



Science & Technology Facilities Council

Daresbury Laboratory

Rare Events & Free Energy

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Introduction

Example



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Example

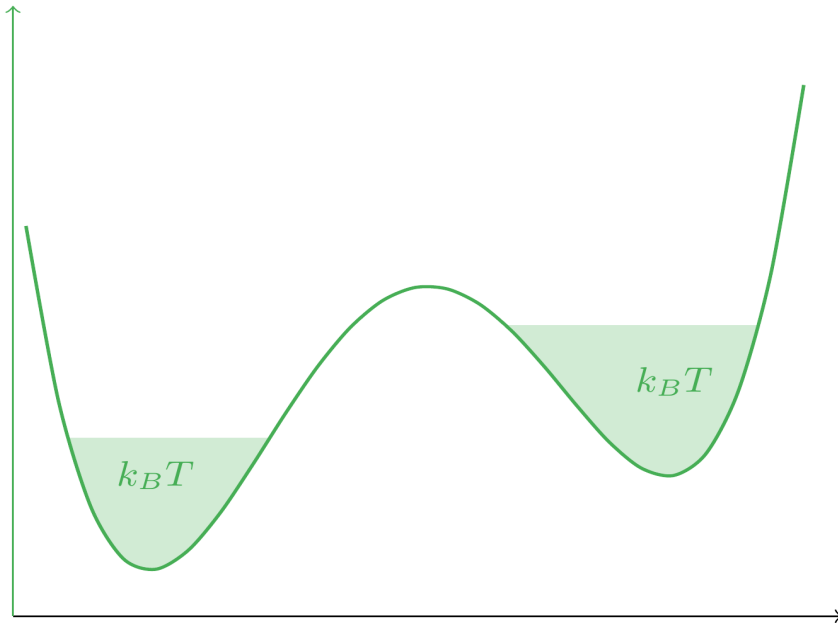


Why?

- ▶ Timescales of molecular dynamics - up to micro seconds with a timestep of 1 fs or less
- ▶ Disparity of timescales in simulated processes These are often dominated by rare events
- ▶ Rare but important events
 - ▶ conformational changes in proteins
 - ▶ some chemical reactions (weak acid deprotonation, ...)
 - ▶ nucleation processes
 - ▶ phase transitions
 - ▶ ...



...



the major bottleneck of simulation these events using traditional computer simulation methods is that the waiting time for a transition between two metastable states can be orders of magnitude longer than the time for the event itself.



How?

1. Reactive flux methods, two step approaches

- ▶ i) free energy profile, ii) transmission coefficient
- ▶ Umbrella sampling
- ▶ Potential of mean constrained force (PMCF)
- ▶ temperature accelerated molecular dynamics/monte carlo
- ▶ metadynamics

2. Path sampling methods, importance sampling of dynamical trajectories

- ▶ transition path sampling
- ▶ string methods
- ▶ Milestoning
- ▶ forward flux sampling



Small stat mech recap and MD

Let us consider a system of N atoms with the associated positions, $\mathbf{x} \in \mathbb{R}^{3N}$, and momenta, $\mathbf{p} \in \mathbb{R}^{3N}$. The dynamics of the system is governed by the Hamiltonian $H(\mathbf{x}, \mathbf{p}) = K(\mathbf{p}) + U(\mathbf{x})$

$$\frac{d\mathbf{x}}{dt} = \frac{\partial H}{\partial \mathbf{p}}; \quad \frac{d\mathbf{p}}{dt} = -\frac{\partial H}{\partial \mathbf{x}}$$

for ergodic dynamics

$$\overline{\mathcal{O}(\mathbf{x})} = \langle \mathcal{O}(\mathbf{x}) \rangle$$

$$\lim_{\tau \rightarrow \infty} \frac{1}{\tau} \int_0^\tau dt \mathcal{O}(\mathbf{x}(t)) = \int d\mathbf{x} d\mathbf{p} \rho(\mathbf{x}, \mathbf{p}) \mathcal{O}(\mathbf{x})$$



...

for a microcanonical ensemble, N, V, E

$$\rho(\mathbf{x}, \mathbf{p}) = \frac{\delta(H(\mathbf{x}, \mathbf{p}) - E)}{h^{3N} N! \Omega(N, V, E)}; \quad \Omega(N, V, E) = \int d\mathbf{x} d\mathbf{p} \delta(H(\mathbf{x}, \mathbf{p}) - E)$$

for a canonical ensemble, N, V, T

$$\rho(\mathbf{x}) = \frac{1}{\mathcal{Z}} e^{-\beta U(\mathbf{x})}; \quad \mathcal{Z} = \int d\mathbf{x} e^{-\beta U(\mathbf{x})}$$

to sample canonical ensemble, new equations of motion are needed,
Langevin, Nosé-Hoover...



