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Rapid Formation of Ortho-Boronoimines and Derivatives for Reversible and Dynamic Bioconjugation Under Physiological Conditions

Authors : Nicholas C. Rose, Christopher D. Spicer

Abstract : The regeneration of damaged or diseased tissues would provide an invaluable therapeutic tool in biological research and medicine. Cells must be provided with a number of different biochemical signals in order to form mature tissue through complex signaling networks that are difficult to recreate in synthetic materials. The ability to attach and detach bioactive proteins from material in an iterative and dynamic manner would therefore present a powerful way to mimic natural biochemical signaling cascades for tissue growth. We propose to reversibly attach these bioactive proteins using ortho-boronoimine (oBI) linkages and related derivatives formed by the reaction of an ortho-boronobenzaldehyde with a nucleophilic amine derivative. To enable the use of oBIs for biomaterial modification, we have studied binding and cleavage processes with precise detail in the context of small molecule models. A panel of oBI complexes has been synthesized and screened using a novel Förster resonance energy transfer (FRET) assay, using a cyanine dye FRET pair (Cy3 and Cy5), to identify the most reactive boron-aldehyde/amine nucleophile pairs. Upon conjugation of the dyes, FRET occurs under Cy3 excitation and the resultant ratio of Cy3:Cy5 emission directly correlates to conversion. Reaction kinetics and equilibria can be accurately quantified for reactive pairs, with dissociation constants of oBI derivatives in water (KD) found to span 9-orders of magnitude (10^{-2}-10^{-11} M). These studies have provided us with a better understanding of oBI linkages that we hope to exploit to reversibly attach bioconjugates to materials. The long-term aim of the project is to develop a modular biomaterial platform that can be used to help combat chronic diseases such as osteoarthritis, heart disease, and chronic wounds by providing cells with potent biological stimuli for tissue engineering.

Keywords : dynamic, bioconjugation, bornoimine, rapid, physiological
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