Proposal ID number: 19802
Title of the Proposal: Energy and Entropy Effects in Dissociation of Non-Covalent Complexes: A Combined Experimental and Theoretical Investigation
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Description of the proposed work and results

Vancomycin is a glycopeptide antibiotic that is widely used for treatment of infections caused by Gram-positive bacterial pathogens. It is known that vancomycin prevents the growth of the bacterial cell wall by binding to the cell-wall peptidoglycan precursors terminating in –L-Lys-D-Ala-D-Ala.

This study presents the first step towards quantifying non-covalent interactions using time- and energy-resolved surface-induced dissociation (SID) experiments. Vancomycin and N_{α},N_{ε}-diacetyl-L-Lys-D-Ala-D-Ala (cell-wall precursors analogue) are used for experimental study. Time- and energy-resolved SID experiments were performed at both the positive and negative modes using a specially designed FT-ICR MS configured for SID experiments. The energetics and dynamics of dissociation were determined using RRKM modeling of the experimental data. The results are compared with the density functional theory (DFT) calculations for a number of model systems.

Here we present first direct comparison between the experiment and theory for the vancomycin–peptide model system, and demonstrate that combination of the SID experiment with theoretical calculations is an effective method for obtaining molecular-level understanding of non-covalent interactions between large biomolecules. The binding energies obtained from experiments are in good agreement with computational results for vancomycin–N_{α},N_{ε}-diacetyl-L-Lys-D-Ala-D-Ala complexes, and we demonstrate that: (a) Charge state affects the composition of vancomycin–peptide complexes, *i.e.*, the positively (+1 and +2) charged complexes are composed of protonated vancomycin (+1 and +2) and neutral peptide ligand, whereas negatively (-1) charged complex contains deprotonated vancomycin (-1) and neutral peptide ligand; (b) Charge state affects the binding energy of vancomycin–N_{α},N_{ε}-diacetyl-L-Lys-D-Ala-D-Ala complex, and the binding energies of complexes increase as the order of the charge state as doubly-protonated < singly-protonated < singly-deprotonated; (c) Proton transfer between charged vancomycin and neutral peptide ligand occurs during the fragmentation of vancomycin–peptide complexes in both positively and negatively charged complexes.

List of publications, awards, recognition

1. Z. Yang and J. Laskin* “Experimental and theoretical studies of the structures and interactions of vancomycin antibiotics with cell wall analogues”, J. Am. Chem. Soc., submitted.

Request for Extensions

Literature results indicate that the stability of doubly protonated charged vancomycin-peptide complexes are independent of the peptide ligand, such that vancomycin looses the selective binding to -D-Ala-D-Ala containing peptides. According to our current preliminary computational results, we assume that the doubly charged complexes of vancomycin/non-D-Ala-D-Ala containing peptides may occur as non-

specifically bound structures, where the peptides are attached to the protonated *N*-methyl-leucine or disaccharide groups of vancomycin without sitting in vancomycin cage. These exo- complexes may have similar stabilities as doubly charged vancomycin/-D-Ala-D-Ala containing peptides. In order to prove this hypothesis we need to do extra experiments by selecting appropriate model molecules. Additional theoretical computations are also needed to enhance and demonstrate the experimental results. Therefore we request the extension of this project for one year and the following resources:

- Mass Spec: FT-ICR-6T, 200 hrs
- MPP2 supercomputer: 100,000 CPU-hours for corresponding theoretical studies