collective variables

- ▶ collective variables(CV) microscopic observables that describe the process of interest, eg. chemical reaction
- ▶ order parameters: CVs that distinguish between initial and final state
- ▶ reaction coordinates CVs that describe the process along its path

mathematically they are functions

$$\theta(\mathbf{x}) : \mathbb{R}^m \rightarrow \mathbb{R}^n$$

with $m \leq 3N$



...

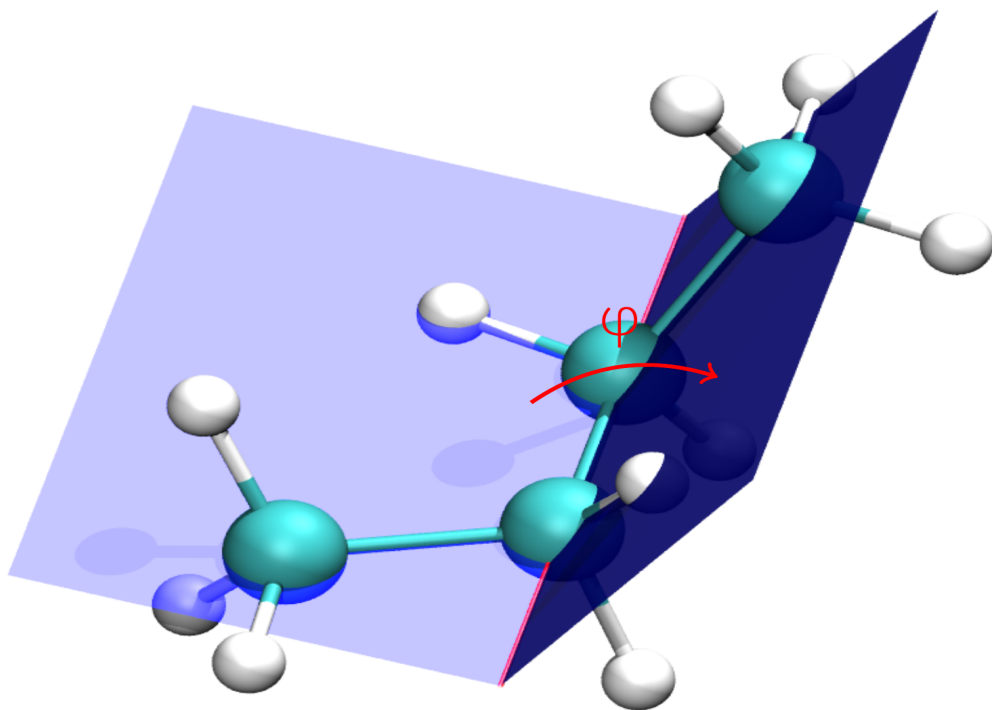
- ▶ $n = 1$, scalar collective variables, the most common case
- ▶ $n > 1$, vectorial collective variables

most common CVs:

