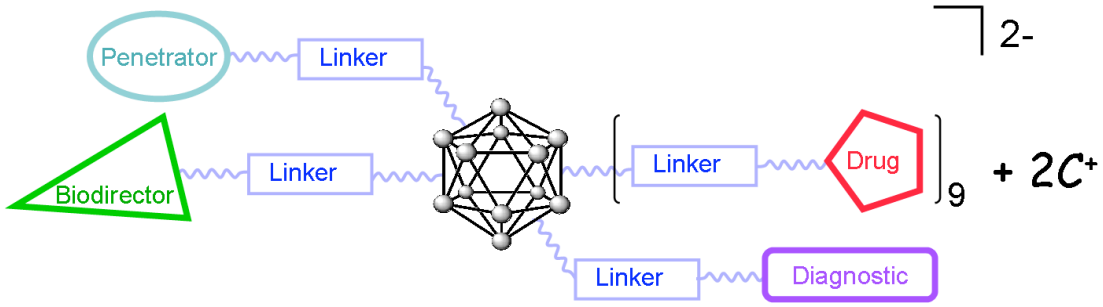
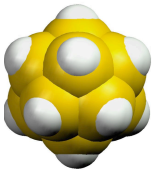
Targeted Delivery of Multifunctinal Nanomolecular Drug Delivery Systems

The major goal of this project is to synthesize monodisperse nanomolecules providing simultaneous cell targeting, diagnostic, therapeutic, and cell penetration functions.

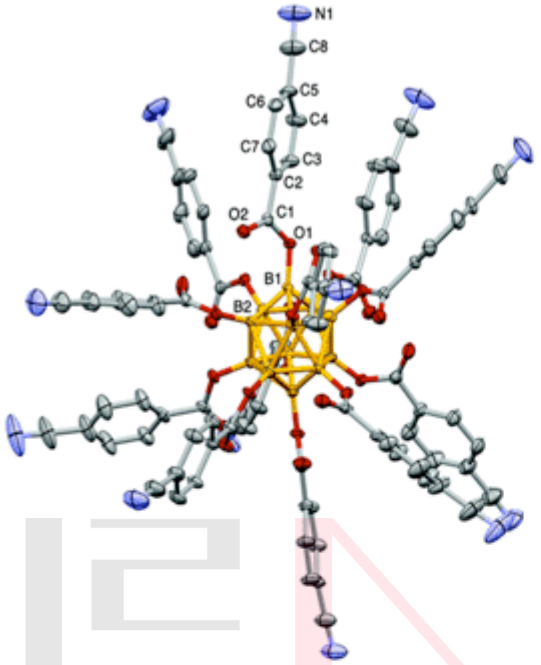


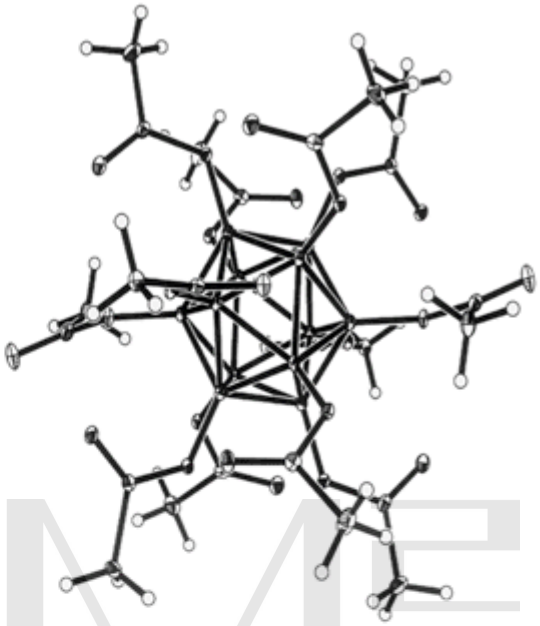
- The ability to differentiate the icosahedra vertices allows the B_{12} core to be mutlifunctionalized with various capabilities.
- Water solubility of the boron drug system can be controlled by cation, C^+ selection.
- The disodium $B_{12}H_{12}$ is a non-toxic scaffold (LD = 1.2g, safe as table salt).



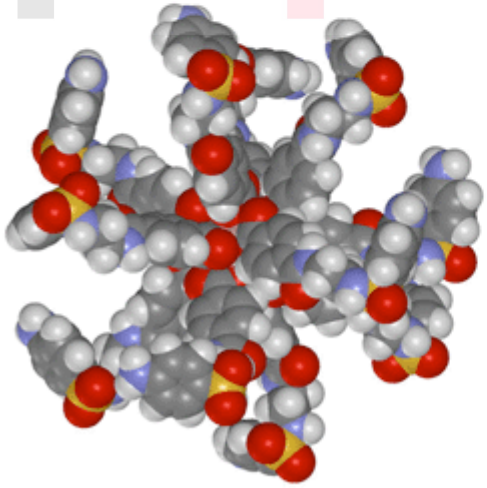
The 12 vertices of the icosohedral borane dianion, *closo*-$[B_{12}H_{12}]^{2-}$, can be precisely functionalized to give a monodisperse prodrug. The synthesis of discrete globular molecules in which precisely constructed organic chains are grown from the vertices of closed polyhedra (defined here as closomers) has undergone rapid development in our laboratories. Recently, twelvefold functionalized dodecaborates bearing a variety of organic substituents linked via ester and ether functionalities were reported by our laboratory. Selected X-ray crystal structures are shown below.

The reactivity of the BOH hydroxyl groups are similar to simple alcohols and lend themselves to simple organic reactions allowing discrete 12-fold functionalization of the B_{12}-icosahedral drug delivery carrier system. Currently we are exploring coupling therapeutics such as antibiotics and anticancer agents to the cage through enzymatically and hydrolytically cleavable linkers. Controlled release of these active therapeutics will enhance their biological activity. Certain tetrapeptides are selectively cleaved by tumor-associated protease, while the hydrolytically cleavable linkers will release therapeutics at sites of lower pH which is typical of the environment found in cancerous tissue.

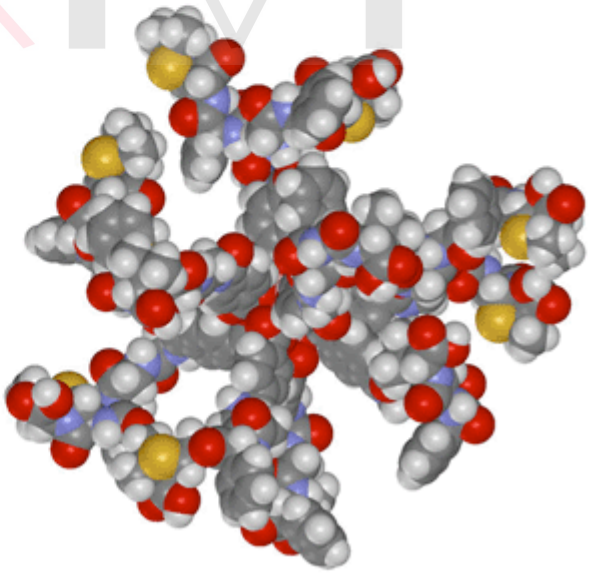




ORTEP depiction of the solid-state molecular structure of $[B_{12}(OCOC_6H_4CN)_{12}]^{2-}$ and of $[B_{12}(OCOCH_3)_{12}]^{2-}$ nanoparticle dianion, respectively.



Space filling model of the B12-sulfanilamide twelvefold conjugate dianion



Space filling model of the B12-ampicillin twelvefold conjugate dianion