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AbbVie Workshop Series in Synthetic Organic & Medicinal Chemistry

4:15 p.m. Friday, April 4, 2014, 331 Smith Hall

Professor

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Studies of SpnF-catalyzed [4+2]-cycloaddition in the biosynthesis of spinosyn A

Research encompasses three general areas with the focus aimed at the elucidation of the mechanisms of novel enzymatic reactions and the design of methods to control and/or regulate their functions, including enzyme mechanism and inhibitor design, metabolic pathway engineering, and protein function regulation.
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Abstract

The Diels–Alder reaction is a [4+2]-cycloaddition reaction in which a cyclohexene ring is formed between a 1,3-diene and an electron deficient alkene via a single pericyclic transition state. This reaction has been proposed as a key transformation in the biosynthesis of many cyclohexene-containing secondary metabolites. Although several purified enzymes have been implicated in biotransformations that are consistent with a Diels–Alder reaction, these enzymes typically demonstrate more than one catalytic activity, leaving their specific influence on the cycloaddition step uncertain. In our studies of the biosynthesis of spinosyn A, a tetracyclic polyketide-derived insecticide from Saccharopolyspora spinosa, we identified a cyclase, SpnF, that catalyzes a transannular [4+2]-cycloaddition to form the cyclohexene ring in the final product. SpnF is unique, because it is the only known enzyme that specifically catalyzes a [4+2]-cycloaddition without introducing any other changes to its substrate. The same cycloaddition also takes place nonenzymatically, but at a much reduced rate. If the reaction catalyzed by SpnF is a concerted process with a single pericyclic transition state, then SpnF would be the first example of a naturally selected Diels-Alderase. In order to investigate this possibility, alpha-secondary deuterium kinetic isotope effects were measured at both points of rehybridization in the diene during both the nonenzymatic and SpnF-catalyzed [4+2]-cycloaddition reactions. This was accomplished using regiospecifically deuterated substrates and electrospray ionization, time-of-flight mass spectrometry to follow changes in deuterium enrichment of the substrate as the reaction progressed. This presentation will describe the measurement of these KIEs and offer a mechanistic discussion of their implications for understanding the SpnF catalyzed [4+2]-cycloaddition.

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