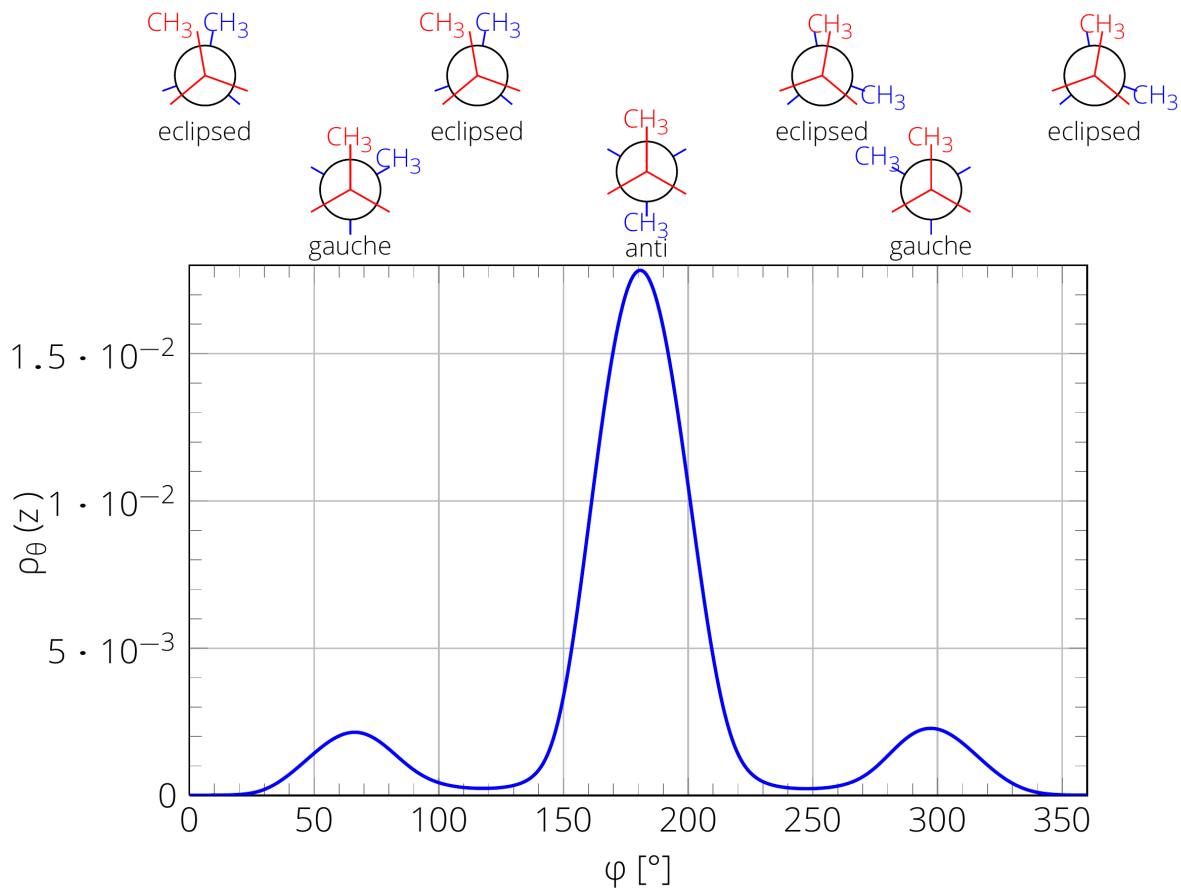
- ▶ bond distances
- ▶ angles
- ▶ dihedrals
- ▶ coordination number
- ▶ radius of gyration
- ▶ depending on the techniques used CVs may need to be differentiable



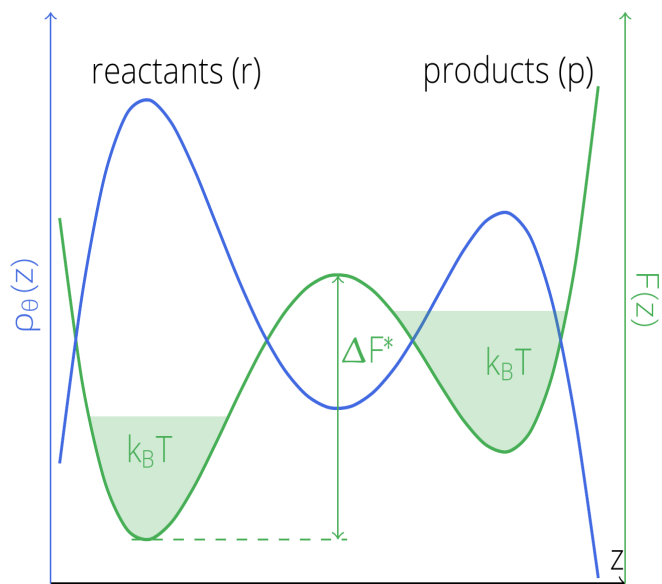
example - butane



example - ...



