Virtual Laboratory : First Principles Simulation of the Catalytic Reaction of Ribozyme

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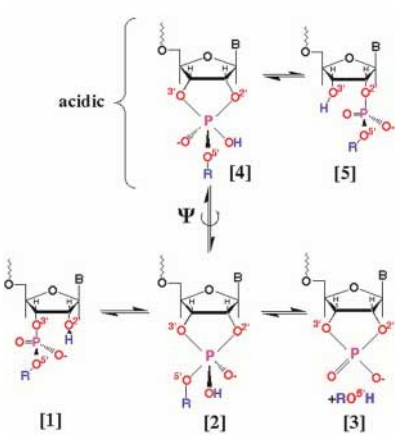
Since their discovery in the early 1980s, catalytic RNA molecules have been at the center of great attention in molecular biology and medical science. Their figure of merit is the fact that RNA enzymes (ribozymes) can be engineered to cleave other target RNA molecules. Hence, ribozymes are very promising therapeutic agents able to inhibit gene expression and suitable for gene therapy of cancer. Yet, the mechanism of the cleavage reaction escapes experimental probes.

By using a first principles moelcular dynamics approach, we have been able to simulate the cleavage process of the ribozyme. The simulation shows that a divalent metal cation Mg^{2+} is essential both in selecting the right reaction path between two possible competing channels and in lowering the activation barrier of the reaction (Fig.).

Another important factor is the role of water, present in all the experiments either *in vitro* or *in vivo*. Water molecules form a continuous hydrogen bond network connected to all the hydrophilic part of the ribozyme. On one hand, this network stabilizes the structure, on the other hand, it provides a path along which a proton can travel, jumping from molecule to molecule, and start the reaction.

On a second instance, we found that the Mg^{2+} cation can make the proton abstraction (the initial stage of the reaction) easier, but can prevent the proton transfer from one site of the ribozyme to another one. In this case, the lost proton is dispersed in the solvent in form of hydronium OH_3^+. This kind of detailed simulation was made possible by the recent advances both in the computational power of the last generation of parallel supercomputers and in the software algorithms. [details in M. Boero, K. Terakura and M. Tateno, *J. Am. Chem*. Soc. **124**, p. 8949 (2002)]



Panel (a) shows the schematic reaction of the cleavage of the RNA molecule (sequence from [1] to [3]) and the competing reaction path ([4] and [5]). Our computer experiment shows that the initial system (i) is driven by Mg^{2+} (blue ball) toward a transition state (ii) and eventually to the cleaved ribozyme (iii).