

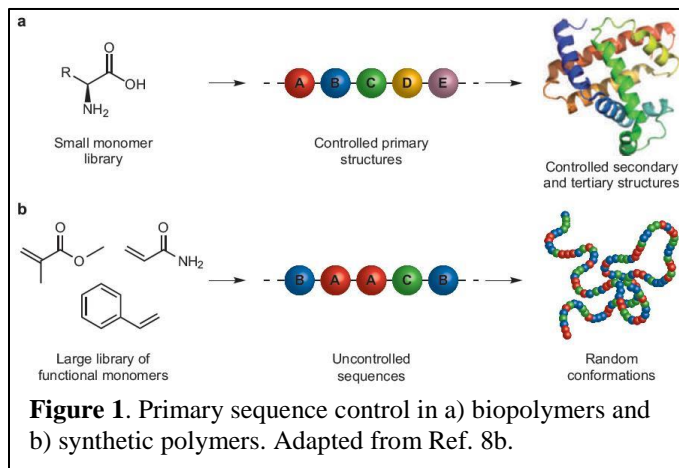
FRONTIERS IN POLYMER CHEMISTRY: THE SEARCH FOR ORDER

Reported by Joshua A. Kaitz

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INTRODUCTION:

The control of primary sequence in synthetic polymers is notoriously difficult.¹ Nature routinely uses sophisticated catalytic machinery in conjunction with templated synthesis to attain perfect sequence control in biopolymers (Figure 1). The importance of primary sequence in natural polymers cannot be overstated—it constitutes the genetic code and governs protein folding and function. Strategies to manipulate polymer stereochemistry² as well as to control molecular weight distributions³ have been developed in recent decades. However, no such general approach has achieved primary sequence control in synthetic polymerization reactions.



PERFECT POLYMERS BY ITERATIVE SYNTHESIS:

Sequential polymer growth by iterative coupling, pioneered by Merrifield⁴ a half-century ago, remains the most effective method for sequence-defined oligomer synthesis. Solid-phase synthesis has been adapted for the preparation of various natural and unnatural step-growth polymers and has been expanded to solution-phase syntheses. However, the technique is limited to relatively short sequences, cannot be applied to vinyl monomers, and gives low overall yields of perfectly sequence-defined polymer. Dendrimers prepared by sequential coupling strategies also represent a unique class of sequence-defined polymers.⁵ Although dendrimer topology can be modestly controlled, dendrimers are generally globular structures that cannot be tuned for advanced functions like linear biopolymers.

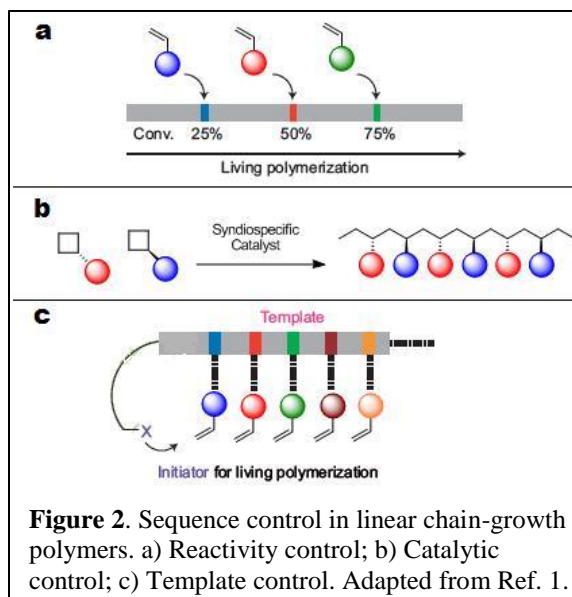
KINETIC CONTROL OF CHAIN-GROWTH:

Sequence control in linear chain-growth polymers would represent a significant advance in polymer chemistry.⁶ Though perfect control over reactive propagating chains has proven difficult to achieve, several innovations have enabled precise manipulation of sequence distributions. The Lutz group, for instance, has pioneered the insertion of functional monomers at precise locations within polymer chains by controlled addition of monomers that preferentially cross-propagate (Figure 2a).^{7a} The method was elaborated to fold polymers into well-defined cyclic and looped morphologies.^{7b} In

another striking example of kinetic control, enantiopure monomers of differing configuration were copolymerized in an alternating fashion using a syndiospecific catalyst (Figure 2b).⁸ Importantly, this extends the scope of alternating polymers to monomers that do not intrinsically cross-propagate.

TEMPLATED CHAIN-GROWTH POLYMERS:

Inspired by Nature, researchers have also sought to employ templated polymerizations to afford sequence control in linear chain-growth polymers. Conventional templation with an added template macromolecule is limited by several complications such as template coiling, non-specific complexation, and product purification. The Ouchi and Sawamoto groups, however, have circumvented these drawbacks by developing template initiators and template monomers (Figure 2c). They



demonstrated that by covalently linking a homopolymer template to a halide initiator, they could exert greater than a 100-fold increase in reactivity between coordinating versus non-coordinating monomers.⁹ In a complementary approach, they covalently attached monomers to a template in an A-B-A fashion to achieve perfectly sequence-regulated copolymers upon template hydrolysis.¹⁰ With further refinement, these techniques could certainly be applied to develop sequence-controlled linear polymers.

SUMMARY:

Several unique approaches have been exploited to control the sequence of synthetic polymers. Though the field is still in its early stages, these strategies lay the foundation towards controlling monomer distribution within polymers. Future technologies will likely entail significant improvements in templation strategies and catalyst development to attain truly perfect control over polymer sequence.

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