Ab-initio dynamics of Gas-phase and Aqueous-phase Hydrolysis of Adenosine Triphosphate

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Abstract

Adenosine triphosphate (ATP) hydrolysis is a well-known biological reaction which plays an important role in many biological processes. In this study, we have modelled the non-enzymatic hydrolysis of ATP in the gas-phase and the aqueous-phase by performing *ab initio* molecular dynamics simulations combined with an enhanced sampling technique. In the gas-phase, we studied hydrolysis of fully protonated ATP molecule and in the aqueous-phase, we studied hydrolysis of ATP coordinated with: a) *two* H⁺ ions (H-ATP), b) Mg²⁺ (Mg-ATP) and c) Ca²⁺ (Ca-ATP). We show that gas-phase ATP hydrolysis follows a two-step dissociative mechanism *via* a highly stable metaphosphate intermediate. The Adenine group of the ATP molecule plays a crucial role of a general base; temporarily accepting protons and, thus helping in the elimination-addition process. In the aqueous-phase hydrolysis of ATP, we find that the cage of solvent molecules increases the stability of the terminal phosphoanhydride bond through a well-known cage-effect. Further, we find that the aqueous-phase hydrolysis happens with the help of nearby water molecules, which assumes the role of a base assisting in proton diffusion through Grotthuss mechanism. We obtained much lower free-energy barriers for the aqueous-phase hydrolysis of ATP coordinated with divalent ions (Mg²⁺ and Ca²⁺) compared to hydrolysis of ATP coordinated with only H⁺ ions, suggesting a clear catalytic effect of the divalent ions. We find a single-step dissociative-type mechanism for Mg-ATP, while we find a S_N-2-type concerted hydrolysis pathway for Ca-ATP.

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