landau free energy



$$\rho_{\theta}(z) = \frac{1}{\mathcal{Z}} \int d\mathbf{x} e^{-\beta U(\mathbf{x})} \delta(\theta(\mathbf{x}) - z)$$

$$\mathcal{Z} = \int d\mathbf{x} e^{-\beta U(\mathbf{x})}$$

$$F(z) = -\frac{1}{\beta} \ln \rho_{\theta}(z)$$

$$F(z_B) - F(z_A) = \int_{z_A}^{z_B} dz \frac{dF}{dz}$$

$$\frac{dF(z)}{dz} = - \lim_{\beta k \rightarrow \infty} \frac{\int d\mathbf{x} k(\theta(\mathbf{x}) - z) e^{-\beta U(\mathbf{x})} e^{-\frac{\beta k}{2} (\theta(\mathbf{x}) - z)^2}}{\int d\mathbf{x} e^{-\beta U(\mathbf{x})} e^{-\frac{\beta k}{2} (\theta(\mathbf{x}) - z)^2}}$$

$$U_k(\mathbf{x}, z) = U(\mathbf{x}) + \frac{k}{2} (\theta(\mathbf{x}) - z)^2$$



references

- ▶ Mark Tuckerman - Statistical Mechanics: Theory and Molecular Simulation (Oxford Graduate Texts)
- ▶ Tony Lelièvre, Mathias Rousset and Gabriel Stoltz - Free Energy Computations A Mathematical Perspective

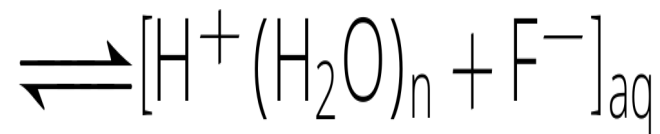
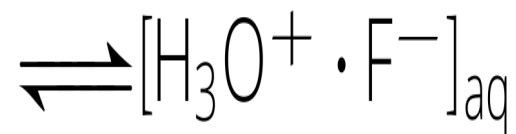
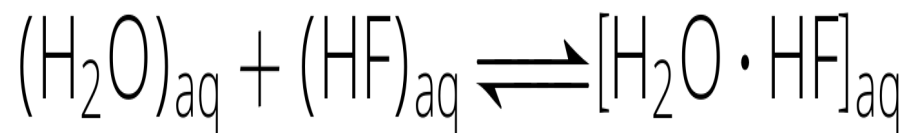


