Bio-科学への計算物理的approach

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Outline

- Brief summary of the computational techniques adopted to compute activation barriers and to follow the reaction path
- Catalytic role of a metal cation (Mg^{2+})
- Reaction of in solution: solvation effects in the absence and presence of Mg^{2+}
- Inclusion of an OH^- in the solvation shell of the cation: proton abstraction/transfer problem
- Conclusions and perspectives

Car-Parrinello Molecular Dynamics

電子と原子は動きます：第一原理分子動力学計算

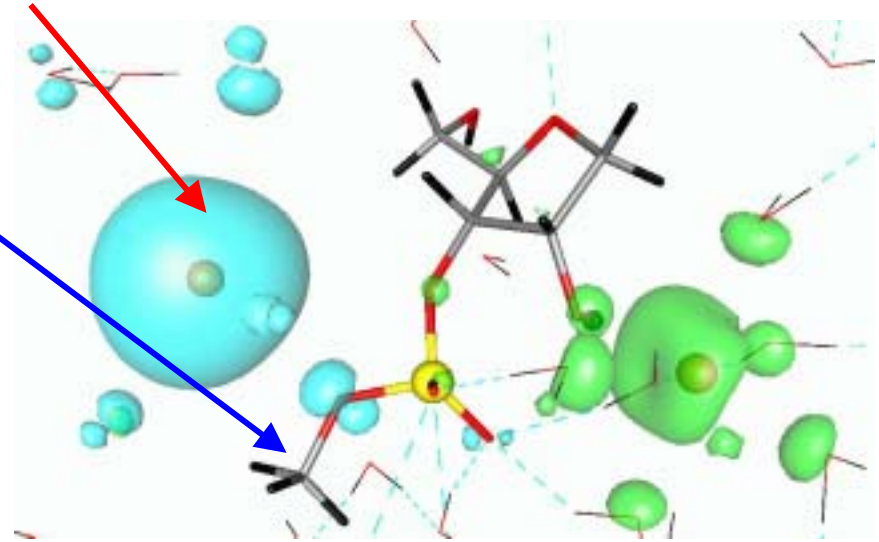
- Euler-Lagrange equations of motion for electrons, ions thermostats & Co.

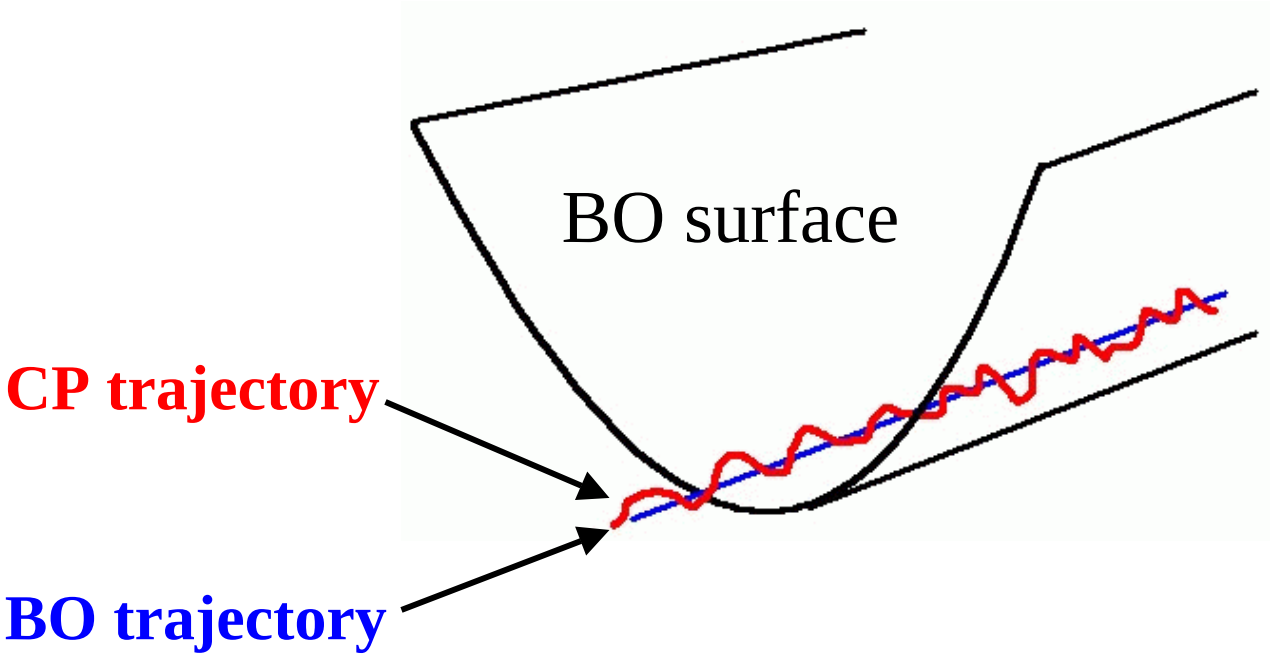
$$\mu\ddot{\psi}_i = -\frac{\delta E^{DFT}}{\delta \psi_i^*} + \sum_j \Lambda_{ij}\psi_j$$

$$M_I\ddot{\mathbf{R}}_I = -\nabla_{\mathbf{R}_I} E^{DFT}$$

$$\mu_q\ddot{\alpha}_q = -\frac{\partial E^{DFT}}{\partial \alpha_q}$$

温度





The difference between the CP trajectories $\mathbf{R}_I^{CP}(t)$ and the Born-Oppenheimer (BO) ones $\mathbf{R}_I^{BO}(t)$ is bound by

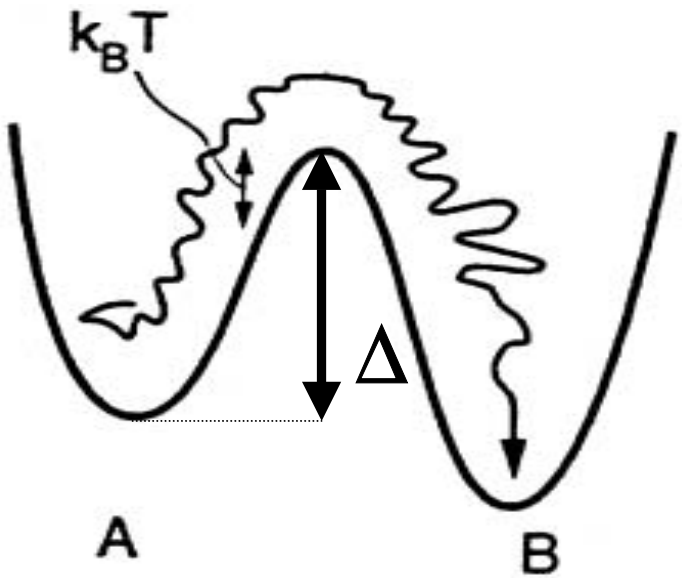
$$| \mathbf{R}_I^{CP}(t) - \mathbf{R}_I^{BO}(t)| < C\, \mu^{1/2}$$

(C > 0) if $\omega_0 = \sqrt{2 \cdot \left(\varepsilon^{LUMO} - \varepsilon^{HOMO}\right)/\mu} > 0$

See F.A. Bornemann and C. Schuette, *Numerische Mathematik* vol.**78**, N. **3**, p. 359-376 (1998)

