Anion - π Interactions in Biological Systems

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Anion -π Interaction

The understanding of noncovalent interactions and the interplay among them[1] are of pivotal importance to the development of fields such as supramolecular chemistry and molecular recognition. The interactions involving aromatic rings are crucial binding forces in both chemical and biological systems.[2] For instance, cation-π interactions are supposed to be an important factor to the ion selectivity in potassium channels.[3] Moreover, π-π interactions are weak non-covalent forces that play an essential role in the folding of proteins, in the structure of DNA as well as in its interactions with small molecules. One important noncovalent interaction that involves aromatic rings is the **anion-π interaction**. It has been clearly evidenced by theoretical[4] and experimental studies.[5] This new field of supramolecular chemistry has been widely developed and some significant new examples of anion-π binding associations are now increasingly described in the literature.[6]

Biological Systems[7]

Urate oxidase belongs to the purine degradation pathway and catalyzes, in the presence of molecular oxygen, the hydroxylation of uric acid into a product identified as the 5-hydroxyisourate (5-HIU) and hydrogen peroxide. In vivo, 5-HIU is rapidly processed by two specific enzymes to [S]-Allantoin. The urate oxidase crystallizes in orthorombic system in Aspergillus flavus. The complete structure has the shape of a barrel 70 Å high, with an inner radius of about 6 Å. Each monomer is associated with one active site located at a dimer interface.

It is known that UOX is inhibited in solution by cyanide with a loss of activity of 90%. The location of the cyanide anion suggests that it inhibits any access to the peroxo hole during the course of the reaction. The cyanide presumably reacts once an intermediate already oxidized by O_2 is formed. This supports that cyanide would mainly compete reversibly with water in the second step of the reaction rather than oxygen in the first step.