Introduction

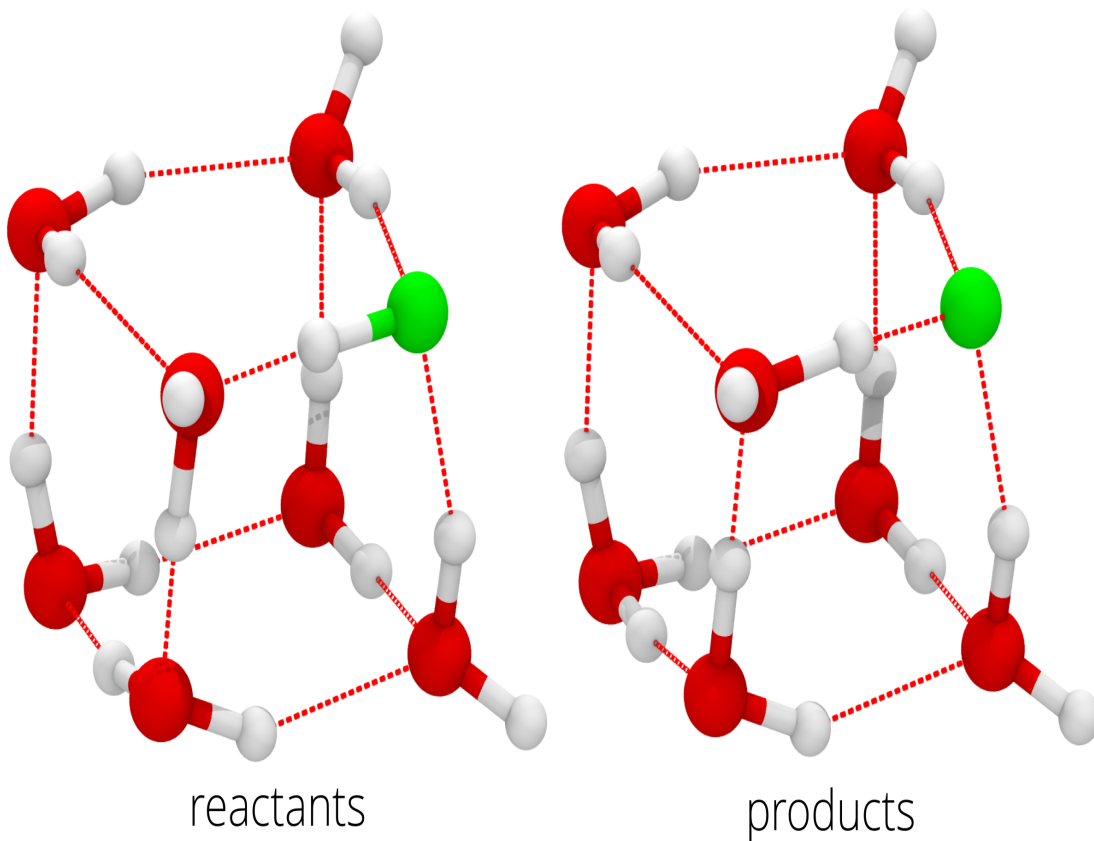
Example



HF deprotonation



Dissociation of HF in $HF(H_2O)_7$

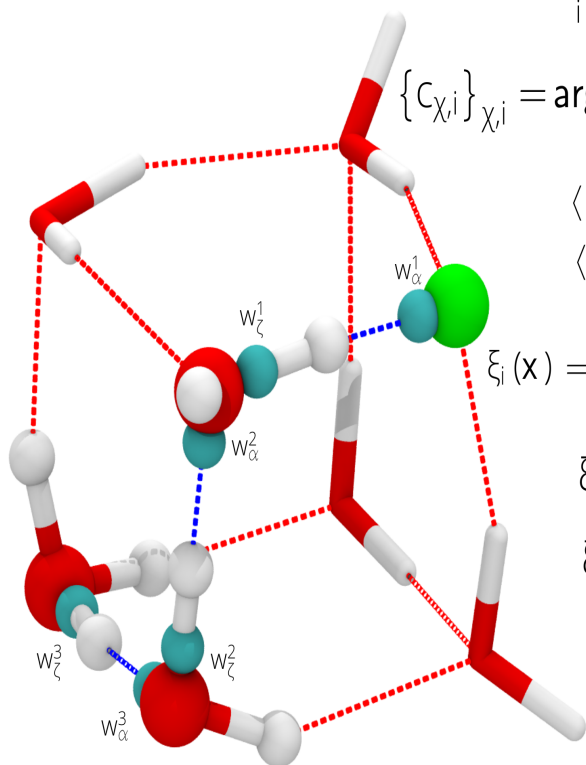


what would we like to know?

- ▶ equilibrium constant
- ▶ reaction mechanism
- ▶ reaction rate



CV



$$w_\chi(\mathbf{r}) = \sum_i c_{\chi,i} \phi_i(\mathbf{r})$$

$$\{c_{\chi,i}\}_{\chi,i} = \arg \min_{\{c_{\chi,i}\}_{\chi,i}} \sum_\chi \left(\langle w_\chi | \mathbf{r}^2 | w_\chi \rangle - \langle w_\chi | \mathbf{r} | w_\chi \rangle^2 \right)$$

$$\langle \mathcal{H}_{\text{KS}} \rangle_\alpha = \langle w_\alpha | \mathcal{H}_{\text{KS}}(\mathbf{x}) | w_\alpha \rangle$$

$$\langle \mathcal{H}_{\text{KS}} \rangle_\zeta = \langle w_\zeta | \mathcal{H}_{\text{KS}}(\mathbf{x}) | w_\zeta \rangle$$

$$\xi_i(\mathbf{x}) = \langle w_\zeta^i | \mathcal{H}_{\text{KS}}(\mathbf{x}) | w_\zeta^i \rangle - \langle w_\alpha^i | \mathcal{H}_{\text{KS}}(\mathbf{x}) | w_\alpha^i \rangle$$

