Molecular dynamics simulation of ion binding in aqueous solution of 18-crown-6 ether

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Abstract. Crown ethers are unique compounds with exceptional ion binding properties. We investigate the 18-crown-6 ether molecule binding selectivity for a set of alkali ions (K\textsuperscript{+}, Rb\textsuperscript{+}, Cs\textsuperscript{+}). We employ combination of umbrella sampling technique with the weighted histogram analysis method to derive free energies of ion–ether association. The obtained results are in a good agreement with experimental values available and represent the ion selectivity feature of the 18-crown-6 ether.

1. Introduction

Crown ethers and other structurally similar macrocycles have the unique property of forming stable complexes with a wide range of cations. These cations include alkali metal and alkaline earth metal ions that do not bind to most organic ligands [1, 2]. Due to this property, crown ethers have a broad spectrum of applications like organic synthesis [3], selective extraction of rare-earth elements [4] and isotope separation [5]. Crown ethers facilitate solvation of ionic compounds otherwise insoluble in some medium as well as significantly affect the transport of ions in it. This makes crown ethers a perspective component of electrochemical energy sources like redox flow batteries. It is important to investigate the formation mechanism and the solution properties of complexes consisting of macrocycle and ion in various solvents including water.

Molecular dynamics (MD) methods allow studying the structure and properties (including thermodynamic and transport characteristics) of ion–macrocycle complexes [6]. Moreover, this method also makes it possible to correct existing models of interaction between ions and organic molecules on account of vast range of available experimental data.

2. Simulation details

2.1. Molecular model

LigParGen web server [7] is used to generate ether molecules topology and force field parameters. This force field is an improved version of OPLS-AA [8] potential that uses localized bond-charge corrections which are made to the partial charges for atoms in specified bond types [9,10]. We use TIP4P [11] water model. Ion force field parameters are taken from the work by Jensen and Jorgensen [12].
Valent interactions of the ether molecule are described as

$$U_{\text{bonded}} = \sum_{\text{bonds}} \frac{1}{2} k_b (r - r_0)^2 + \sum_{\text{angles}} \frac{1}{2} k_a (\theta - \theta_0)^2 + \sum_{\text{dihedrals}} \sum_{n=1}^{4} \frac{1}{2} k_{dn} [1 + (-1)^{n+1} \cos(n\varphi)],$$  \hspace{1cm} (1)

where $k_b, r_0$ and $k_a, \theta_0$ are the force constants and equilibrium values for bond stretch and angle bend respectively, $k_{dn}$ is the torsion energy barrier and $n$ is the periodicity. The SHAKE algorithm [13] is used to constrain bonds in water molecules. Non-bonded interactions in the system have the form of Lennard-Jones potential with Coulomb term

$$U_{\text{non-bonded}} = 4\varepsilon_{ij} \left( \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right) + \frac{q_i q_j}{r_{ij}},$$  \hspace{1cm} (2)

where $r_{ij}$ is the separation distance between atoms $i$ and $j$ with partial charges $q_i$ and $q_j$. The cutoff radius for non-bonded interactions is set to 12 Å. We use geometric mixing rules to obtain all of the cross interaction parameters.

2.2. Computational methodology

Free energy of ion–ether association is derived from

$$\Delta G = -RT \ln K_a,$$  \hspace{1cm} (3)

where $R$ is the universal gas constant, $T$ is temperature and $K_a$ is the association constant which is computed using [14]

$$K_a = N_A \int_0^c 4\pi r^2 \exp(-W(r)/RT) dr,$$  \hspace{1cm} (4)

where $W(r)$ is the ion–ether potential of mean force (PMF), $r$ is the center-of-mass distance between crown ether and cation, $N_A$ is the Avogadro’s constant and $c$ is the geometric limit for association. In our simulations we define $c$ as the distance that corresponds to the top of the first energy barrier of the PMF.