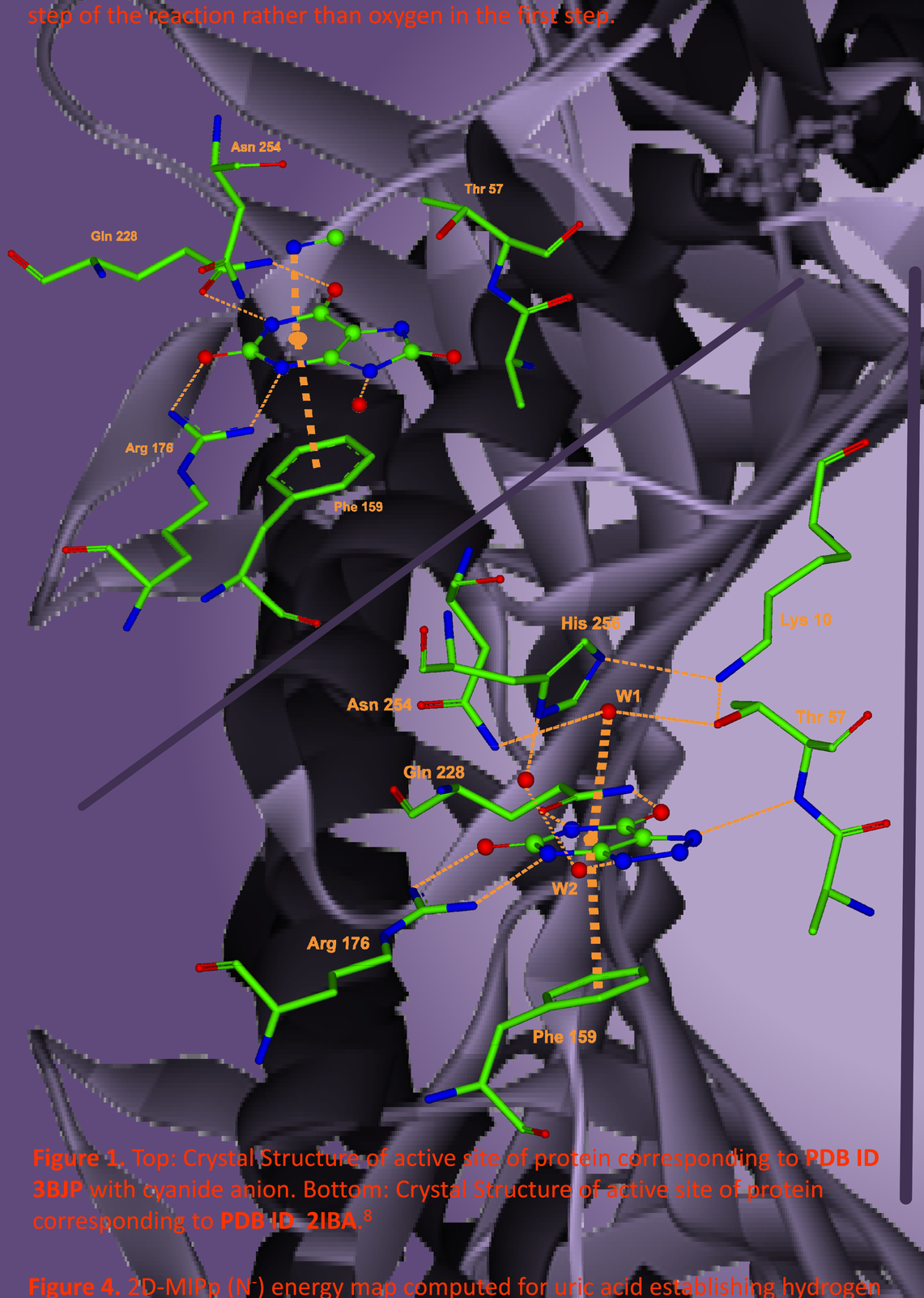

Figure 1. Top: Crystal Structure of active site of protein corresponding to **PDB ID 3BJP** with cyanide anion. Bottom: Crystal Structure of active site of protein corresponding to **PDB ID 2IBA**.[8]

