The Influence of Ligand Binding on Protein Flexibility

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The issue of protein flexibility upon ligand binding is addressed in this poster. The influence of ligand binding on protein flexibility is examined by analyzing a large number of proteins crystallized with and without ligands. A baseline comparison of the natural variation of protein structure with and without ligands is first established, and then differences between the apo and holo are analyzed. It is shown that, in general, ligand binding stabilizes the protein and results in a smaller backbone RMSD among holo proteins structures compared the backbone RMSD of the apo proteins structures. Furthermore, the holo structures appear to sample a smaller subset of the space inhabited by apo structures, because the difference between apo and holo structures is smaller than variation seen among apo structures themselves. The size of the ligand binding does not appear to matter in determining the rigidification. While ligand binding does generally not induce large changes to the backbone, they are significant. Ligand binding does, however, have distinct impact on the active site, as revealed by all-atom, active-site RMSD and the range of χ_1 angle variation. Apo structures are observed to have a certain range of flexibility in their active sites, just as holo structures have a similar, but smaller degree of variation among their active sites. Greater variation has been found, however, between these two groups compared to variation within either group by themselves. This suggests that ligand binding induces active-site side chains to occupy a different conformational space than before. The influence on the active site could not be easily attributed to features such as ligand size, resolution, protein function, or catalytic composition. This study does illustrate, however, the usefulness of large carefully annotated datasets for studying protein-ligand interactions.