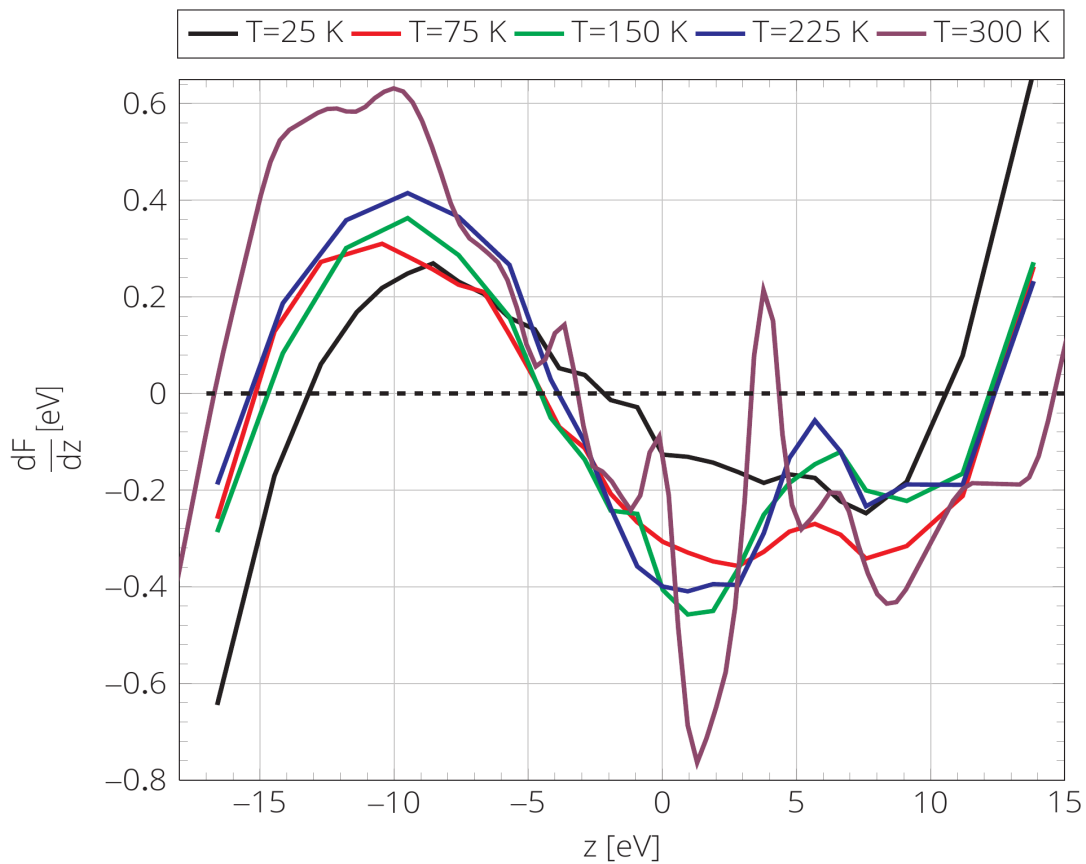
$\xi_i < 0$ covalent bond at α

$\xi_i > 0$ covalent bond at ζ

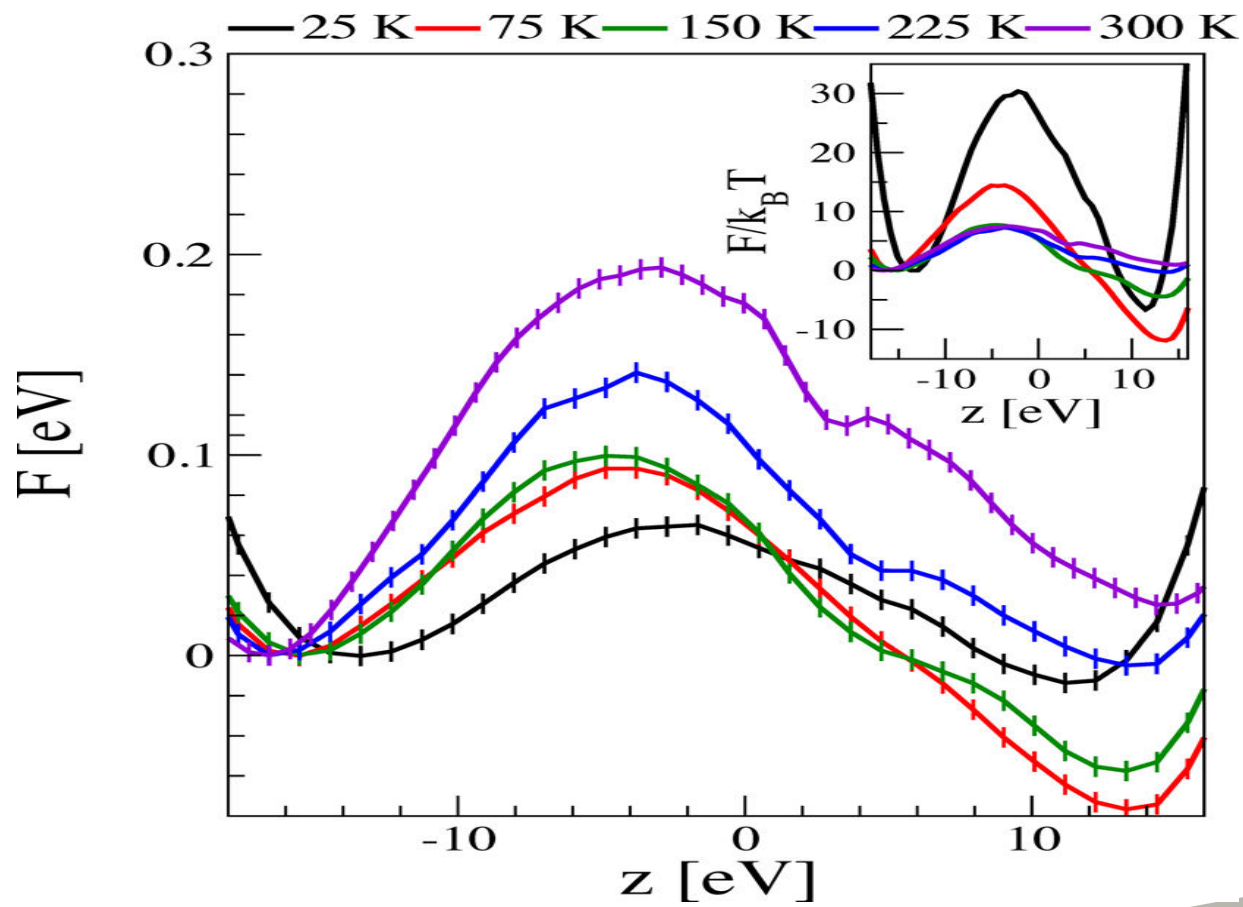
$$\theta(\mathbf{x}) = \sum_{i=1}^3 \xi_i(\mathbf{x})$$



