

Department of Chemistry and Molecular Biology
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A New Strategy in Synthetic Biology: From Enzyme Inhibition, Natural Products Synthesis to PET Imaging by 6- π -Azaelectrocyclizations

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Abstract

During inhibitory studies of the hydrolytic enzyme by aldehyde-containing natural products, a reaction involving 6- π -azaelectrocyclization with lysines was discovered. Substituent effects within the 1-azatriene systems, the precursor of cyclization, accelerated the reaction. Structure-reactivity studies showed that the azaelectrocyclization, which usually proceeds in low yield at high temperatures, could be performed quantitatively in less than 5 min at rt. The asymmetric chiral piperidine synthesis and the one-pot library synthesis of pyridines on solid-supports were applied to the synthesis of pyridine / indole alkaloid-type natural products.

A lysine-based labeling of biomolecules based on rapid 6- π -azaelectrocyclization has also been developed. Both DOTA as a metal chelating agent (either for MRI, PET, or other radiopharmaceutical purposes, e.g., SPECT with gamma emitters) as well as fluorescent groups were introduced efficiently and selectively into lysine residues within 10 min at concentrations even at 10^{-8} M. The DOTA-labeled somatostatin, glycoproteins, and glycoclusters were then radiometallated with ^{68}Ga and the receptor-mediated accumulation of somatostatin in pancreas was observed. Further, oligosaccharide dependent circulatory residence of glycoproteins, and the specific accumulation of the *N*-glycan-clusters could be visualized for the first time by microPET.

"A whole cell-based *in vivo* imaging" via direct chemical labeling of living cells, the chemical engineering of antibodies and/or cell surfaces by natural *N*-glycans based on azaelectrocyclizations, and the combined solid-supported/microfluidic technologies toward oligosaccharides synthesis, will also be presented.