A57 Molecular Dynamics Simulation of Peptides

Group:
Betreuerin:

April 20, 2024

This experiment provides an introduction to force field methods as well as molecular dynamics simulations using the example of peptides, through which knowledge about the structure and stability of biomolecules can be gained.

1 Theoretical Background

1.1 Empirical Force Fields

Molecular mechanic force fields help to reduce the complex movements, bonding ability and energies of large biomolecules into physical terms, which are usable for simulations.
There are bonding and non-bonding terms. The bonding terms include Bond lengths which are similar to the Hooke's spring and can be described by

$$V(r) = \frac{1}{2} \cdot k(r - r_0)^2, \tag{1}$$

with potential V, spring constant k, bond length r and equilibrium bond length r_0.
Another bonding term are the bond angles which use bond angles θ and other parameters for k and θ_0.

The last bonding term is the dihedral angles, it describes the rotation of two atoms around a bond.

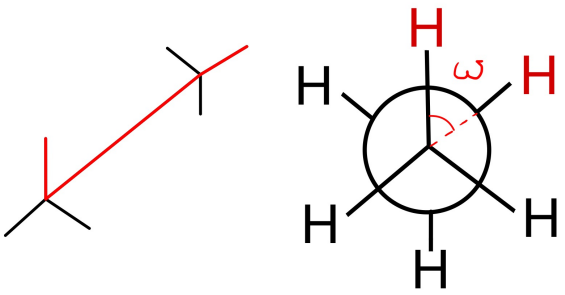


Figure 1: Dihedral angle ω in ethane

The angle ω is periodically every 360°. Therefor it is described as a cos function with a maximum of energy at 0° and a minimum at 180°. The equation is

$$V(\omega) = \frac{1}{2} \cdot V_0 \cdot cos(n\omega) \tag{2}$$

with V_0 as rotational barrier and n as the multiplying factor of how often the same energy barrier occurs.

The two non-bonding terms that are relevant are the Coulomb interactions and the Van-der-Waals interactions. The Coulomb interactions are partially positive or negative charges which are a lot weaker than the bonding terms the difference between a neutral and partially charged atom is used to get a potential, with the formula:

$$V(r) = \frac{1}{2} \cdot \sum_{ab} \frac{\Delta q_a \cdot \Delta q_b}{r_{ab}}. \tag{3}$$

The Van-der-Waals interactions are weakly bonding complexes, they don't form chemical bonds but temporarily induced dipoles. There is an equilibrium between the London dispersion and the Pauli repulsion. The sum is described by the Lennard-Jones potential:

$$V(r) = 4\varepsilon \cdot ((\frac{\sigma}{r})^{12} - (\frac{\sigma}{r})^6). \tag{4}$$

The potential of a molecule is then the sum of all potentials of all atoms in the molecule. The structure is described with a vector for each atom. The change of the potential is described as the derivative of energy in one direction. For the force at the current coordinates, the potential energy has to be differentiated (gradient of energy):

$$\vec{F_a} = -grad(E_{pot}) = -\begin{pmatrix} \frac{\partial E}{\partial x_a} \\ \frac{\partial E}{\partial y_a} \\ \frac{\partial E}{\partial z_a} \end{pmatrix} \tag{5}$$

1.2 Geometry Optimization

Geometry Optimization are used to find the structure with the lowest energy. The point is found by following the potential gradually downwards until a minimum (really small energy changes per step) is found. The two problems that can occur are finding a saddle point, or finding a local instead of the global minimum.

1.3 Molecular Dynamics Simulations

Molecular Dynamics Simulations (MD) is used for simulating molecules under specific factors (e.g. temperature, under force,...). The calculated energy's are used to derive a force from which it is possible to model the structure after a Δt. Thereby Δt as to be as short as the fastest movement(here vibration), so a time step has to be shorter then 1 fs. Because MD is used to look at real processes there are a number of requirements.
First, all coordinates and velocities must be known. Second a method is needed which can calculate each new structure at every time step. For this the Velocity-Verlet Method is used. It is based on a free throw an can be calculated with:

$$x(t + \Delta t) = x(t) + v(t) + \frac{1}{2}(a(t) + \Delta t)^2, \tag{6}$$

for a the the equation of Newton's second law $a = \frac{F}{m}$ is used. For the next step the velocity is calculated as:

$$v(t + \Delta t) = v(t) + \frac{1}{2} \cdot (a(t) + A(t + \delta t)) \cdot \Delta t \tag{7}$$

These equations are the essential part of the Velocity-Verlet-Algorithm which is used in most MDs.
The last requirement for a successful simulation is to control the temperature, in this case with the Berendsen Thermostat. In this process the velocity of the atoms is rescaled to get a realistic simulation. to get realistic temperature jumps the velocity is changed ofer larger periodes of time. The Berendsen Thermostat

does exactly that, by introducing the consatant τ into the equation:

$$\frac{dT}{dt} = \frac{1}{\tau} \cdot (T_0 - T(t)). \tag{8}$$

T_0 equals the desired Temperature.
This methode causes the velocitys to not get unrealistic high and the results stay logical to work with.