From reactants A to products B:
how to climb the mountain

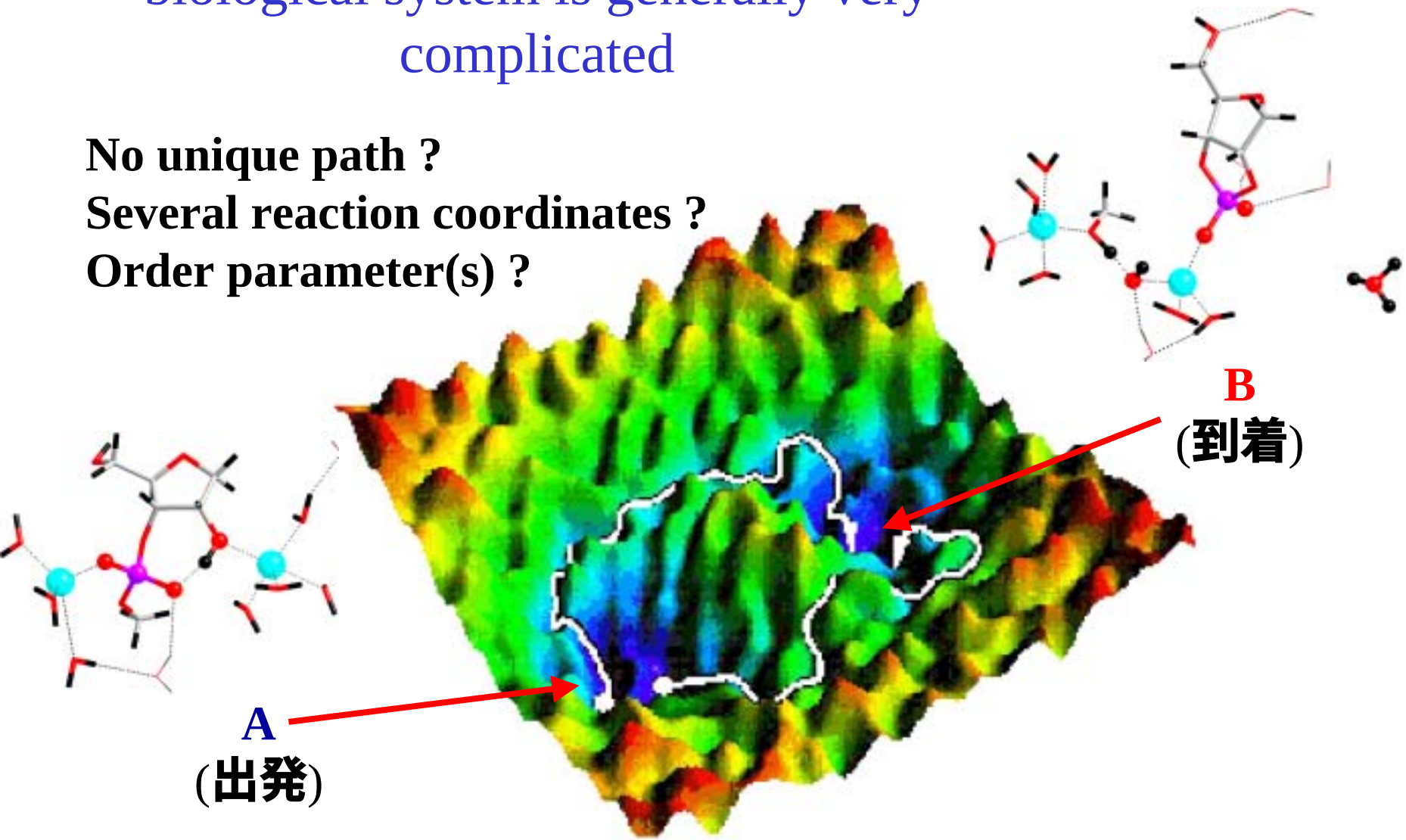
- A general chemical reaction starts from reactants A and goes into products B
- The system spends most of the time either in A or in B
- …but in between, for a short time, a barrier is overcome and **atomic** and **electronic** modifications occur
- Time scale: $\tau \sim \tau_{mol} e^{\frac{F^*}{k_B T}}$



$F^* \sim \Delta$

The potential energy landscape of a biological system is generally very complicated

No unique path ?
Several reaction coordinates ?
Order parameter(s) ?



What we know & what we assume:

1) **The atomic coordinates of our initial system are known**
(e.g. from X-ray, Protein Data Base (PDB), etc…)

$$\left\{\vec{R}_1,\ldots,\vec{R}_N\right\}_{t=0}$$

2) **We assume that some known functions of few of them (collective variables) are *necessary* and *sufficient* to describe the process we are interested in**

$$s_\alpha(\vec{R}_I) \qquad \alpha = 1,\ldots,n < N_{Ions}$$

3) **…so that the FES is a function (smoother) of these slow variables**

$$F(\vec{s}) \qquad \vec{s} \equiv \vec{s}(t) = \left\{s_\alpha(t)\right\}_{\alpha=1,\ldots,n}$$

Meta-variables controlling the reaction added to the Car-Parrinello lagrangean + history dependent potential:

$$L = L^{CP} + \sum_{\alpha} \tfrac{1}{2} M_{\alpha} \dot{s}_{\alpha}^{2}(R_I) - \sum_{\alpha} \tfrac{1}{2} k_{\alpha} \left[s_{\alpha}(R_I) - s_{\alpha}^{0} \right]^2 + V(s_{\alpha}, t)$$

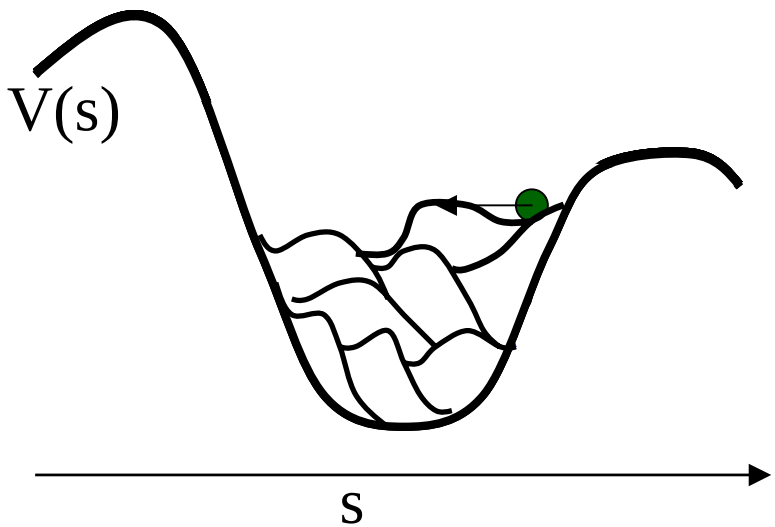
History dependent gaussian potential

Harmonic potential around $\boldsymbol{s}_{\alpha}^{0}$

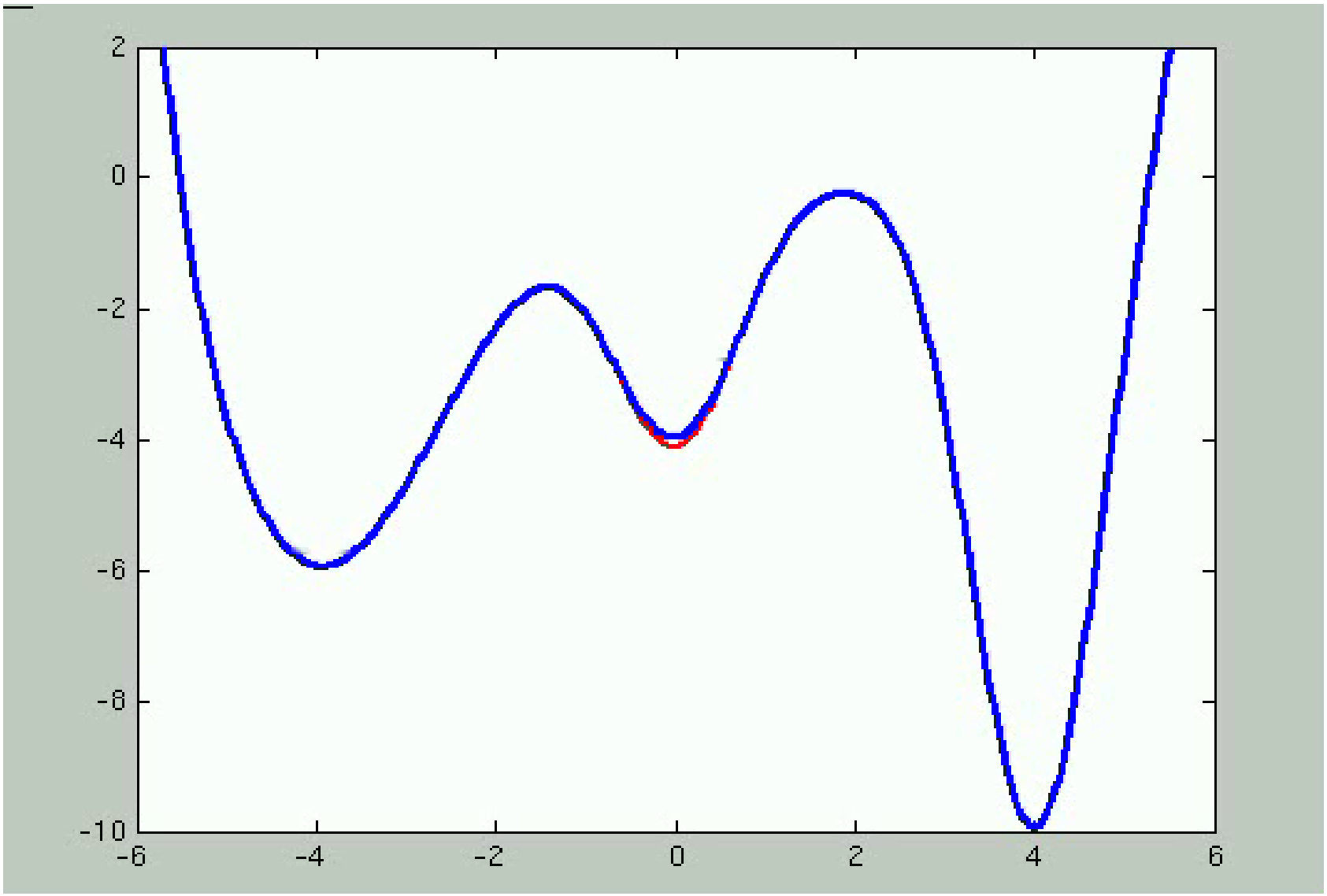
Chemical reactions: escaping from the minima of the FES and overcoming energy barriers

