive inhibitors of serine proteases for more than twenty-five years.[1] Nonetheless, interest in these compounds remains high due to their potential clinical uses,[2] and their ability to act as structural probes of enzyme binding sites.[3] Despite numerous X-ray and NMR studies, some of the details concerning the structures of the enzyme/inhibitor complexes remain controversial, particularly when the inhibitors are simple, "non substrate-like" boronic acids.[4] In some cases there is clear evidence for a covalent tetrahedral adduct with the active-site serine hydroxyl.[4,5] In other cases there is no doubt that the boron is coordinated to the active-site histidine.[6]

Our interest in this area stems from our recent efforts to develop molecular transport devices using boron acids.[7] While conducting experiments with diphenylborinic acid, **1**, we became curious about its ability to inhibit serine proteases. Inhibition with asymmetric borinic acids has been reported before,[8] the most recent study by the Jones research group.[9] In general, borinic acids are better inhibitors than boronic acids. The major detraction with borinic acids is their susceptibility to air oxidation. Diarylborinic acids, however, are reasonably air stable compounds. For example, a solution of **1** in phosphate buffer, at pH 7.4, was found to be > 90 % pure after standing on the bench top for 24 hours. Compound **1** has a pK_a of 6.2.[10] At neutral pH it readily combines with vicinal diols to form anionic, tetrahedral "ate" complexes.[7] The expected inhibitory ability of **1** was hard to predict, *a priori*, since it was difficult to estimate the relative importance of various opposing factors such as increased acidity, enzyme binding site specificity, inhibitor hydrophobicity, loss of a potential active-site hydrogen, etc. We felt that if **1** were a good protease binder then it may have utility in clarifying some of the structural and mechanistic ambiguities concerning this class of transition-state-analogue inhibitors.



1 **2** **3** **4**

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