Exploring the binding of photoacids to the surface of insulin amyloid fibril by docking and all-atom simulations

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The proliferation and societal cost of amyloid diseases makes the research of new diagnostic tools as well as the treatment and prevention of amyloid formation highly important. Here, we examine the surface of insulin amyloid fibrils and follow the binding of small molecules (photoacids) that differ according to the number and location of their sulfonic group.We used docking and molecular dynamics simulations to explore the binding mode of the photoacid that can result in the unique kinetic rates and diffusion properties its dissociated proton, where we also suggest a proton transfer process between one of the photoacids to a proximal histidine residue. We support this hypothesis by contrasting the finding with the photoacid binding to insulin fibrils made by a histidine mutant protein. We compare our simulations with the results of steady-state and time-resolved fluorescence combined with a spherically-symmetric diffusion theory to show that the binding mode of different photoacids determines the efficiency of proton dissociation from the photoacid and the dimensionality of the proton's diffusion. We suggest that due to the change in the fluorescence properties of the photoacids as they bound to the fibrillar structure they can be used as fluorescent markers for following the progression of amyloidogenic processes. The detailed characterisation of different binding modes to the surface of amyloid fibrils paves the way for the design of new markers and, possibly, inhibitors of the amyloid formation.