- Free MD with an additional penalty potential
- Always move along the minimum energy path (Car-Parrinello)
- Accounting for many-fold reaction coordinates (complex chemical and biologic systems)

(M. Iannuzzi, A. Laio and M. Parrinello, *Phys. Rev. Lett.* **2003**, *90*, 238302
M. Boero, T. Ikeshoji, C. C. Liew, K. Terakura and M. Parrinello, *J. Am. Chem. Soc.* **2004**, *126*, 6280)



Adding gaussians iteratively = filling the wells



Reconstruction of the FES: what the $V(\mathbf{s},t)$ potential does

The (meta)dynamical gaussian potential $V(\mathbf{s},t)$ has the shape

$$V(\vec{s},t) = \sum_{t'<t} W \cdot \exp\left(-\frac{\left|\vec{s} - \vec{s}^{\,t'}\right|}{2\,\delta\sigma^2} \right)$$

and when it has completed its job (large t) and filled all the local minima, then its shape is similar to the FES:

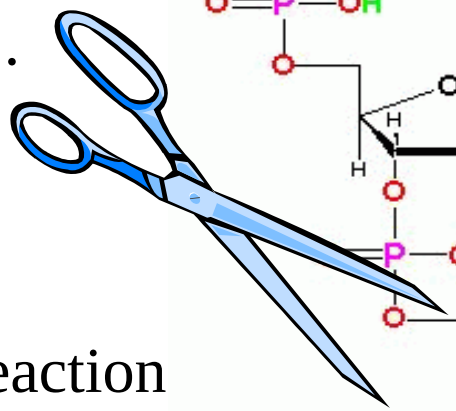
$$\lim_{t\to\infty} V(\vec{s},t) = F(\vec{s}) + const.$$

In practice: the number of gaussians required to fill a minimum is proportional to $(1/\delta\sigma)^{n}$ (n = dimensionality of the problem) and

$$W / \delta\sigma\, e^{-1/2} = \gamma \left\langle f_\alpha^2 \right\rangle^{1/2} \qquad \gamma \approx 0.5$$

RiboNucleic Acid

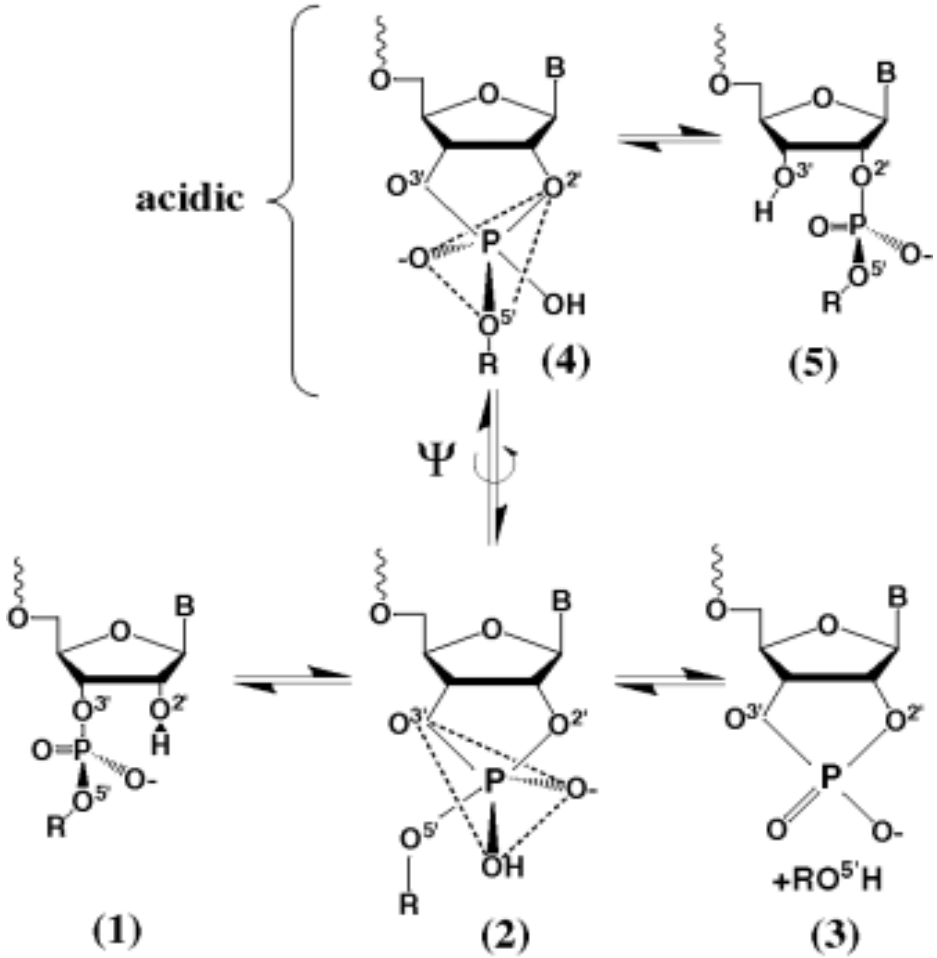
We want to cut the RNA at a specific site when a genetic defect (**がん**!) occurs…