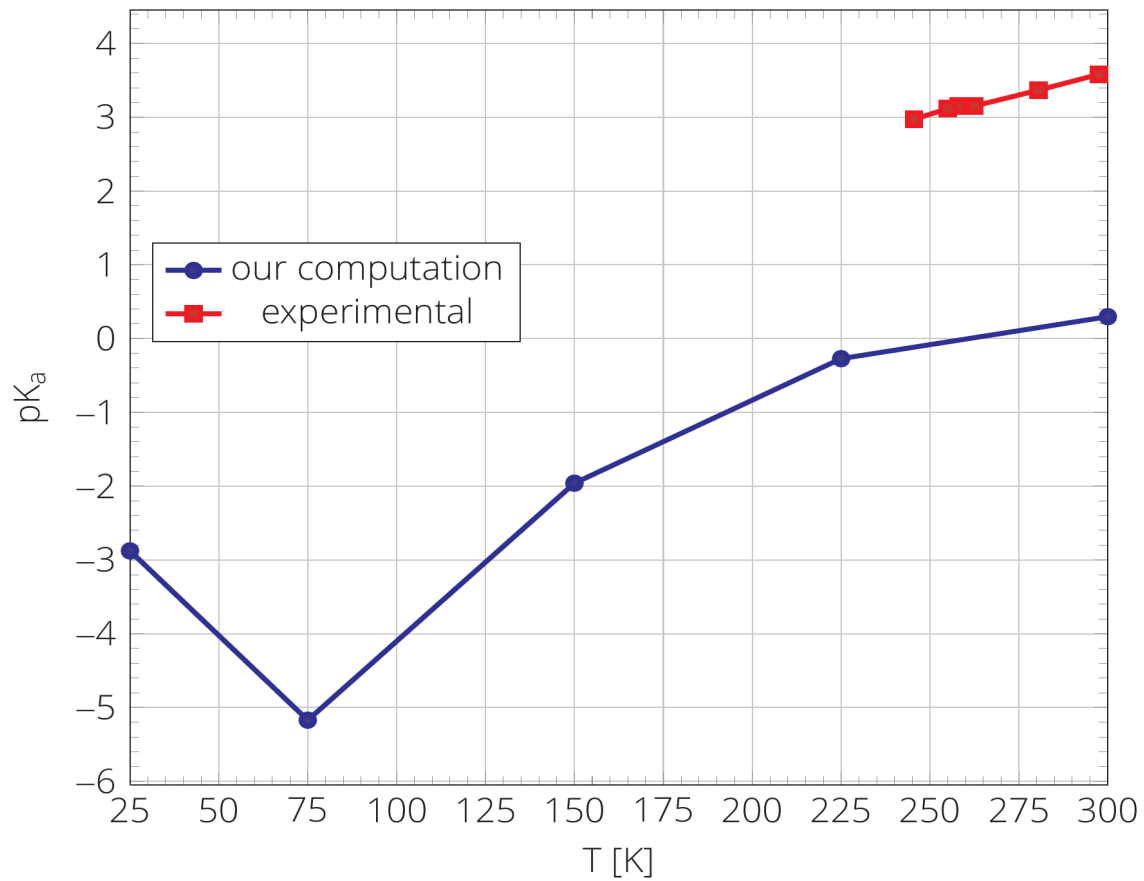
mean force



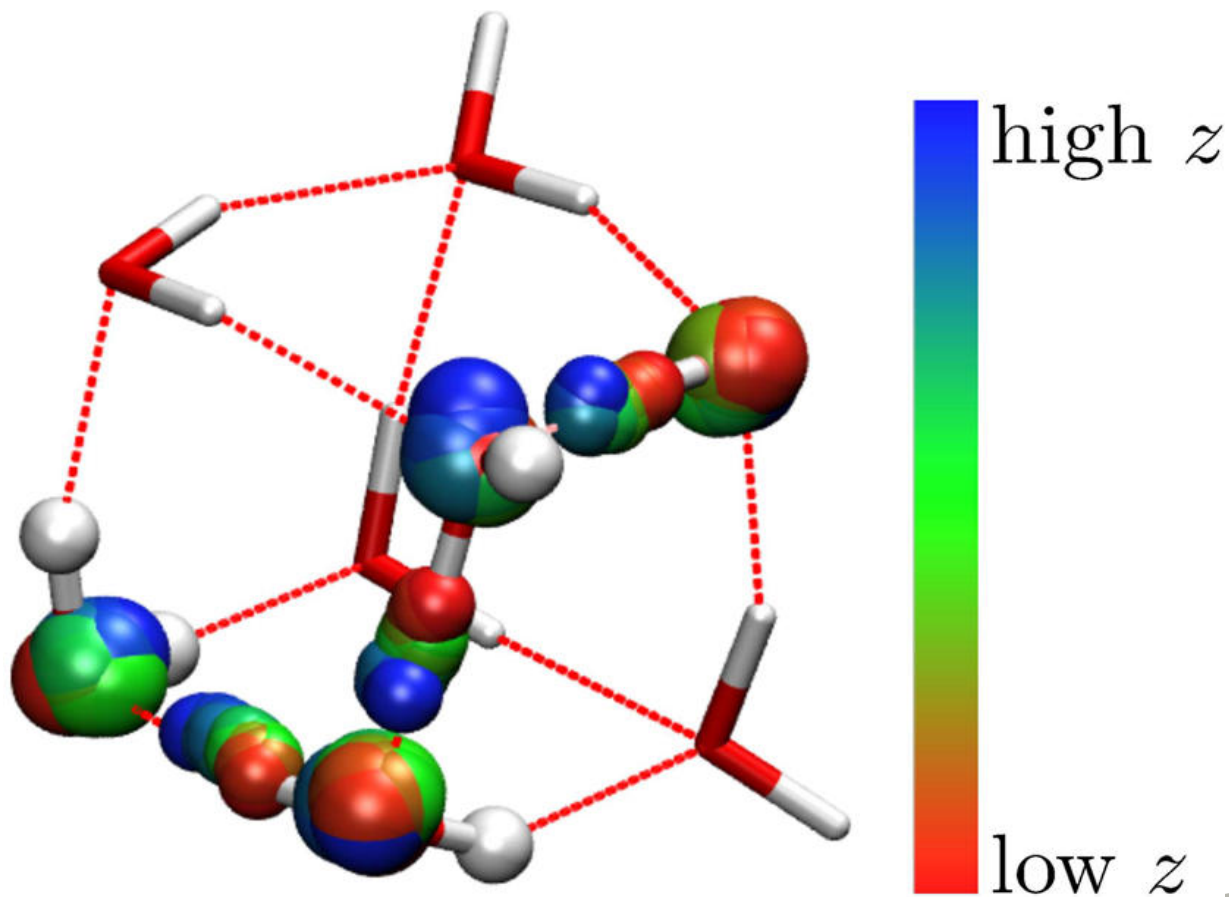
free energy profile



pKa



mechanism of reaction



more info

J. Phys. Chem. A 2013, 117, 49, 13039-13050, 10.1021/jp406982h

