INTRODUCTION

Polymerases are among the most impressive examples of processive enzymes. Processivity is defined as the ability of an enzyme to repetitively catalyze transformations without dissociating from its substrate. From a synthetic viewpoint, processive enzymes allow an extraordinary level of control for the synthesis, modification, and degradation of biopolymers. This Review will highlight the ability of supramolecular systems to mimic processive enzymes as a strategy towards molecular factories for the synthesis of polymers and small molecules.

ROTAXANES

Rotaxanes are mechanically interlocked supramolecular structures that contain a macrocycle threaded with a long molecule or polymer. Recognizing the similarity in architecture between processive enzymes and rotaxanes, Nolte and co-workers created the first catalytically active rotaxane system in 2003. In this system, a polybutadiene polymer is threaded through a macrocycle containing a manganese(III) porphyrin (Mn1). Upon activation of the metal center, the metalloporphyrin unit repeatedly catalyzes the epoxidation of polybutadiene. However, kinetic studies of the threading and sliding process of Mn1 suggest that unlike nature’s sequentially processive enzymes, epoxidation of the polybutadiene polymer is randomly processive.

Leigh and co-workers introduced another rotaxane-based processive enzyme mimic for the synthesis of short peptides. The rotaxane is synthesized by threading a template strand linked to amino acid groups through a macrocycle. A cysteine thiolate on the macrocycle initiates the transfer of each amino acid from the template strand to the growing peptide chain via an \( S,N \)-acyl shift. Sequential processivity is achieved because the macrocycle is blocked by each tethered amino acid. As sequential processivity will be essential for more complex polymers, this represents a fundamental advance.

DNA-TEMPLATED SYNTHESIS

DNA-templated synthesis (DTS) employs a DNA template to recruit reagents linked to complementary oligonucleotides for the synthesis of polymers and small molecules (Figure 2). A major
goal of DTS is to use DNA to direct multistep syntheses with all reagents simultaneously present in solution, just as DNA polymerase uses single-stranded DNA to direct the synthesis of the complimentary strand. While early efforts towards multistep DTS required the sequential addition and removal of reagents, more recent advances allow all reagents to be simultaneously present in solution.\(^5\) One example involves the use of a DNA walker. In this system, a “DNA track” is created by annealing reagent-linked oligonucleotides to the template DNA. A “DNA walker” then moves unidirectionally along the track, initiating specific chemical reactions as it arrives at each reagent.\(^6\) Mimicking DNA replication, the products are predetermined by the template DNA.

A vital feature of the efficiency for DNA replication is the ability to replicate many unique DNA strands simultaneously. Likewise, DTS also has the ability to synthesize multiple products in a single solution, as the chemical sequences of individual products are dependent on individual DNA template strands rather than the identity of other reagents present in solution. Therefore, large libraries of molecules can be synthesized by DTS in a single solution.\(^7\) Liu and coworkers synthesized a library containing 13,824 macrocycles that was used to identify a novel kinase inhibitor.\(^8\)

**SUMMARY**

Rotaxane and DTS-based processive enzyme mimics allow for the synthesis of diverse polymers and small molecules. These mimics lack the degree of speed, product size, and efficiency observed in nature. Nevertheless, they offer great promise as a compliment to processive enzymes due to the diverse range of chemical reactions and substrates that can be utilized. Continued advances in these fields may lead to the development of highly efficient molecular factories for diverse applications in materials science and drug discovery.

**REFERENCES**