(molecular) scissors = **chemical** (**catalytic**) reaction

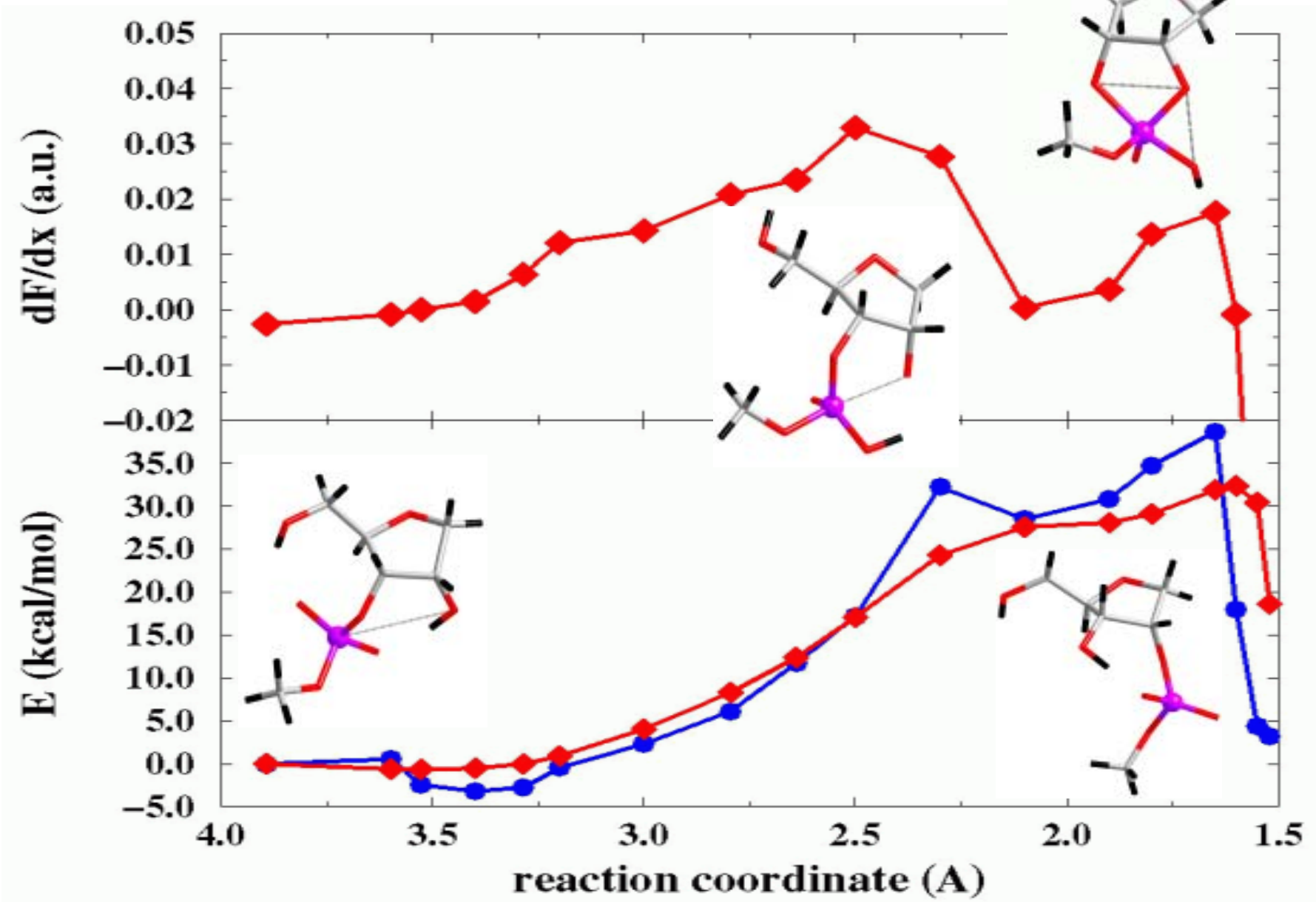
see e.g. D. Zhou and K. Taira, *Chem. Rev*. **98**, 991 (1998)

General reaction mechanism

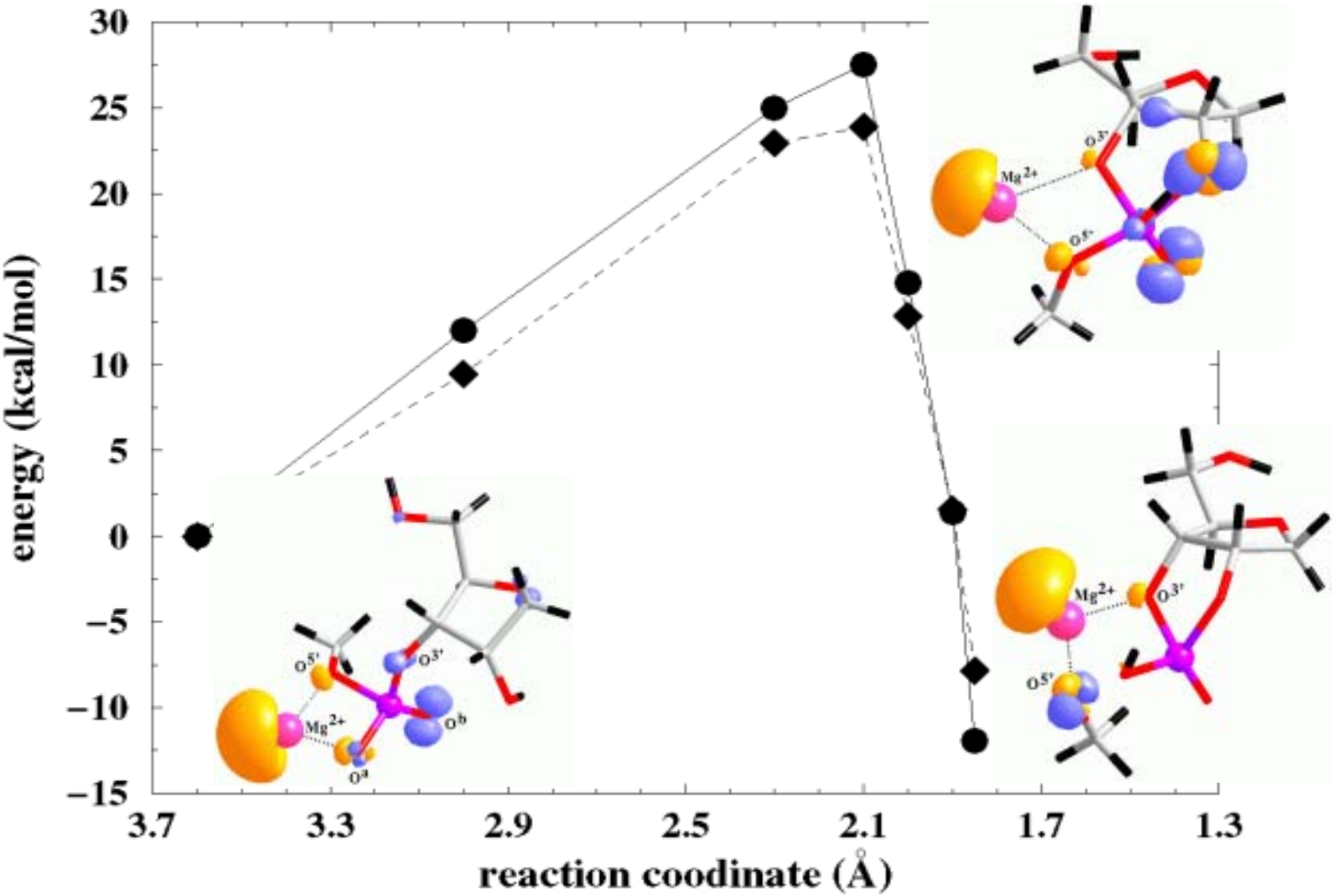


Ψ = ***pseudorotation*** leading to the migration product [5] with 2', 5'-linkage (exchange)

