Poster

Decoding Amino Acid@Cucurbit[7]uril through X-ray diffraction: Balancing Hydrophobicity and Ion-Dipole Interactions

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Molecular recognition plays a crucial role in a wide range of chemical and biological processes, encompassing phenomena such as crystallization, molecular assembly, enzyme catalysis, cellular signaling, and protein-protein interactions. Despite often being characterized as a binary association between two partners, molecular recognition typically occurs within an aqueous environment characterized by precise pH and ionic strengths, involving numerous water molecules, and ions. This complexity makes understanding the process challenging. CB7, cucurbit[7]uril, a model hydrophobic pocket, offers insight into the interplay between non-covalent interactions (NCI) and solvation, influencing the change in free energy (ΔG) of binding. Notably, CB7 exhibits a preference for binding molecules with positively charged amine groups, often accompanied by the release of water molecules from its binding pocket. Molecular dynamics simulations estimate that water release contributes significantly to the enthalpy of binding (ΔH), reaching -102 kJ/mol for CB7 [1]. Given water release's pivotal role, binding affinity likely depends on volume. We explore whether ion-dipole interactions at the negatively charged portal of CB7 remain constant across amino-containing ligands and how solvation affects these weak interactions. Our study involves measuring binding affinities (ITC), crystallizing CB7 complexes with amino acids (XRD), and examining ion-dipole interactions (fSAPT), and solvation changes (COSMO-RS). While certain amino acids, like Phenylalanine (Phe), exhibit strong affinities due to minimal solvation penalties in water, crystallization studies of Phe, Tyrosine (Tyr), Tryptophan (Trp), Leucine (Leu), Methionine (Met), L-DOPA, and Histidine (His)[2] reveal the complex nature of ligand-CB7 interactions. CB7's shielding effect alters ligand pKa values, leading to diverse protonation states and the presence of water molecules within the CB7 cavity, impacting the positioning of amino groups and, consequently, the strength of ion-dipole interactions. While ion-dipole interactions play a role, interactions involving the hydrophobic portions of amino acids are also significant. On average, ion-dipole interactions for zwitterionic amino acids contribute approximately -266 kJ/mol, while for positively charged amino acids, it reaches around -314 kJ/mol. However, the most substantial variability is observed in the interaction energies of the side chains with CB7. Predicting ΔG remains an ambitious goal with profound implications for ligand design. However, our study highlights the challenges and the progress required to achieve this goal, even for the relatively small, rigid cavity of CB7.

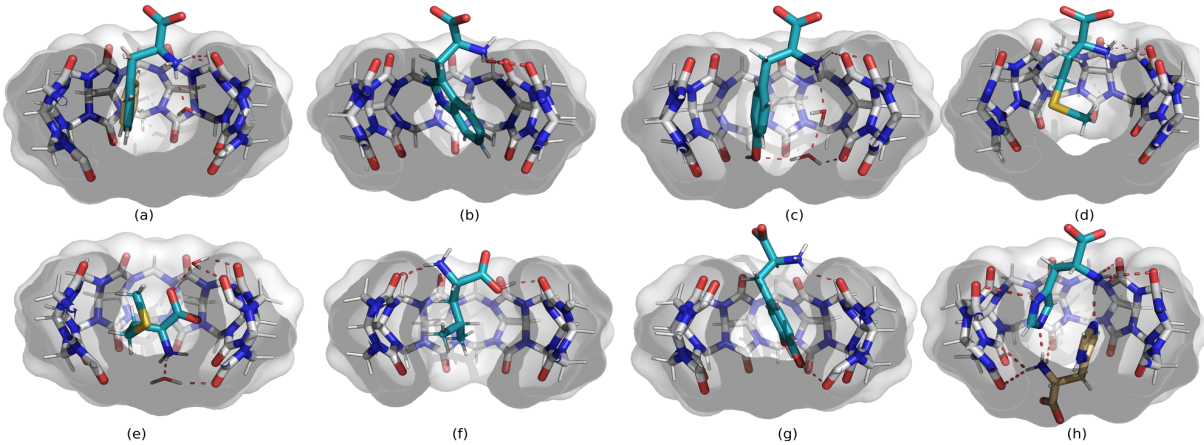

Figure 1. CB7 with Phe (a), Trp (b), Tyr (c), Met (d), Met (+1) (e), Leu (+1) (f), L-DOPA (g), and 2 His (h) in the asymmetric part of the unit cell of the crystal structures. CB7 molecules are depicted partially to better show the ligand position.

[1] Biedermann, F.; Uzunova, V. D.; Scherman, O. A.; Nau, W. M.; De Simone, A. (2012). *J. Am. Chem. Soc.,* **134**, 15318.

[2] Zaorska E., Malinska M. (2023). *Chem. Eur. J.*, e202302250.

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