PMF is constructed using a combination of the umbrella sampling technique [15] with the weighted histogram analysis method (WHAM) [16]. The umbrella sampling is a series of simulations with the biasing potential along the reaction coordinate of the ion–ether complex association.

The system under study is prepared by creating a gas mixture of the considered components and compressing it to the density of 1 g/cm$^3$ for 0.1 ns. This is followed by relaxation in the $NVT$ ensemble for 0.3 ns. Umbrella sampling is performed in the $NVT$ ensemble. The distance between ion and crown ether center of mass is chosen to be the reaction coordinate for the complex association, the biasing potential is set to be harmonic with the force constant of 30 kcal/mol. The equilibrium distance for the biasing potential is varied from 0 to 11 Å with the step of 0.25 Å. Each step is simulated for 0.16 ns. At least 11 independent simulations are performed for each of the considered cations.

2.3. Simulation parameters

The simulation box consists of one crown ether molecule, 300 water molecules and one cation. The temperature is set to 300 K. Periodic boundary conditions are used. Long-range Coulomb interactions are treated with particle-particle particle-mesh solver [17]. The equations of motion are integrated using rRESPA scheme [18] with 0.2 fs timestep for valent and 2 fs timestep for non-bonded interactions. The MD simulations are performed using LAMMPS package [19].
3. Results and discussion

The calculated PMFs for 12 independent simulations of K$^+$ ion to 18-crown-6 ether are shown in figure 1(a). These curves are similar to each other but have varying potential well depths from $-5$ to $-8$ kcal/mol. This is due to varying initial conditions in each calculation. At 11 Å, all of the curves decay to zero which implies that at this distance there is no interaction between the crown ether and the cation. This fact justifies the choice of this terminating distance for umbrella sampling calculations.

The average PMFs for the considered cations are shown in figure 1(b). The curve minimum for K$^+$ is almost at the crown ether center of mass whereas the minima for Rb$^+$ and Cs$^+$ ions are 1.2 and 1.6 Å away from the center of mass. This depicts the fact that the potassium ion fits into the center of the molecule while the radii of rubidium and cesium ions are larger than the size of the ether holding area.

Table 1 represents the resulting binding free energies of the ion–ether association. It also contains experimental values by Izatt [20] and results obtained by Dang [14] who applied similar technique to calculate $\Delta G$ but the different force field.

The values for each ion denoted as method 1 are obtained by integrating the PMF from every independent simulation [see figure 1(a)] and averaging the results. The values for each ion denoted as method 2 are obtained by averaging the PMFs from independent simulations and integrating the resulting curves [see figure 1(b)]. These two methods of finding the average value of $\Delta G$ demonstrate the convergence of the results.
The calculated $\Delta G$ value for potassium is within the error of the experimental result. The calculated value for rubidium is closer to the experiment than the one obtained by Dang. Less stable complexes are formed going from K$^+$ to Cs$^+$ (i.e., smaller absolute values of the binding free energy) in our simulations as well as in the Dang’s work. This trend represents the 18-crown-6 ether binding selectivity for K$^+$ ion observed in experiments.

The similar calculations for Na$^+$ ion are required to capture the effect of 18-crown-6 ether particular affinity for K$^+$. However, due to the complex effect of the water solvation shell around the Na$^+$, this is to be investigated in the future work.

4. Conclusion
We perform molecular dynamics simulations of the water-solvated 18-crown-6 ether molecule with the set of alkali ions. We use the modern OPLS-AA force field with the corrected partial atomic charges to parametrize crown-ether molecule. The TIP4P force field is used to define interactions of water molecules. Potentials of mean force of interaction between ether and cations are obtained by implementing the umbrella sampling with the weighted histogram analysis method. Using these potentials binding free energies are calculated. The resulting values resemble the general trend and the 18-crown-6 ether selectivity for potassium ion holds true.

Acknowledgments
The work is supported by the Russian Science Foundation, grant No. 18-19-00734.

The calculations have been performed on the Desmos and Fisher supercomputers of the Joint Institute for High Temperatures RAS.

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