

Calculations of free energy profiles with the quantum mechanical – molecular mechanical (QM/MM) potential energy functions using DFT approximations in the QM subsystem

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Estimates of free energy profiles from the first principles is computationally demanding due to:

- Extensive sampling of configuration space by using molecular dynamics (MD)
- Calculation of MD forces 'on the fly' from quantum equations

In practice, the potential of mean force (PMF) along the reaction coordinate is computed as follows

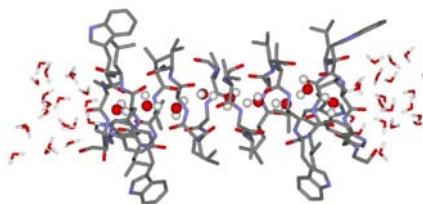
$$W(\xi) = W(\xi^*) - k_B T \ln \left[\frac{\langle \rho(\xi) \rangle}{\langle \rho(\xi^*) \rangle} \right]$$

$$\langle \rho(\xi) \rangle = \frac{\int d\mathbf{R} \delta(\xi[\mathbf{R}] - \xi) e^{-U(\mathbf{R})/k_B T}}{\int d\mathbf{R} e^{-U(\mathbf{R})/k_B T}}$$

where $U(\mathbf{R})$ is a potential energy function.

$U(\mathbf{R})$ may be evaluated by using the methods of electronic structure theory.

For extended biomolecular systems, the combined quantum mechanical – molecular mechanical (QM/MM) theory is a useful tool for modeling $U(\mathbf{R})$.



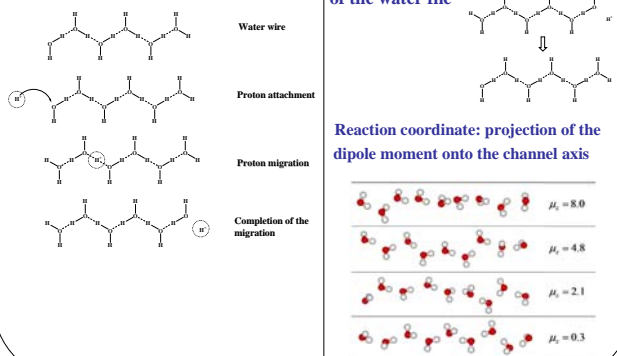
Here the ball-and-stick representation shows the QM-part of the system, in which energies and forces are computed by quantum equations, and the stick representation is used to show the MM-part, in which empirical potential functions are applied.

We apply the algorithms [1,2] of the rigid-body molecular dynamics to describe behavior of the MM-subsystem, which in our QM/MM version [3] is a flexible composition of effective fragments.

To estimate PMF for water re-orientation in the gramicidin channel we use:

- (1) constant temperature MD simulations for the canonical ensemble in conjunction with the Nose-Poincare thermostat [J Comp Phys 1999, 151, 114]
- (2) umbrella sampling technique [Comp Phys Comm 1995, 91, 275]
- (3) weighted histogram analysis method [J Comput Chem 1992, 13, 1021]
- (4) flexible effective fragment QM/MM technique
- (5) B3LYP/6-31G* approximation in the QM-subsystem
- (6) AMBER force field parameters in the MM-subsystem

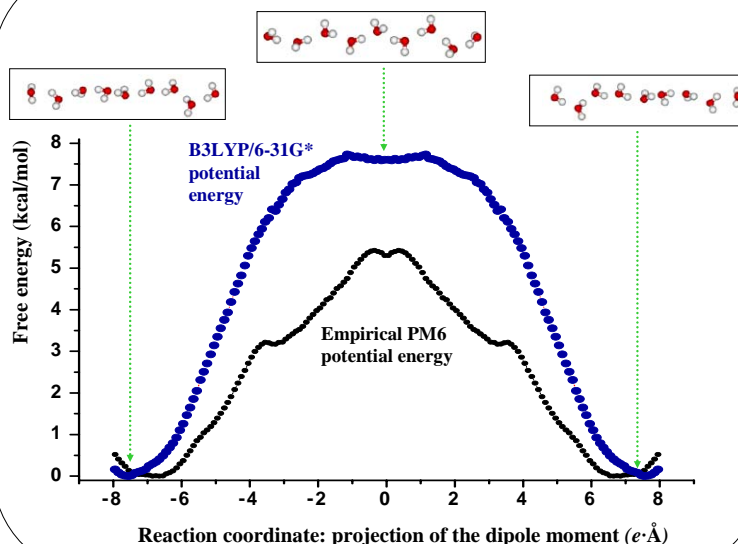
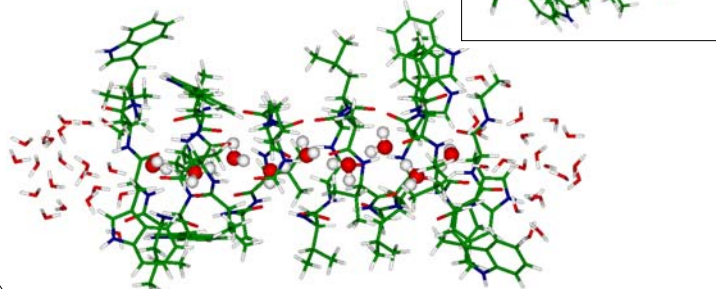
Mechanism of proton conductance in the gramicidin channel.....includes the stage of re-orientation of the water file



Molecular model for the gramicidin A channel

The transmembrane ion channel gramicidin A (gA) is a head-to-head dimer each unit of which consists of 15 alternating D- and L-amino acids: L-Val L-Gly L-Ala D-Leu D-Ala D-Val L-Val D-Val L-Trp D-Leu L-Trp D-Leu L-Trp D-Leu L-Trp.

The inner cavity is filled with nine water molecules. Additional water molecules are placed at the ends.



Summary

We present the results of potential of mean force (PMF) calculations with the non-empirical quantum mechanical – molecular mechanical (QM/MM) potential energy functions for the reorientation of the water file inside the gramicidin A ion channel. The chain of water molecules constituted the QM part is described by the DFT (B3LYP/6-31G*) approximation. We obtained the activation free energy barrier of 7.7 kcal/mol in excellent agreement with experimental studies.

References

1. Moskovsky A., Vanovschi V., Konyukhov S., Nemukhin A. Intern. J. Quantum Chem., 2006, 106, 2208.
2. Akimov A., Nemukhin A., Moskovsky A., Kolomeisky A., Tour J. J. Chem. Theory & Comput., 2008, 4, 652.
3. Nemukhin A., Grigorenko B., Topol I., Burt S. J. Comput. Chem., 2003, 24, 1410.