Comparative Study of Thrombin Binding of Potassium vs. Sodium

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Thrombin, a critical serine protease responsible for blood coagulation, is an allosteric enzyme that binds an alkali metal cation near the substrate-binding site. We have obtained a crystal structure to a resolution of 1.9 Å for the potassium-bound form of thrombin and compared it to the existing structure of sodium-bound thrombin.[1]

The crystal packing of K+-bound thrombin is quite different from that of Na+-bound thrombin. Crystal contacts in K+-bound thrombin distort the cation-binding site of one of the two molecules of the asymmetric unit such that the residues that normally coordinate the alkali metal are disordered. However, the cation-binding site of the other molecule is intact and can be compared with the sodium-binding site of Na+-bound thrombin.

Potassium in K+-bound thrombin is 7-coordinate with three-backbone carbonyl oxygen atoms and four water molecules as ligands. The key water molecule that communicates with the substrate binding site is the water molecule that bridges the cation and the side chain of Asp189. The distance between this water and the cation is about 0.5 Å longer in the K+-bound form than in the Na+-bound form.

[1] Pineda A. O., Carrell C. J., Bush L. A., Prasad S., Caccia S., Chen Z., Mathews F. S., di Cera E., *J. Biol Chem.* 2004, **279**, 31842.

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