Structure and Stability of Protein-Ligand Complexes in the Gas Phase

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The structure and stability of a number of desolvated protein-ligand complexes have been investigated using experimental and computational methods. Time-resolved blackbody infrared radiative dissociation (BIRD) measurements, implemented with Fourier-transform ion cyclotron resonance mass spectrometry, were combined with a functional group replacement (FGR) strategy to probe the nature of the stabilizing intermolecular in three protein-ligand complexes: a single chain variable fragment of the monoclonal antibody Se155-4 and specific trisaccharide ligand Gal[Abe]Man, the high affinity interaction between the homotetrameric protein streptavidin and biotin, and the hydrophobic interactions between bovine β-lactoglobulin and saturated, unsaturated and branched fatty acids. Comparison on the interactions identified in the gas phase by BIRD-FGR with those present in aqueous solution indicates that specific interactions are generally preserved upon transfer from solution to the gas phase with electrospray ionization. Furthermore, the strengths of individual intermolecular interactions measured in the gas phase are found to be in good agreement with calculated or experimental values reported for model systems. Deuterium kinetic isotope effects measured for select complexes reveal a late dissociative transition state, wherein the ligand is fully removed from the binding cavity. Finally, the first direct comparison of the Arrhenius parameters for the dissociation of protein-ligand complexes in their solvated and desolvated states was carried out. Notably, the differences in the activation parameters measured in solution and the gas phase can be quantitatively explained by the differential hydration of the ligand in the bound state and in the putative transition state.