

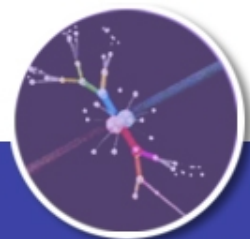
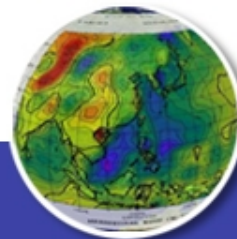


Applicability of Free Energy Calculations using High-Throughput Grid Approach

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Outline



- **Analysis purpose**
- **Free energy calculations**
 - Adaptive Biasing Force (ABF) methods
 - Multiple Walkers Approach (MWA)
- **Studied molecular system**
- **Utilized infrastructure**
- **Results and future prospects**

Purpose of the analysis

- **Feasibility of study**
 - to evaluate the applicability of novel free energy calculations technique
 - to investigate possibility of deployment and run of high-throughput chemical applications
 - to provide a test case before a massive utilization of large-scale application runs
- **Simultaneous testing of available infrastructure under EUAsia virtual organization**

Free energy calculations



- **Free energy (FE)**
 - important quantity to describe properties and dynamic behavior of (bio)molecular systems at atomic level
 - **chemical kinetics**
 - how fast chemical reactions proceed
 - detailed reaction mechanism
 - **thermodynamics**
 - self-organization of molecular structures

Free energy calculations



- **FE use and determination**
 - used to study where and how molecules interact, key for pharmacology, nanotechnology, medicine, ...
 - FE is calculated using statistical thermodynamics
 - many computational approaches developed
 - most promising **Adaptive Biasing Force** (ABF)
 - other methods
 - Metadynamics
 - Umbrella sampling

Free energy calculations



- **Calculations have to result in energy profiles with absolute error of about cca 1kcal/mol**
- **To provide reliable and converged data **extremely long simulations** are required**
- **Critical factors for FE run evaluation**
 - simulation length
 - satisfactory sampling allowing appropriate exploration of conformational space (formed by atomic coordinates)

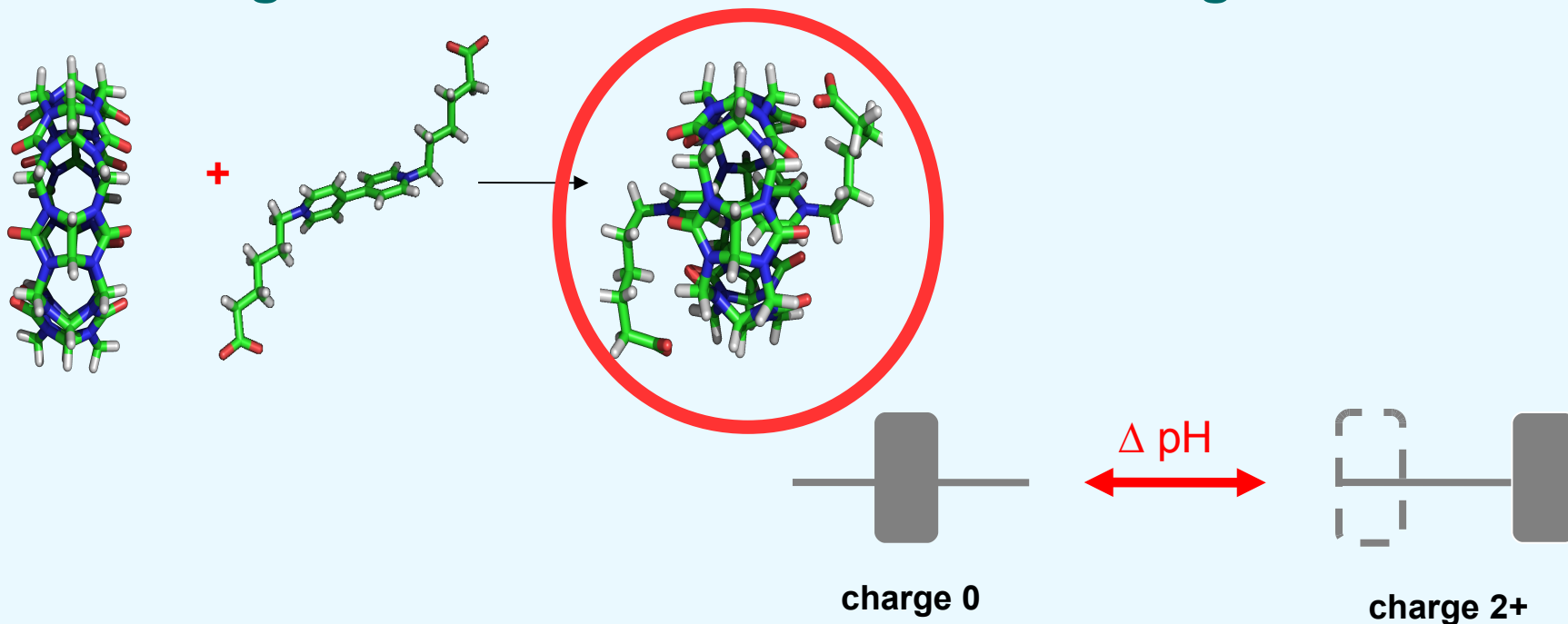
Free energy calculations



- **How to shorten, precise, and accelerate free energy computations?**
- **Multiple Walkers Approach (MWA)**
 - parallel runs (so-called walkers) starting from the same or different structural conformations
 - simulations will diverge and this increase the efficiency of the search in conformational space

