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Ligand Protonation and Changes of the Water Inventory Determined by High-Resolution Neutron Structures upon Trypsin Complex Formation

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Hydrogen atoms are usually neglected in protein structures due to experimental difficulties in their detection; nevertheless, they play an important role in ligand recognition and protonation states of ligand and protein. In hydrogen-bond interactions, and as part of water molecules, hydrogen atoms indicate the geometry of hydrogen-bonding networks and help to classify the rotational states of water molecules in protein environments. High resolution neutron diffraction enables the detection of hydrogen atoms and thus allows to address the above mentioned points. We determined exceptionally high resolution neutron structures (better than 1.45Å) of trypsin in its apo state and in complex with a series of similar, small molecule ligands. These structures were complemented with corresponding high resolution X-ray structures. At first, we investigated binding of the structurally related molecules aniline and 2-aminopyridine to trypsin. Neutron structures revealed different protonation patterns of the two ligands and indicate a large Ka shift for aniline.[1] In a second study, we investigated the water structure of uncomplexed trypsin and corresponding changes upon benzamidine and N-amidinopiperidine binding. Observed changes in the solvation pattern and ordering states of water molecules might give an explanation for the strength of inhibitor binding.[2]

[1] Schiebel, J. et al. (2017) Angew. Chem. Int. Ed. 56, 4887-4890.
[2] Schiebel, J. et al. (2018) Nat. Commun. 9, 3559.

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