2 Implementation and Observation

2.1 Polyalanine in the optimized geometry

In the first part of the experiment the Alanine molecule is plotted and the systematic names for the atoms are shown (the Names are generated by the program), this is displayed in figure 2.

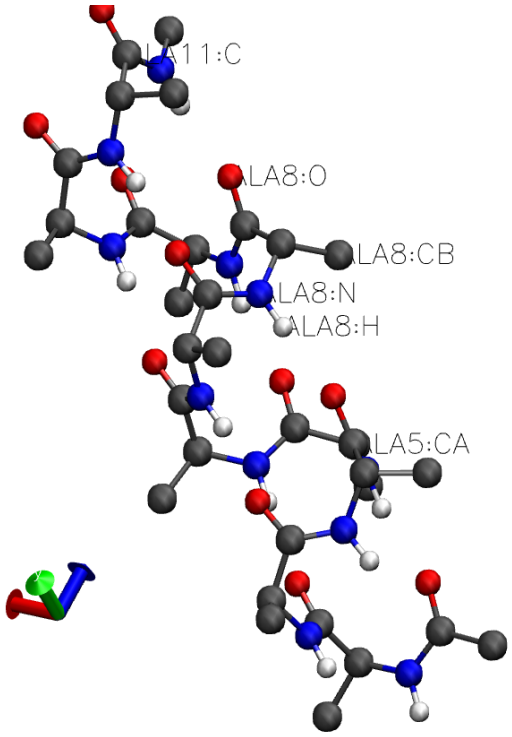
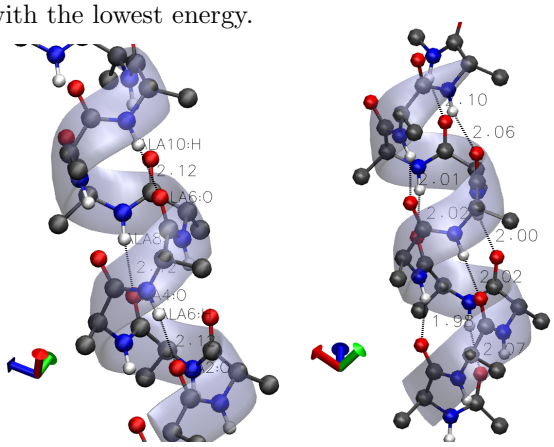


Figure 2: Alanine with names for the Atoms

The different names for the C-atoms are C, CA and CB to differentiate between their positions in one Alanine substructure. The atom with the name "C" bonds with one N and one O and is sp^2 hybridized. "CA" is one place further in the chain and bonds with "C", "CB", H and N. Therefor it is sp^3 hybridized. "CB" is only connected with "CA" and (for us relative unimportant) H, therefor is is also sp^3 hybridized. The simulation differentiates between these three because they have different functions for the Alanine.
In figure 3(a) the α-helix-structure is illustrated, also the length of the hydrogen bonds are depicted, their value is 2.12 Å. But figure 3(a) only shows typical values for such bonds. Figure 3(b) is the realistic Alanine with the lowest energy.



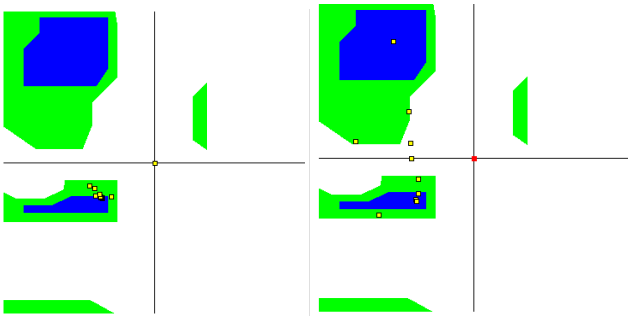
(a) typical (b) realistic

Figure 3: hydrogen bond length

It's noticeable, that the bond length decreases for the lower energy form. Also the bond lenghts haven't the same value anymore. For middle bonds the value is lower because there is a higher concentration of hydrogen bonds than at the ends of the molecule.

2.2 Polyalanine at room and higher temperature

To determine the structure and stability of Alanine by various temperatures a Ramachandran-plot can be generated. The x-axis describes the φ-angle and the y-axis the ψ-angle. The relation of the angles correlates with the structure of the molecule. Figure 4 shows the Ramachandran-plot for Alanine.
The yellow points represent one of the Alanine segments in the Polyalanine. Dependent on the quadrant the point is in (and with it the relation of the dihedral angles), the molecule performs an α-Helix or an β-sheet structure in this Alanine piece. The second quadrant displays the β-sheet form, the third the α-Helix. The other two quadrants are irrelevant for this experiment. In figure 4(a) the points are all in the α-Helix quadrant, therefor the molecule exists in this structure. In conclusion the molecule is by 300 K stable in the α-Helix form.



