Intramolecular Phosphodiester Bond Cleavage: Implications for RNA Backbone Self-Cleavage

Vojtěch Mlýnský

Department of Physical Chemistry, Faculty of Science, Palacky University Olomouc

The catalytic effect of enzymes can be defined as a difference in reactivity between the enzyme catalyzed reaction and the reference uncatalyzed reaction in water.[1] A group of small ribozymes (RNA enzymes) is required for site-specific cleavage and ligation of RNA substrates. Nucleobases and Mg^{2+} ions are proposed to participate directly as general acid/bases and/or in electrostatic stabilization.[2] We exploit the cleavage of 3'-(1'-amino-4'-methylribose)-5'-methylphosphodiester model and analyze an effect of all possible combinations of N9-methylguanine, N9-methyladenine, N1-methylcytosine and two hydrated Mg^{2+} ions in catalysis. We have carried out density functional theory calculations using Gaussian 09 software package.[3] The dianionic reaction mechanism, where the 2'-O^- group attacks the negatively charged phosphate has comparable barrier (33.0 kcal/mol) with monoanionic reaction mechanism (31.8 kcal/mol) representing a nucleophilic attack of 2'-OH to phosphoryl group. Both nucleobases and Mg^{2+} ions in the position of general base alone do not significantly affect the overall barrier and the exocyclic cleavage represents the rate limiting step. In contrast, the involvement of general acid lowers significantly the overall barrier and shifts the rate limiting step to the initial nucleophilic attack. Altogether, we observe the maximal decrease of overall barriers (towards 14-15 kcal/mol) in the presence of hydrated Mg^{2+} ions acting directly as general acids.

References

[1] WARSHEL, Arieh, Pankaz K. SHARMA, Mitsunori KATO a et al. Electrostatic Basis for Enzyme Catalysis. *Chemical Reviews*. American Chemical Society, 2006, **106**(8), 3210–3235.

[2] WILCOX, Jennifer, L., Amarpreet K AHLUWALIA a Philip C BEVILACQUA. Charged nucleobases and their potential for RNA catalysis. *Accounts of Chemical Research*. American Chemical Society, 2011, **44**(12), 1270–1279.