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## Theoretical Study of Mechanisms for Double Proton Transfer in Adenine–Uracil Base Pair via Steered Molecular Dynamic Simulations

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### Abstract

Gibbs free energy profiles for the A–U  $\rightleftharpoons$  A\*–U\* tautomeric equilibrium between the canonical and non-canonical base pair in aqueous solution have been obtained by applying Steered Molecular Dynamic (SMD) technique. Concerted and stepwise mechanisms have been considered to explain the double proton transfer process. Among the different mechanisms studied, the stepwise mechanism was the fastest due to the lower energy barrier ( $\Delta G^\ddagger = 31.72 \text{ kcal}\cdot\text{mol}^{-1}$ ) respect to the concerted process, both having a reaction energy about  $25 \text{ kcal}\cdot\text{mol}^{-1}$ . The inclusion of two water molecules to assist the transfer process slightly modified the reaction energy ( $\Delta G = 28.09 \text{ kcal}\cdot\text{mol}^{-1}$ ), while increasing the barrier considerably ( $\Delta G^\ddagger = 65.76 \text{ kcal}\cdot\text{mol}^{-1}$ ). From the results obtained, we can say that the A-U pair of bases presents a Gibbs free energy profile similar to the A-T pair and that it could participate in a process of spontaneous genetic mutation depending on the mechanism followed. Finally, the stationary points along the energy profile for all the mechanisms were analyzed at molecular dynamics levels, finding that the transition states have geometries very similar to those of the products.

**Keywords:** Adenine-uracil, tautomeric equilibrium, proton transfer in solution, steered molecular dynamics simulations, reaction mechanisms, Gibbs free energy profile.

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