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On the Right “Track” to Artificial Assemblers

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The design of synthetic analogs to biological molecular machines offers a new vista for chemists. In this issue of *Chem*, McTernan et al. report an artificial synthesizer reminiscent of natural assemblers. This molecular machine is capable of forming sequence-defined oligomers by the Wittig reaction, a transformation not found in nature.

In living organisms, countless molecular machines perform myriad tasks simultaneously, from ATPases producing adenosine triphosphate to the motor proteins responsible for the transport of cellular cargo. One of the most famous and well-studied biological machine is the ribosome. Essential for the synthesis of proteins, the ribosome uses the codons of a messenger RNA (mRNA) strand as a “barcode” to sequentially add amino acid monomers to a nascent peptide. The mechanism by which the ribosome synthesizes various proteins has been investigated in great detail and is quite remarkable in that it is sequence specific. Each codon, consisting of three DNA bases, encodes the introduction of a specific amino acid into the growing chain. This peptide elongation is immediately followed by a shifting of the mRNA strand, exposing the next codon to the ribosome. Thus, the ribosome can be seen as a kind of molecular walker because it moves stepwise along the mRNA track used for protein synthesis in the translation step.

Biological machines are extremely efficient, yet this comes at the cost of high complexity and heavy specialization. This is one of the reasons chemists have been trying to develop simplified synthetic molecular machines for decades. By trying to mimic mother nature, simpler and smaller molecular machines have been capable of similar exploits.¹ To this date, we cannot compete with nature’s efficiency, yet the toolbox of reactions, reagents, and stimuli available to the synthetic chemist is almost limitless in comparison to the biologically relevant environment.² Fundamental operations such as substrate transport, artificial muscle actuation, or stepwise motion^{3,4} using artificial and biohybrid machines have been achieved. In order to move forward, the field must now focus on two different challenges: bridge the gap between artificial and biological molecular machines and extend the scope of what nature can do.

In this issue of *Chem*, McTernan et al. report the design of an artificial ma-

chine that can synthesize all-carbon oligomers by consecutive Wittig olefinations.⁵ The machine’s backbone is based on a rotaxane skeleton. Rotaxanes are mechanically interlocked molecules composed of two subunits: a macrocycle and a rod. By careful design of the steric bulk of the end groups of the rod, a macrocycle can be threaded and trapped on the elongated track. Despite the absence of covalent bond—and, in some cases, of any non-covalent attractive interactions—between the macrocycle and the thread, the two subunits are joined by what is termed a mechanical bond.⁶ An interesting property arising from this peculiar interaction is that the position, movement, and local environment of the macrocycle can be controlled by designing suitable interactions.

The structure of rotaxanes can somewhat be viewed as a stepwise assembling machine. Indeed, although the threading of the macrocycle yields defined molecular assemblies, the back-and-forth shuttling by relative

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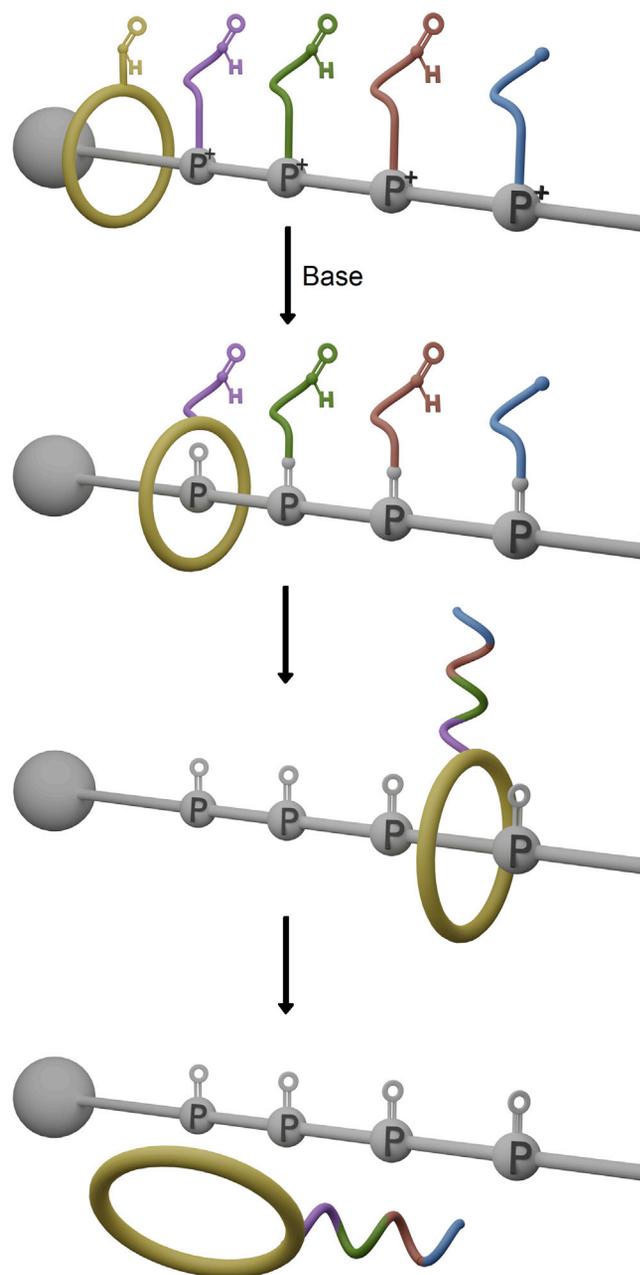


