DE NOVO ENZYME DESIGN

The *de novo* design of catalysts for specific purposes remains an inspired goal for chemists and biochemists. Ken Houk and David Baker have been pursuing this goal, and their recent paper on the design of a catalyst for the bimolecular Diels-Alder[1] is a real significant step forward.

Their model enzyme is one that will provide a hydrogen bond acceptor to the carbamate proton of **1***and* a proton donor to the carbonyl oxygen of the amide **2**. This model is sketched in Figure 1. Glutamine or asparagines will serve as the acceptor and serine, threonine, or tyrosine will serve as the proton donor. The catalytic site is then modeled, and then this active site is fit within 207 protein scaffolds. About 10^{19} active site configurations are reduced to about 10^{6} possible protein scaffolds. Optimization of these led to 84 protein designs.

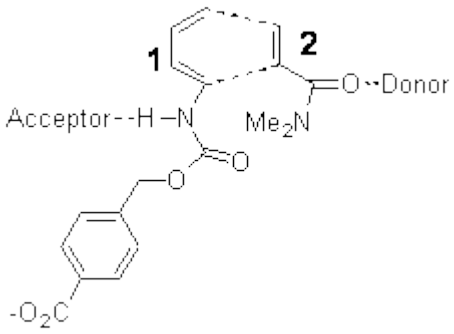
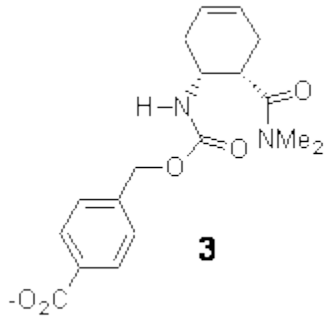


Figure 1. Enzyme model

These 84 possible proteins were then synthesized within *E. coli* and then tested for catalytic behavior

in the Diels-Alder reaction of **1** + **2**. Only 2 enzymes have activity, and with some protein modifications, quite reasonable enzyme activity is found. These enzymes show strong selectivity for the substrates – addition of a methyl group significantly diminishes catalytic activity. Perhaps most important is that of the 8 possible isomers that can be formed (4 isomers are produced in the uncatalyzed reaction) only 1 is produced here, the 3*R*,4*S* isomer **3**.



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All-in-all, a quite remarkable accomplishment!

Source: http://comporgchem.com/blog/?p=1100