Purpose

- To describe the pH dependent switch emerging in **pseudorotaxane complex**
- Energetic evaluation of different binding modes

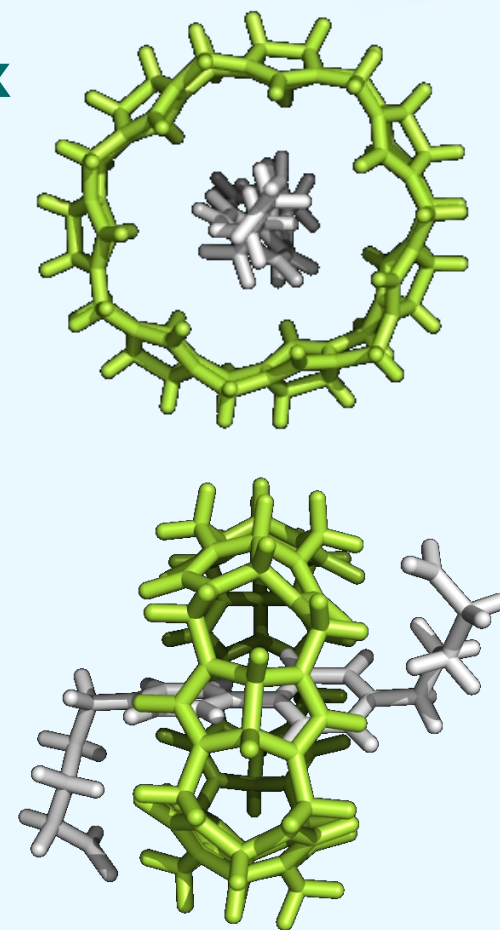


System composition

- Pseudorotaxane is a stable complex where the wheel like molecule is threaded on an axle like molecule
- The wheel is prevented from dissociation due to energetic reasons

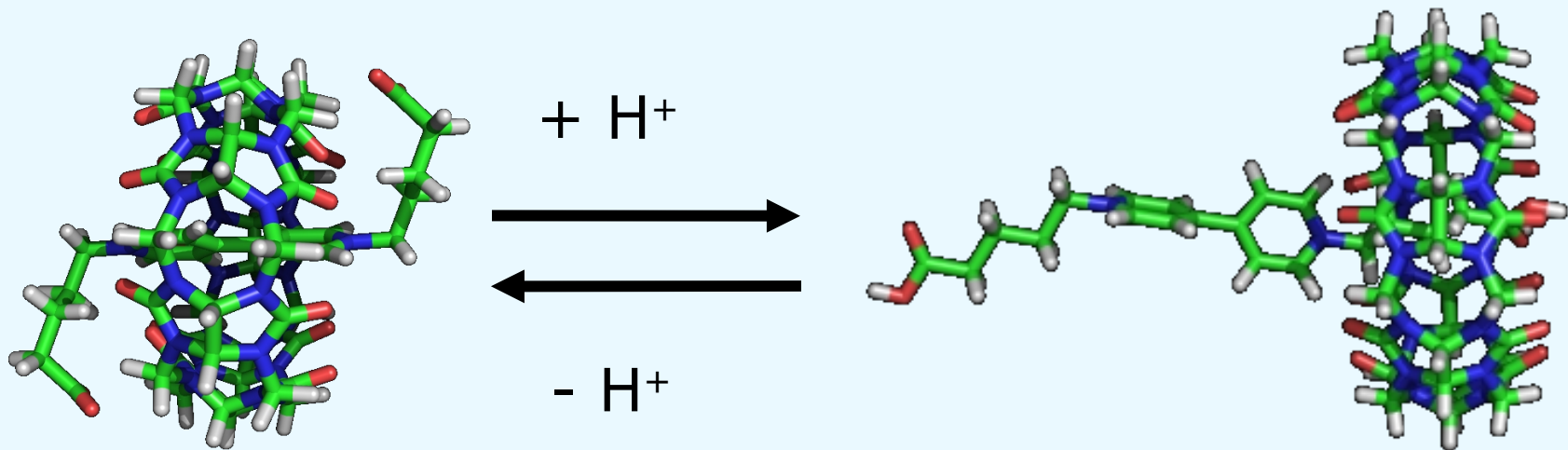
Wheel cucurbit[n]uril

Axle 4,4'-bipyridinium based



Studied system

- Pseudorotaxane-based switch mechanism



- **MWA implementation**
 - **server and clients system**
 - independent clients run for short time exploring individual parts of total free energy hypersurface
 - intercommunication with server for data accumulation
 - server has to communicate with all clients during the whole time period of calculation, server must be fully functional all the time
 - useful to have server running outside the dynamic „not-always-reliable“ grid environment