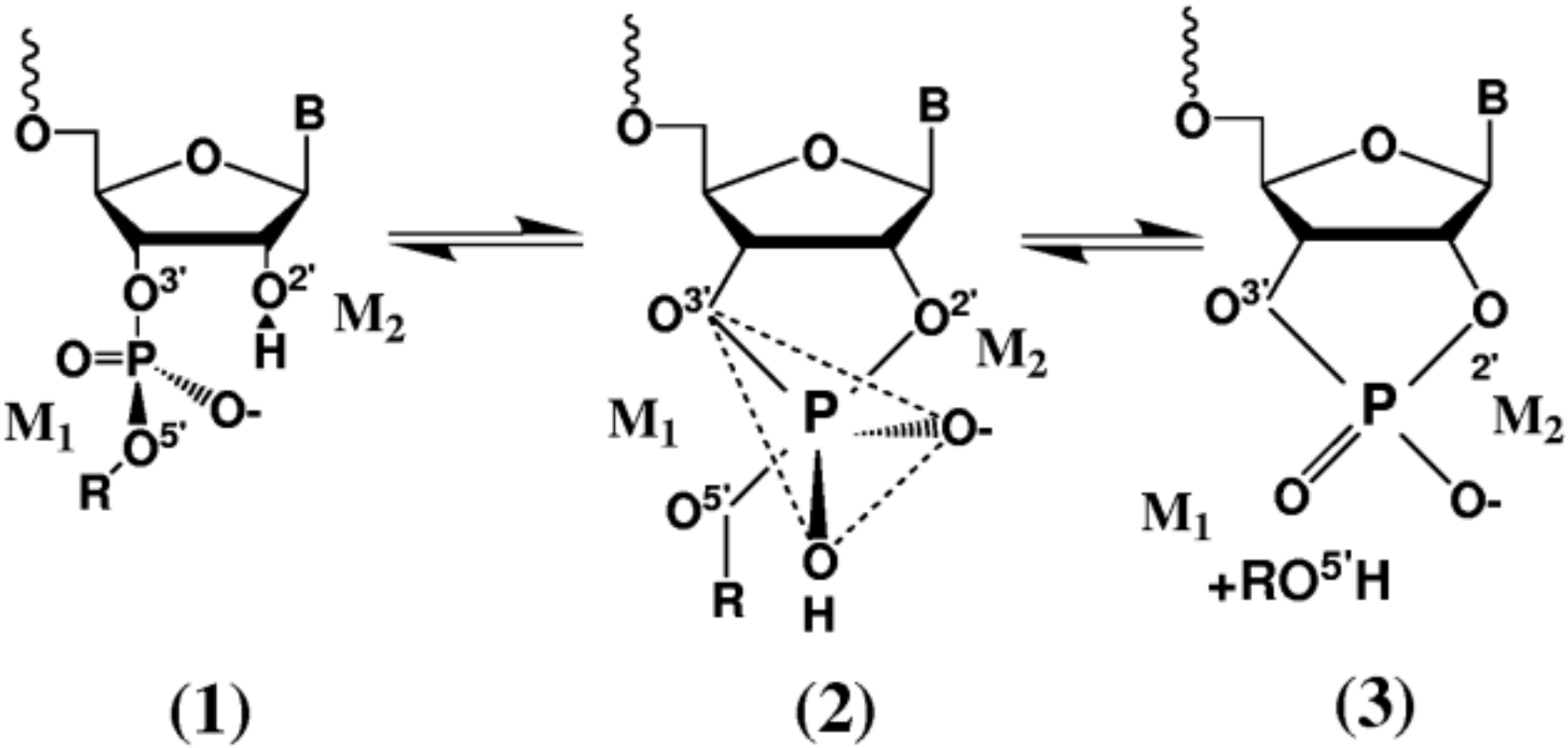
Reaction in the absence of metal ions



The catalytic role of Mg^{2+}: cleavage of the P-$O^{5'}$ bonds (the right reaction at a lower energy cost !)



