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Antithrombin is a member of the serpin family of protease inhibitors and the major inhibitor of the blood coagulation cascade. It is unique amongst the serpins in that it circulates in a conformation that is inactive against its target proteases. Activation of antithrombin is brought about by a conformational change initiated upon binding heparin or heparan sulphate. Two isoforms exist in the circulation, alpha-antithrombin and beta-antithrombin, which differ in the amount of glycosylation present on the polypeptide chain; beta-antithrombin lacks the carbohydrate present at Asn135 in alpha-antithrombin. Of the two forms, beta-antithrombin has the higher affinity for heparin and thus functions as the major inhibitor in vivo even though it is the less abundant form. The reason for the differences in heparin affinity between the alpha and beta-forms have been shown to be due to the additional carbohydrate changing the rate of the conformational change. Here, we describe the most accurate structures of alpha-antithrombin and alpha-antithrombin+heparin pentasaccharide reported to date (2.6A and 2.9A resolution, respectively, both re-refinements using old data), and the structure of beta-antithrombin (2.6A resolution). The new structures have a remarkable degree of ordered carbohydrate and include parts of the antithrombin chain not modeled before. The structures have allowed a detailed comparison of the conformational differences between the three. They show that the structural basis of the lower affinity for heparin of alpha-antithrombin over beta-antithrombin is due to the conformational change that occurs upon heparin binding being sterically hindered by the presence of the additional bulky carbohydrate at Asn135.

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