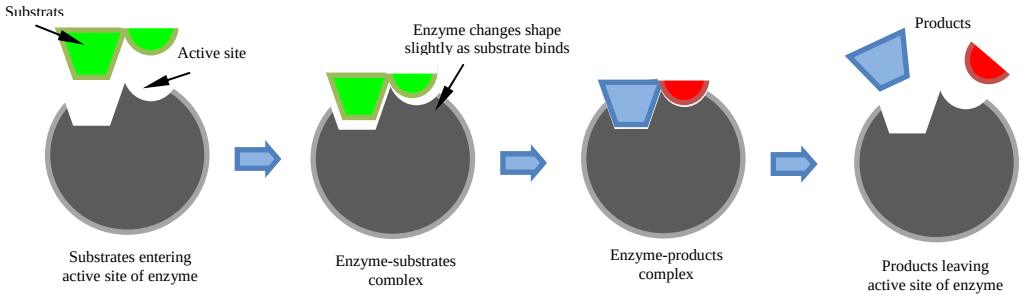
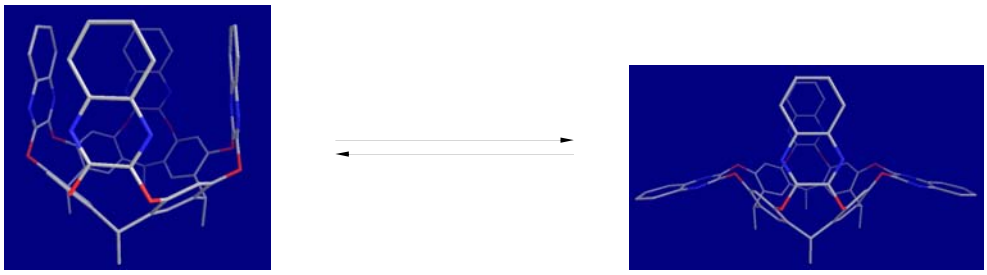
Molecular Grippers – Controllable Delivery Vehicle

1. *Summarize the research project. Include the primary hypothesis/research question/research objective governing your research project.*

Background: Drug delivery today has evolved into the strategic designs of molecular vehicles capable of enhancing the efficacy of therapeutic agents through controlled release. An effective and targeted drug delivery often requires a specific molecular recognition. The initial inspiration for molecular recognition came from the realm of biology, in which specific intermolecular forces such as hydrogen bonding provide the basis of the working features of enzyme reactions (Figure below). Artificial molecular receptors of increasing sophistication such as clefts, armatures, tweezers, bowls, and other vehicles have been designed and synthesized for the study of these interactions, both in aqueous and nonaqueous solutions. In the last decade, researchers have prepared an amazing number of different synthetic receptors for binding and recognition of guest molecules. One giant group of these structures is modified cavitands – macrocyclic compounds featuring a cavity that is sealed at one end and has different molecular fragments as flexible "arms" built at the other end. These added fragments help the cavitand to temporarily capture a smaller molecule inside like a mechanical gripper.



One of the most fascinating classes of receptors for molecular recognition studies comprises the resorcin[4]arene cavitands bridged by four quinoxaline moieties introduced by Nobel laureate Donald J. Cram and co-workers (Figure below). A particularly interesting property of these systems is the reversible, temperature-dependent switching between a *kite* conformation with opened arms and a *vase* conformation with closed arms, which forms a cavity suitable for guest encapsulation. Since the switching between the vase and the kite conformations is very fast, one of the greatest challenges for further application is to keep the guest molecule inside the cavity of the "vase", but avoid the "kite".



Vase conformation cavitand (side view) **Kite conformation cavitand (side view)**

What if we introduce a certain intermolecular binding feature, for instance, hydrogen bonding or coordination with a metal ion, on the tops of these flapping "arms"? Holding the "arms" together with these additional intermolecular forces will keep the guest molecule inside the cavity for a longer time. More importantly, if the intermolecular forces could be turned on and off by an external stimulus, a switchable molecular gripper will be formed. The controllable switching of modified resorcin[4]arene cavitands resembles the movement of a mechanical gripper: the cavitand captures a single molecule in the vase form and holds it during translocation, then releases it upon changing to the kite conformation. Therefore, the releasing of the guest molecule can be controlled by varying external conditions. Applications of this molecular-gripper-type delivery vehicle could also be envisioned in the development of nanoscaled dynamic receptors, sensors, and molecular machines.