Ribozymes reaction: known to be catalyzed by divalent metal ions

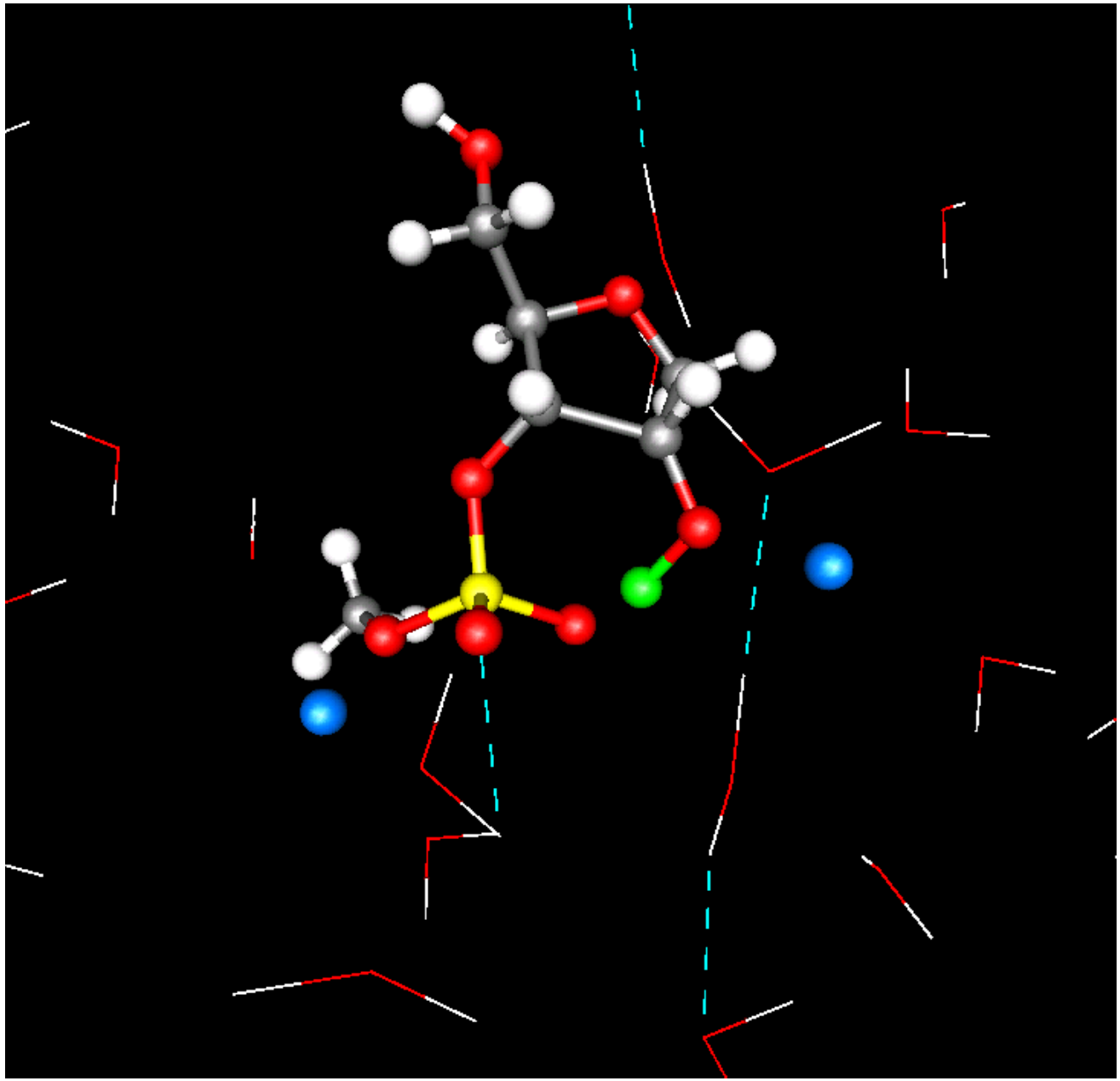


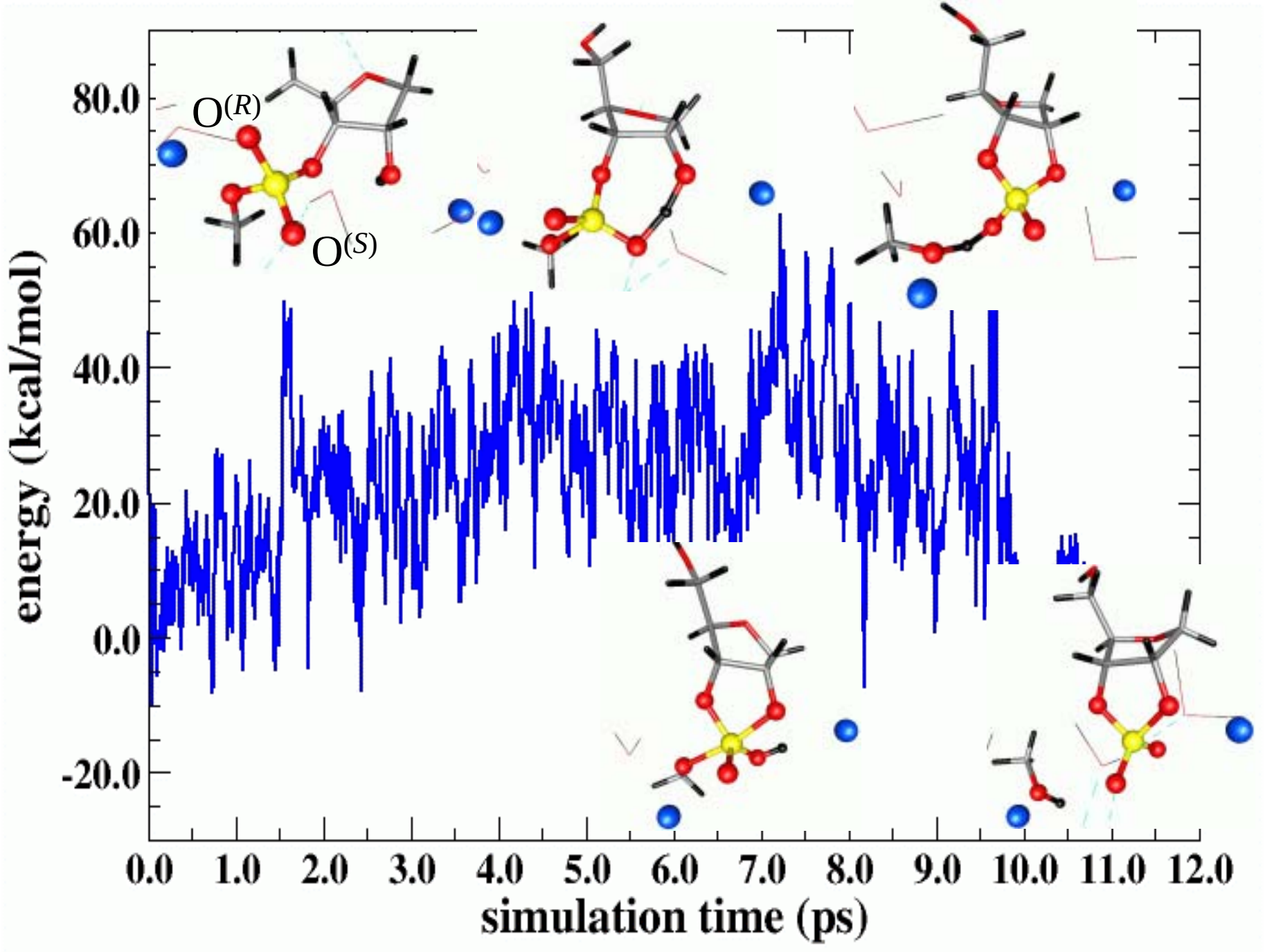
A. M. Pyle, *Science* **261**, 709 (1993**)**

K. Taira *et al*. *Nucleic Acids Res*. **30** ,2374 (2002)

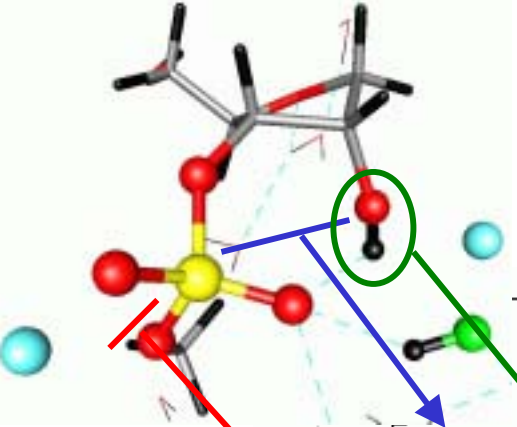
Evolution of the system under metadynamics

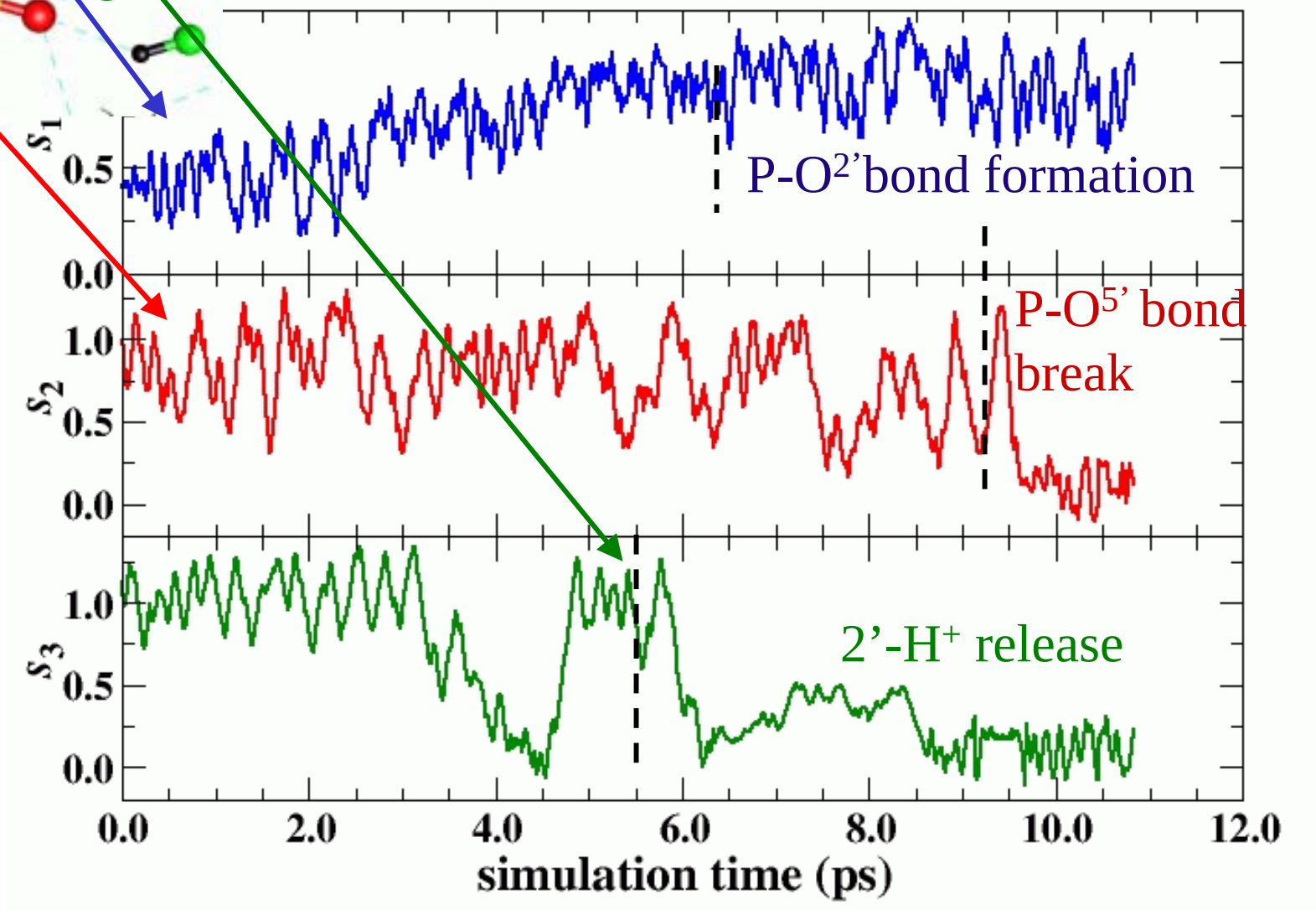
The proton of the –**O$^{2'}$**-**H** group is only temporarily transferred to RNA, but eventually is donated to the departing R-**O$^{5'}$** group




O(R)
O(S)
80.0
60.0
40.0
20.0
0.0
-20.0
energy (kcal/mol)
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
simulation time (ps)