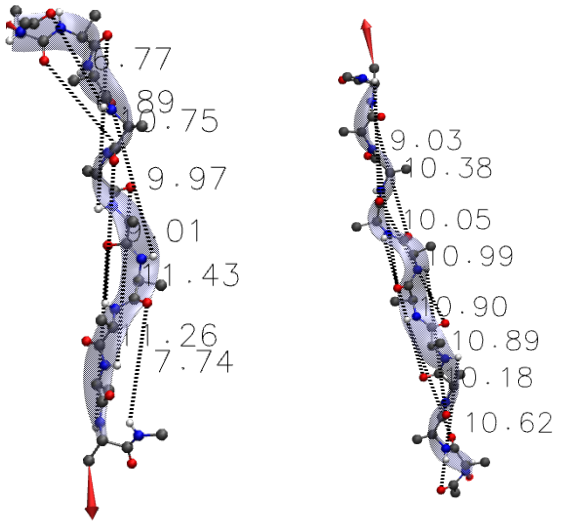
(a) 300K (b) 500K

Figure 4: Ramachandran plot

Figure 4(b) on the other hand shows the Alanine by 500 K after 53000 fs. This is the time needed for the Analine in α-Helix structure to decompose (visible by the points scattered out of the third quadrant). The points move to the second quadrant, which is dedicated to the β-sheet structure.

2.3 Simulation of stretched peptide

In the next step of the experiment forces are applied at both ends of the molecule to stretch it. By stretching it the molecule transforms from the α-Helix in to the β-sheet structure.
In figure 5 the stretched molecule is shown: 5(a) directly after the transformation into β-sheet and 5(b) after a while then the molecule is stretched widely. It takes approximately 770000 fs to convert the molecule



(a) 7700000 fs (b) 931000 fs

Figure 5: stretched Alanine

In figure 6 is thr potential energy over the time during the simulation shown.

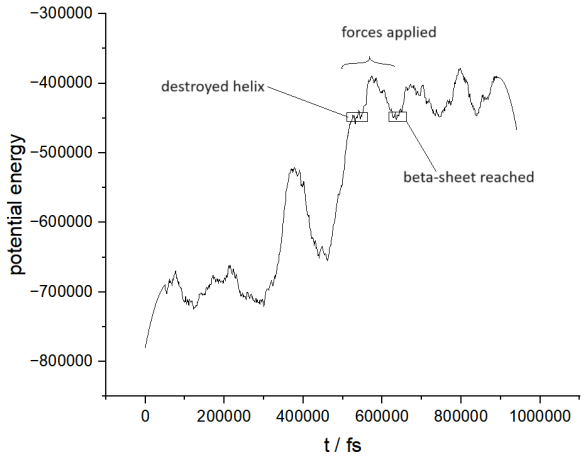


Figure 6: potential energy of Alanine over the simulation time

In the diagramm are the points marked, that shows then the α-helix is destroyed, the fores are applied and the β-sheet is reached.

3 Discussion

The fundamental difference is the application of the methods. The geometry optimization is used to find the molecule structure with the lowest potential energy. On the other hand the MD simulation is used to simulate the molecule under different conditions other time. With the MD simulation the potential energy of a molecule and its structure under real circumstances can be simulated.
The experiment shows that at higher temperatures, molecules irreversibly change their structure. That's because of the energy that the molecules absorb from the added heat, they move faster, and their hydrogen bonds break and re-bind in a different way.
The thermodynamic driving force of the α-helix is the gibbs energy. In formular (9) is shown, that the Gibbs energy decreases with higher temperature because of the last section.

$$\Delta G = \Delta H - t \cdot \Delta S \tag{9}$$

The Gibbs energy becomes negative $\Delta G \leq 0$. The destruction of the α-helix and forming of the β-sheet is due to this and not a spontaneous reaction.
β-sheet forms typically between more than one molecule and forms hydrogen bonds parallel and antiparallel. The amino sequences are further apart in the β-sheet than in the α-helix, thats why β-sheet has higher energy. The side chains of the amino acids can interact which gives the β-sheet more stability.

4 Good scientific practice

Scientific integrity is the basis for the public's trust in research. At KIT, the statutes for safeguarding good scientific practice oblige all members to comply with the basic principles of good scientific practice. This includes the disclosure of all resources used. In addition to the sources listed in the bibliography, the following resources were used in the preparation of this report (please mark with a cross if used):
☐ ChatGPT or equivalent programs:
☐ Legacy protocols:
☑ (Lecture) scripts: A57 manuscript
☐ Internet sources that cannot be cited scientifically
☑ Correction and other aids: Pons translator