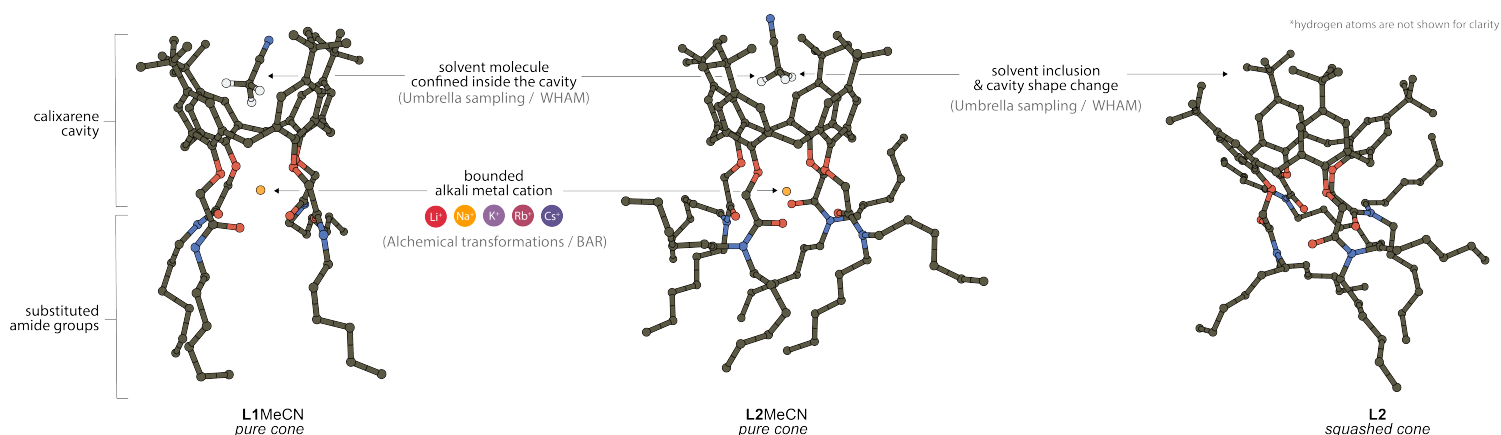# Designing selective ion receptors: complexation affinities of calix[4]arene amide derivatives towards alkali-metal cations

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Abstract

Currently, one of the major challenges in supramolecular chemistry is the development of molecular ion receptors with specific affinities for a given molecule or ion. Calixarenes are macrocycles made of phenolic subunits which upon functionalization of phenol oxygen atoms can become selective and sometimes specific ion binders. Furthermore, the hydrophobic cavity which is comprised of phenolic aromatic rings, is an adept binding site for smaller neutral molecules, usually that of the solvent. Although designing supramolecular host-guest complexes is a well suited problem for computational investigation, few such studies were done by methods other than Free Energy Perturbation theory.

We explore binding affinities of a secondary (L1) and a tertiary (L2) amide calix[4]arene derivatives towards alkali-metal cations in acetonitrile (MeCN) and benzonitrile (PhCN) by means of molecular dynamics simulations and two popular Free Energy calculation methods, namely Bennet Acceptance Ratio (BAR) and Weighted Histogram Analysis Method (WHAM).

Alchemical transformations were used to mutate Van der Waals and mass parameters between pairs of alkali-metal cations both in complex and bulk solvent in order to calculate relative binding affinities of calixarene ligands. Absolute binding affinities were obtained by transmuting the cation in the complex into a dummy atom accompanied by the appearance of the cation in bulk solvent, where both Coulomb and Van der Waals interactions were decoupled. Relative and absolute Gibbs free energies of complexation were calculated by BAR and were shown to agree reasonably well with available experimental data, thereby validating our approach.

The inclusion of MeCN and PhCN molecules into the calixarene cavity of free ligands, as well as their complexes, can have a positive positive effect on the binding affinity for cations. In order to quantify the named processes, Umbrella Sampling simulations were performed and the corresponding free energies were calculated by WHAM. In these simulations the solvent molecules were pulled from the hydrophobic cavity into the bulk which coincides with a conformational change of the calixarene cavity from a pure cone to a squashed cone shape.

We conclude that free energy calculations of complexation affinities could enable fast and accurate screening of potential candidates for the synthesis of selective supramolecular cation receptors. Such receptors might then find their use as ion channels and sensors for the membrane of ion selective electrodes as well as ion extraction agents.[1][2][3]

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