Figure 1. The Artificial Assembler Sequentially Adds Carbon-Based Monomers to an Elongating Oligomer

motion of the subcomponents make rotaxanes molecular walkers. In fact, the Leigh group previously reported a rotaxane-based molecular machine that mimics the role of the ribosome.⁷ By installing a cysteine pendant arm on the macrocycle of a rotaxane as well as amino acid stations on the rod, the authors demonstrated the stepwise incorporation of up to four amino acid

monomers into a short peptide.⁸ In their work described in this issue of *Chem*, McTernan et al. now expand the scope of the artificial synthesizer to perform a C=C bond formation step via a Wittig reaction, otherwise unheard of in nature.

Their design is schematically represented in Figure 1. The macrocycle is

minimally functionalized, incorporating a pyridine group for ease of synthesis (see below) and a reactive aldehyde group. On the rod, multiple phosphonium ylide stations bearing 2,2-diarylpropane groups act as both a monomer transfer agent as well as a physical barrier to prevent random shuttling of the macrocycle along the thread. These reactive stations are connected through a rigid array of aryl rings to prevent folding of the track. This track is terminated at one end by a bulky stopper to prevent dethreading of the macrocycle, and the other end is left open for release of the product.

The rotaxane is first constructed by using an active metal template strategy. By copper-catalyzed azide-alkyne cycloaddition, the rod's stopper and the first phosphonium station are clicked together by a triazole group. This is where the pyridine-functionalized macrocycle comes in handy, given that the incorporation of a copper-coordinating moiety in the ring allows this cycloaddition to be performed across the ring, effectively threading the rotaxane in one step. Iterative cycloadditions were then used to elongate the track to up to four stations bearing different monomers.

Upon treatment of the rotaxane with a resin-bound superbase, formation of phosphonium ylides on the rod triggers consecutive Wittig reactions with the elongating macrocycle's aldehyde. The formation of a C=C bond on the macrocycle specifically incorporates the monomer of the closest phosphonium ylide station, transforming the latter into the corresponding phosphine oxide. Conveniently, the reduced size of the phosphine oxide now allows shuttling of the macrocycle to the next station, where the subsequent monomer can be introduced. By iterative addition of the 2,2-diarylpropane groups onto the macrocycle, the oligomer is elongated until the last monomer is incorporated and the macrocycle can slide off the thread.

After the successive Wittig reactions and dethreading of the ring, an oligomer exclusively based on a carbon-carbon bond backbone is obtained. From this new design, compounds that could not be obtained with a biological machine were isolated. Each station was functionalized with differently substituted 2,2-diarylpropane monomers. Arguably, these substituents should not have a great effect on the reactivity of the corresponding phosphonium ylide, and thus would yield a statistical mixture of products should this reaction be performed in solution. But the very way this synthesizer works, namely by iterative addition of spatially separated monomers, allows the sequence-specific introduction of these structurally similar monomers. Furthermore, although the *E/Z* selectivity of each Wittig reaction should be improved, the authors calculated that an *all-Z* product isomer would adopt a helical conformation. The secondary structure of peptides is intrinsically linked to their biological properties and is therefore of prime importance. What the authors thus demonstrated is that an artificial machine can *de novo* synthesize artificial products that might share resemblance in their secondary structure to natural compounds.⁹

Undoubtedly, there is still a long way to go before an artificial synthesizer can

be applied for the efficient synthesis of complex structures. Many key points are raised by the authors for the field to develop further. Among them, one major challenge to overcome is the reusability of the whole synthesizer. Re-functionalization strategies are necessary in order to reset the synthetic machine. The difference in activity compared with that of their biological counterpart is also important. Although the ribosome can assemble multiple amino acids per second, this artificial machine requires up to 5 days to make 4 bonds. Reading and translating information in the assembly process is also a major challenge.¹⁰ But the game is worth the candle. Biological synthesizers are limited in their substrate scope. The ribosome can assemble polyamides, DNA polymerases can stitch nucleosides together, but the myriad reactions available to the synthetic chemist renders limitless the applications of artificial synthesizers.

In this paper, Leigh and colleagues report the design, synthesis, and performances of an artificial molecular machine synthesizing unnatural substrates by performing reactions that are absent in the biological world. By taking inspiration from biological assemblers, the authors blur the lines between artificial and natural molecular machines and bring a new twist to the biomimicry approach.

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