Evolution of the collective variables during the metadynamics



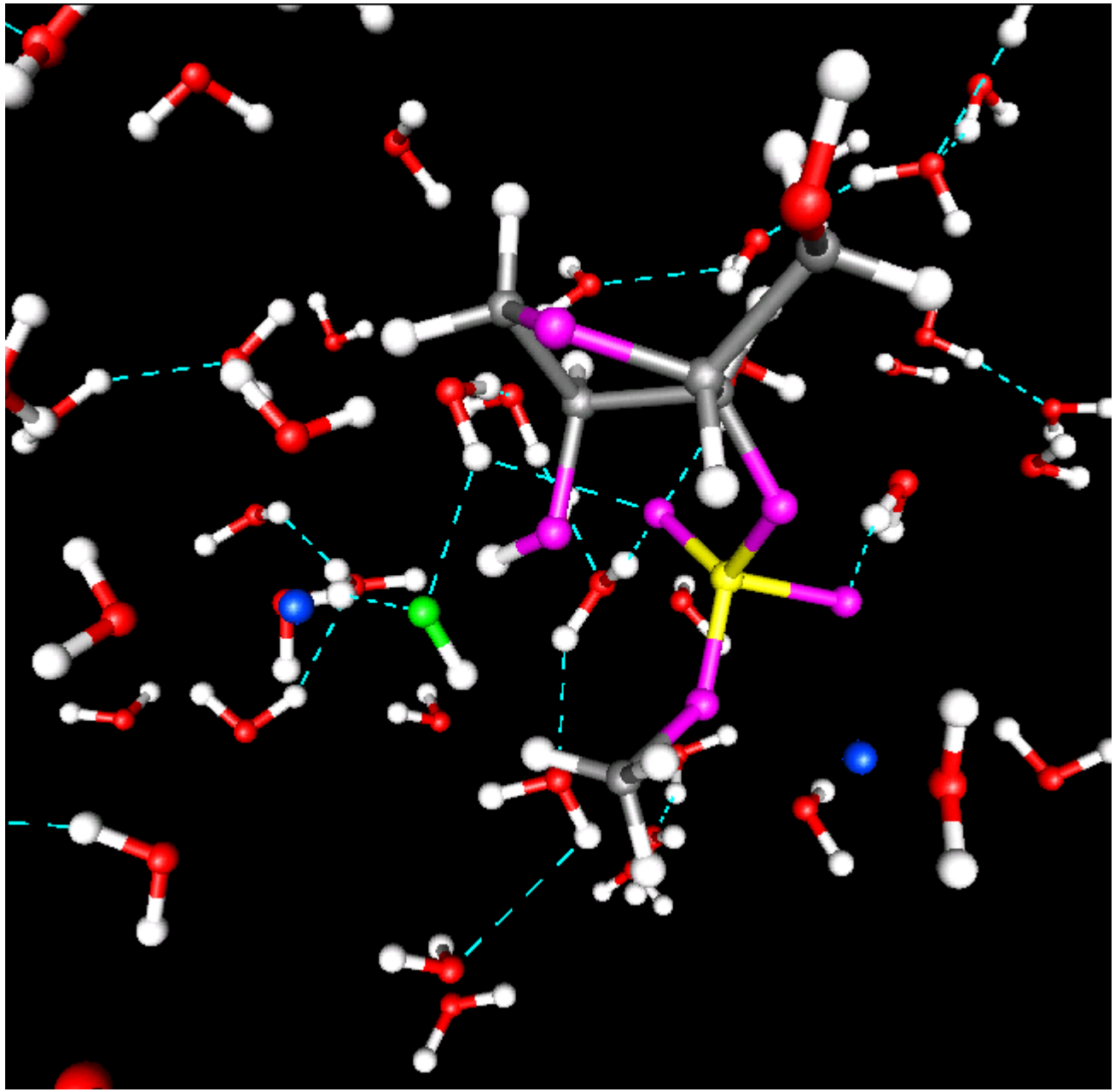


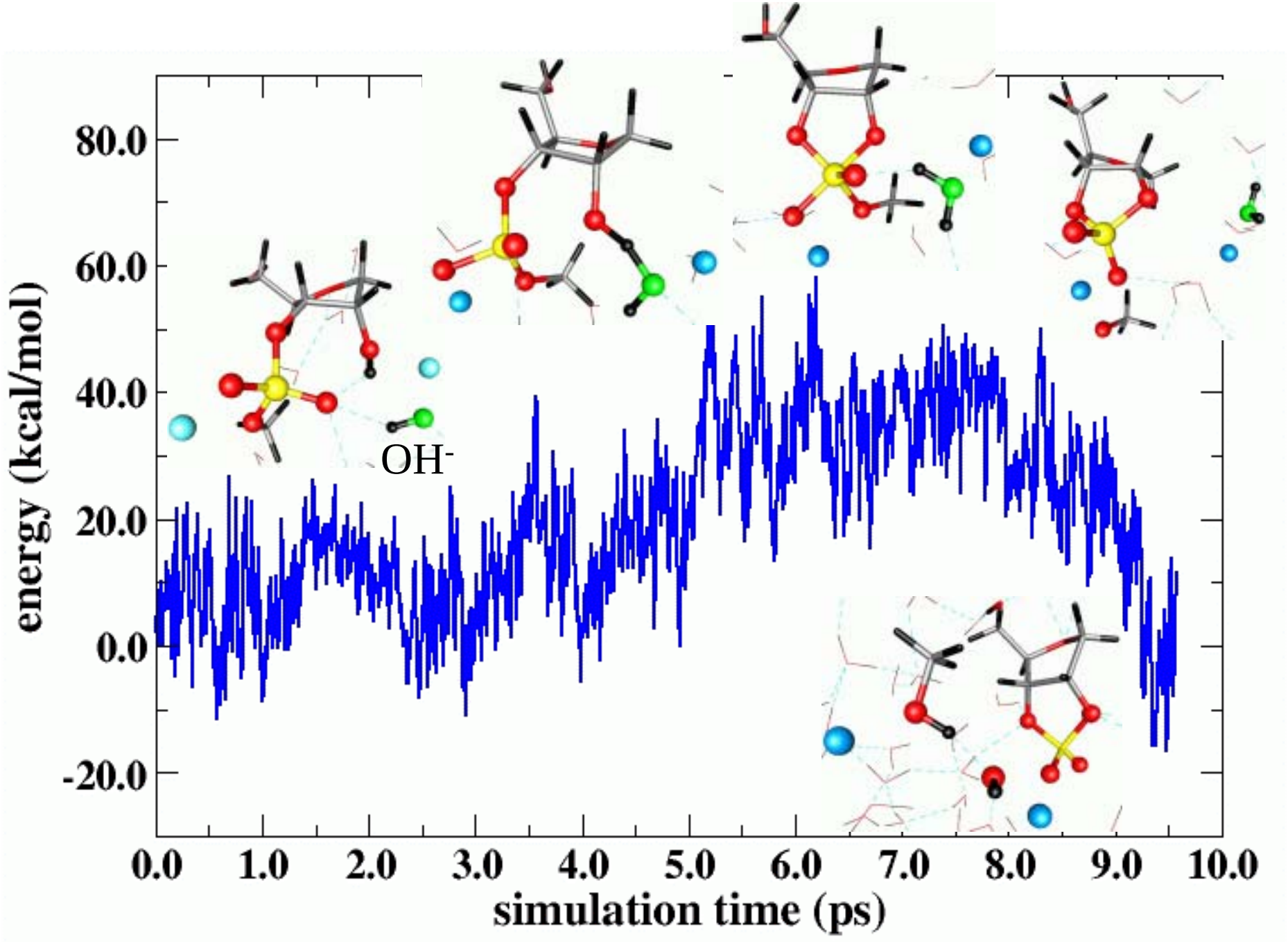
Role of OH^-

同じシステム

同じ反応

違うpH




80.0
60.0
40.0
20.0
0.0
-20.0
energy (kcal/mol)
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
simulation time (ps)
OH-