Utilized environments

- **All computation performed within EUAsia VO**
- **EUAsia virtual organization (VO)**
 - regional, catch-all virtual VO
 - generic, application neutral
 - supporting testing of developed applications before large-scale deployment
- **Inter grid communication**
 - MWA clients running in EUAsia VO
 - MWA server running outside the EUAsia VO to ensure stable and reliable accumulation of clients data

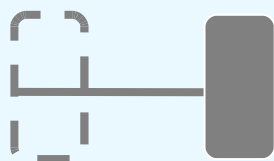
Results



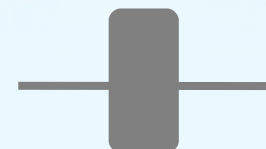
- **Successful implementation and testing** of the MWA scheme in combination with ABF method to the Grid environment
- **Client computations processed in EUAsia VO**
- **MWA server running at MetaCentrum (Czech National Grid Environment)**
- **Current methodology enables nearly linear speed up**
- **Usability within generic grid environment was proven**

- **Simulation Details**
 - 25 ns of molecular dynamics simulations
 - 2 different starting conformation of the complex
 - 50 independent walkers for ABF MWA
 - ABF calculation was **nearly 50 times faster** compared to conventional ABF run
 - cca 50 ns of simulations process in 3 days
 - standard run usually 1 ns ~ 3 days

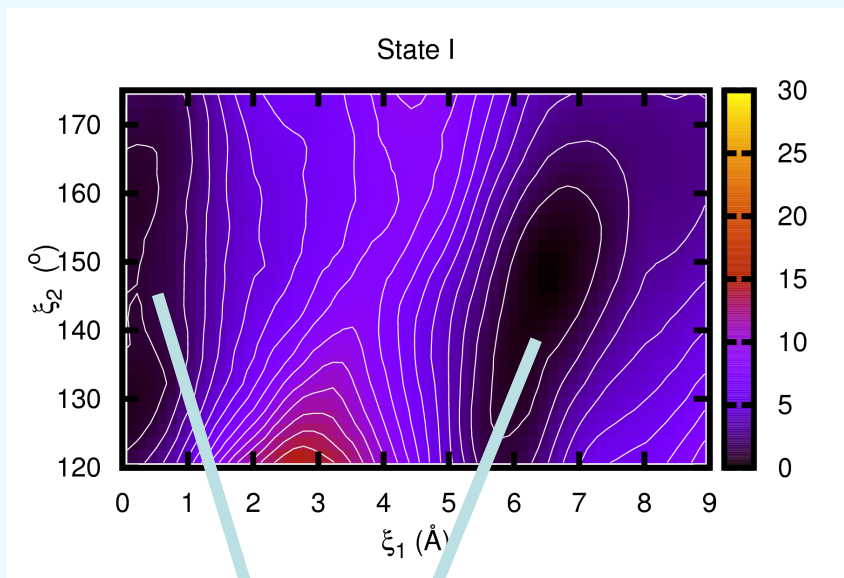
Results



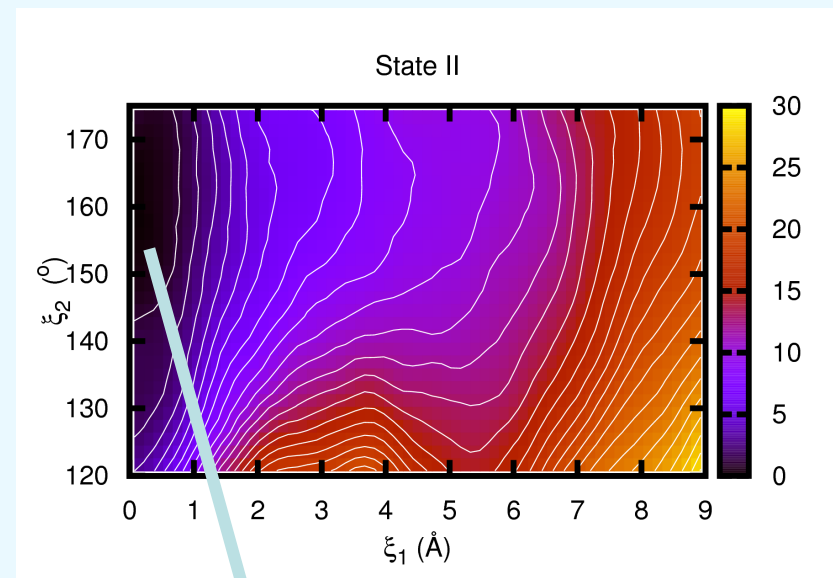
charge 2+



charge 0



Two equal minima



Global minimum

15

- **Issues to be considered**
 - **security of communication** between individual clients
 - utilization of plain password authentication to be substituted by an SSL encrypted communication
 - bottleneck in the utilization of the **one and only server**
 - during server failure all accumulated data would be lost
 - plan to utilize more mutually interconnected servers
 - smaller communication bandwidth
 - minimization of data loss as the accumulated data due to duplication among the servers