The search for Artificial Enzymes: from Antibodies to Dendrimers

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Enzymes are remarkable because their properties are not conceivable at the level of their constituent amino acids. In de novo enzyme design one attempts to replicate this emergence phenomenon in synthetic systems, most often based on design and selection ideas. In my group we have investigated catalytic antibodies obtained by immune selection for binding to transition state analogs and contributed to the development of high-throughput screening and fingerprinting assays for biocatalysis. Most recently we focus on artificial enzymes identified in combinatorial libraries of peptide dendrimers, a strategy which circumvents the problem of protein folding.

The peptide dendrimers are particularly attractive enzyme models because they can be synthesized automatically from commercial building blocks and modified by amino acid exchanges, which facilitates structure-activity relationship studies. For example, we find that the activity of esterase peptide dendrimers with a single catalytic residue at the core is controlled by the periphery of the dendrimer composed of hydrophobic and aromatic residues. These interactions takes place within a relatively compact conformation similar to a molten-globule (Figure) [1]. Similar interactions between the dendrimer core and the periphery are also apparent in dendrimers selected as ligands for Vitamin B_{12} [2]. Recent progress in controlling the dendrimer conformational states, as well as our efforts to improve and simplify combinatorial methods [3], will also be discussed.

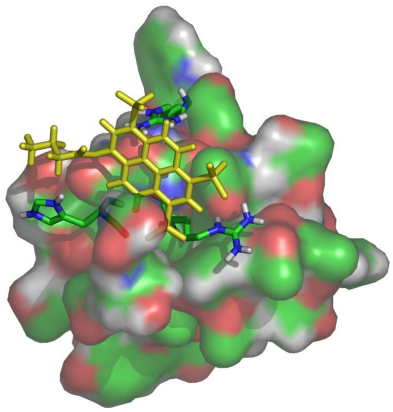

Figure. Model of an esterase peptide dendrimer from molecular dynamics simulations [1].

[1] S. Javor, E. Delort, T. Darbre, J.-L. Reymond. A Peptide Dendrimer Enzyme Model with a Single Catalytic Site at the Core. *J. Am. Chem. Soc.* **2007**, *129*, 13238-13246.
[2] A Peptide Dendrimer Model for Vitamin B_{12} Transport Proteins. P. Sommer, N. A. Uhlich, J.-L. Reymond, T. Darbre, *ChemBioChem*, in press.
[3] J. Kofoed, J.-L. Reymond. A General Method for Designing Combinatorial Peptide Libraries Decodable by Amino Acid Analysis.*J. Comb. Chem.* **2007**, *9*, 1046-1052.