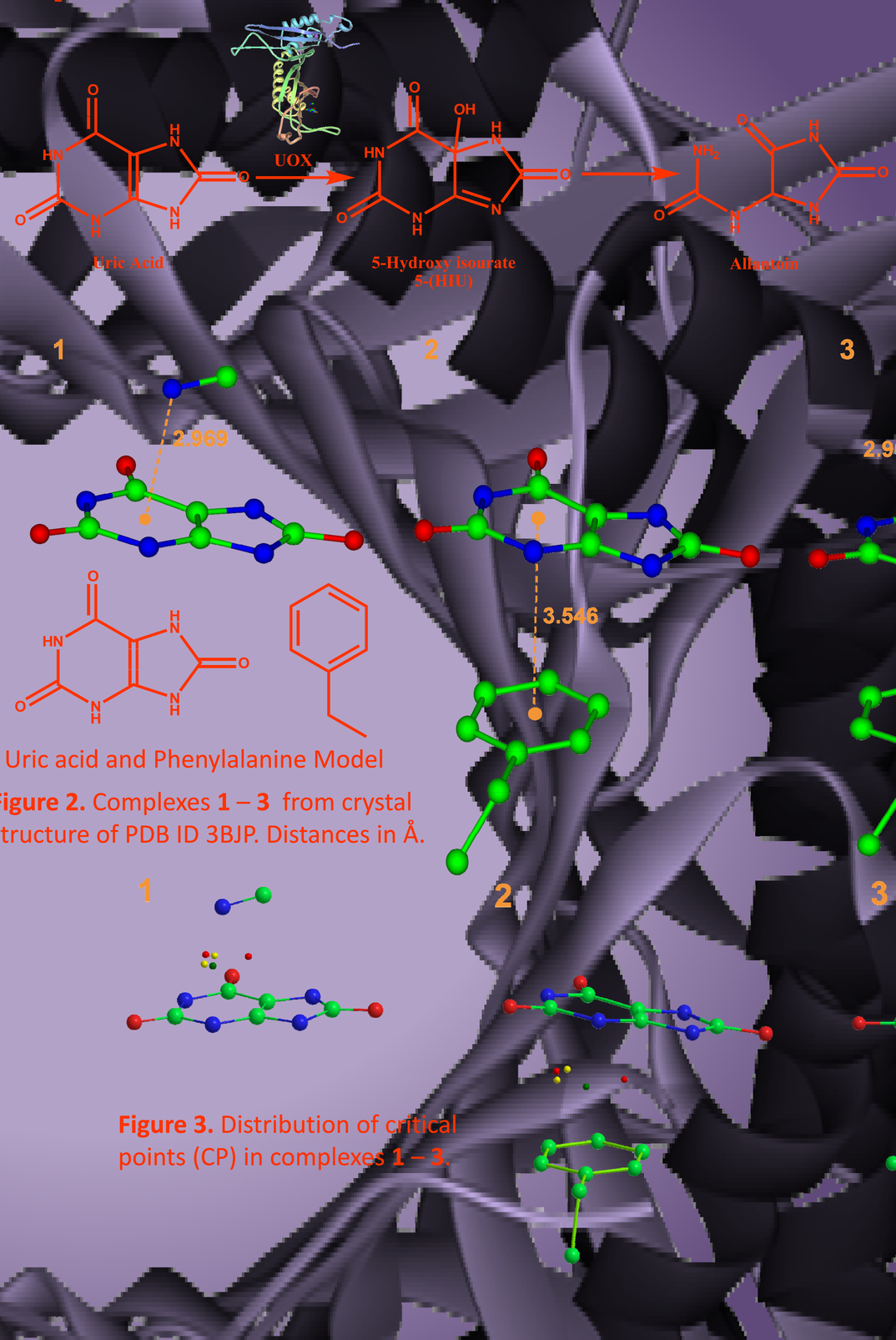

Figure 2. Complexes **1 – 3** from crystal structure of PDB ID 3BJP. Distances in Å.

Figure 3. Distribution of critical points (CP) in complexes **1 – 3**.

Figure 4. 2D-MIPp (N^-) energy map computed for uric acid establishing hydrogen bonding interactions at 3.5 Å above the molecular plane (kcal mol^{-1}). The values in parenthesis correspond to the Interaction Energy for uric acid alone.
E_t = -5.24 (-13.55)
E_e = 2.56 (-7.42)
E_{pol} = -6.46 (-5.65)
E_{vdW} = -1.34 (-0.49)

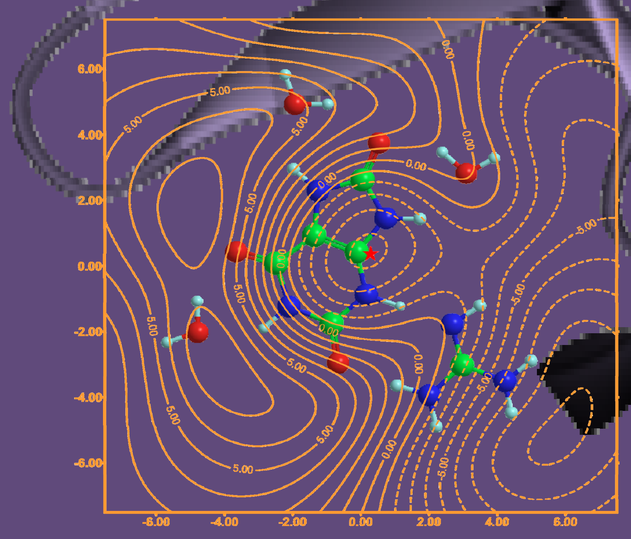

Table 1. Binding Energies without and with the BSSE Correction (E and E_{BSSE}, kcal mol^{-1}, respectively) at the RI-MP2(full)/aug-cc-pVDZ, RI-MP2(full)/aug-cc-pVTz and RI-MP2(full)/CBS (E_{CBS}, kcal mol^{-1}) Levels of Theory, for Complexes **1 – 3.** Equilibrium Distances (R_e, Å) from crystal structure of the protein. Electron Charge Density Values (ρ, a.u.) at the MP2(full)/aug-cc-pVDZ// RI-MP2(full)/aug-cc-pVDZ Level of Theory Measured at the Cage CP.

	E (AVDZ)	E_{BSSE} (AVDZ)	E (AVTZ)	E_{BSSE} (AVTZ)	E_{CBS}	R_e	Charge Density (ρ)
1	-19.08	-16.24	-19.20	-16.70	-19.25	2.969	0.5913
2	-15.74	-8.61	-14.74	-9.13	-14.32	3.456	0.2941
3	-33.77	-23.34	-33.23	-24.35	-32.99	2.969/3.247/3.456	0.5913/0.2969

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