Activation barriers in solution for the different cases considered

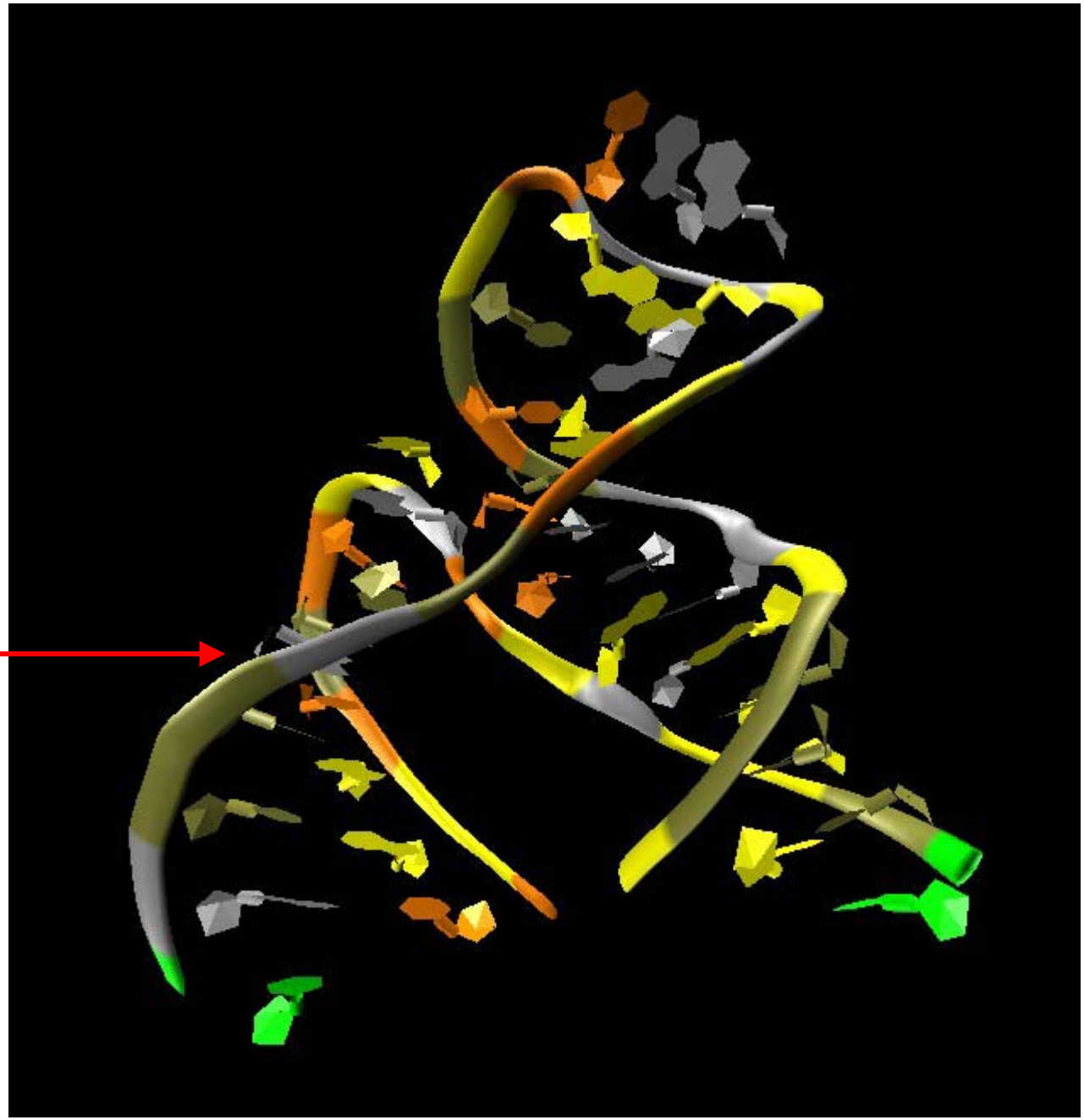
	No metal ions	One Mg^{2+} **(close to $O^{2'}$)**	One Mg^{2+} **(close to $O^{5'}$)**	Two Mg^{2+}	Anion solution +2 Mg^{2+} +OH^-
ΔE (kcal/mol)	60.1	57.3	55.2	46.5	43.8
ΔF (kcal/mol)	58.5	55.5	54.0	44.7	41.9

Error bar ~ 2.0 kcal/mol

Full Ribozyme (Hammerhead) in ribbon-like representation

(H_2O not shown for clarity !)

Catalytic site

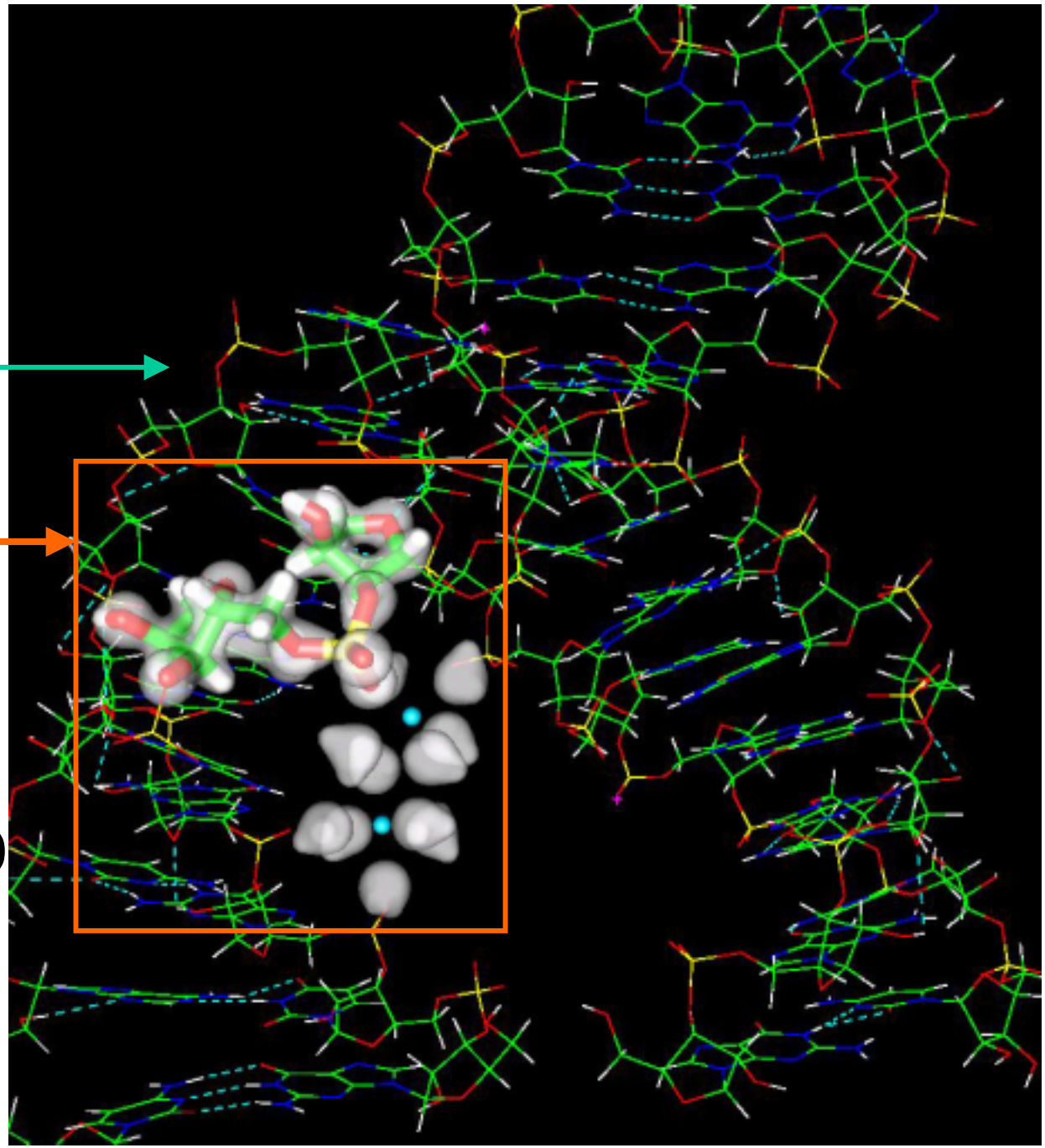


Hammerhead Ribozyme
(H_2O not shown)

MM system: the rest of the world

QM subsystem

This QM/MM system size can run on a PC cluster (16 PCs/2 CPU)



Conclusions and perspectives

- The cleavage and trasesterification mechanism of RNA has been studied for the first time at a first principles level
- A possible (mediated) proton transfer in metalloenzymes and the role of the two different divalent metal ion have been clarified
- The importance of an OH^- in the proton abstraction from $O^{2'}$-H and in the observed absence of H^+ transfer to the ribozyme been unraveled.
- With OH^- no H^+ transfer to either *pro-S* or *pro-R* oxygens occurs, but a formation of a water molecule, with the hydroxyl anion participating to the proton abstraction process

Related publications:
M. Boero, K. Terakura and M. Tateno, *J. Am. Chem. Soc*. **124**, 8949 (2002)
M. Boero, *AIST Today*, No. **11**, vol. **2**, pag. 17 (Nov. 2002) [in Japanese]