DNA-Templated Synthesis: More Versatile than Expected

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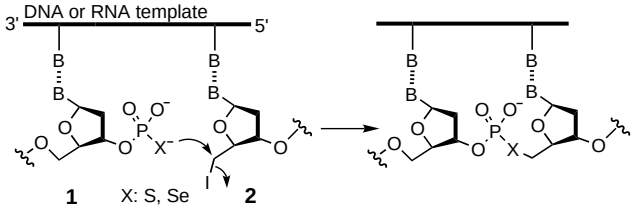
It has been known for almost twenty years that nucleic acids may promote chemical reactions. Catalytic nucleic acids can be found in nature or evolved through in vitro selection processes.[1] Structural and functional investigations suggest that catalytically active nucleic acids act in a similar manner to enzymes: they promote chemical reactions through the precise spatial alignment of the reaction partners, the stabilization of transition states, and binding of reaction products in an elaborate manner.[1] Recent reports reveal new facets of nucleic acid promoted chemistry and indicate that DNA strands are able to promote chemical reactions by bringing reaction partners in close proximity of each other rather than by precisely aligning the reactive groups. Herein we focus on recent progress made in this diverse field.[2] For deeper insights we refer to the literature cited in the references.

The ability of nucleic acid templates to promote coupling of adjacently annealed reaction partners to form the corresponding ligation products has been known.[3] This feature has been exploited in the race for the development of new and efficient methods for the detection of nucleotide variations such as single nucleotide polymorphisms (SNPs) in genes. Kool and co-workers have reported chemical autoligation processes, including the reaction of a phosphothioate or -selenoate anion **1** on one strand with a 5′-carbon atom **2** that bears an iodide leaving group on the other strand (Scheme 1).[4]

Efficient ligation is only observed when complementary templates are applied for the binding of the oligonucleotide reagents **1** and **2**. Mattes and Seitz recently demonstrated that



Scheme 1. Chemistry of the phosphothioate and -selenoate autoligation of DNA.[4] B = nucleobase.

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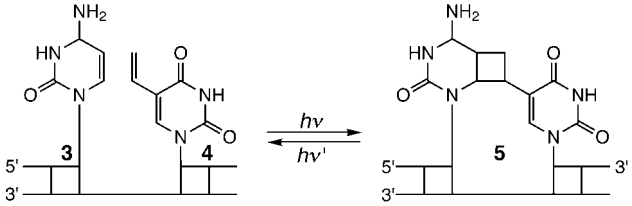
two modified peptide nucleic acid (PNA) strands that are complementary to an adjacent DNA target sequence can be sequence-specifically ligated.[5] These results indicate that sequence specificity is not limited to a DNA phosphodiester backbone.

Saito and co-workers reported the photoreversibility of DNA-mediated ligation of oligonucleotides through 5-vinyldeoxyuridine (Scheme 2).[6] The different photochemical properties of the starting materials **3** and **4** and of the [2+2] adduct **5** facilitates switching between ligation and the reverse process. The authors suggest that this photoligation approach may find applications in DNA engineering and nanotechnology.



Scheme 2. DNA-templated photoreversible ligation of oligonuleotides through 5-vinyldeoxyuridine.[6] DNA double stranded regions are represented as a ladder for simplicity. hν: $\lambda = 366$ nm, hν′ = 302 nm.

A new aspect of DNA-templated synthesis was described by Czlapinski and Sheppard, who reported the assembly of metallosalen–DNA conjugates. These compounds provide a new class of metal–DNA hybrids, which are potentially useful for targeted nucleic acid cleavage or for the development of biosensors (Scheme 3).[7] The formation of these assemblies is presumably driven by several template effects. First, two salicylaldehyde moieties of modified oligonucleotide reagents are brought into close proximity of each other by a complementary DNA template. The resulting complex in turn serves as a template for binding a metal ion (Mn^{II}, Ni^{II}), which subsequently drives salen formation as a result of a metal-templated reaction between the aldehydes and ethylenediamine.

A recent publication by Gartner and Liu indicated that DNA is able to direct chemical reactions sequence-specifically in a more versatile way than was previously thought.[8] Two different DNA architectures, helix terminus (**T**) and hairpin (**H**), were equipped with electrophiles and treated with nucleophiles linked to a complementary DNA oligonucleotide (Figure 1). Both approaches led to the formation of

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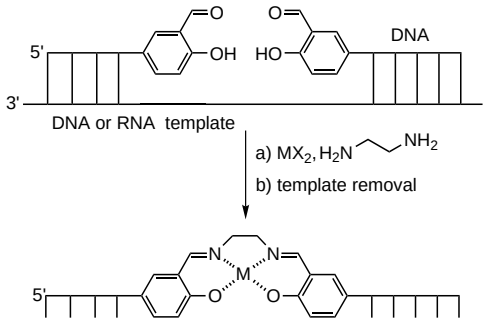
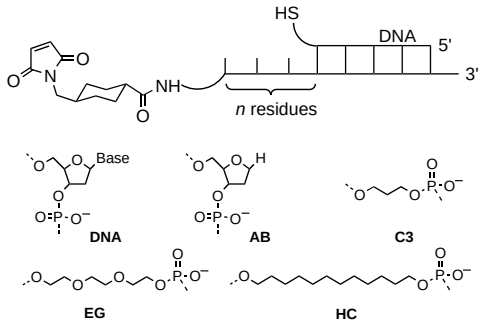


Scheme 3. Nucleic acid templated metallosalen–DNA assembly.[7] M = Mn^{II}, Ni^{II}.



Scheme 4. Distance dependence of DNA-templated synthesis.[8] Investigated constructs: n = 1–30 (**DNA**), 9 (**AB**), 9 (**C3**), 6 (**EG**), 5–6 (**HC**).

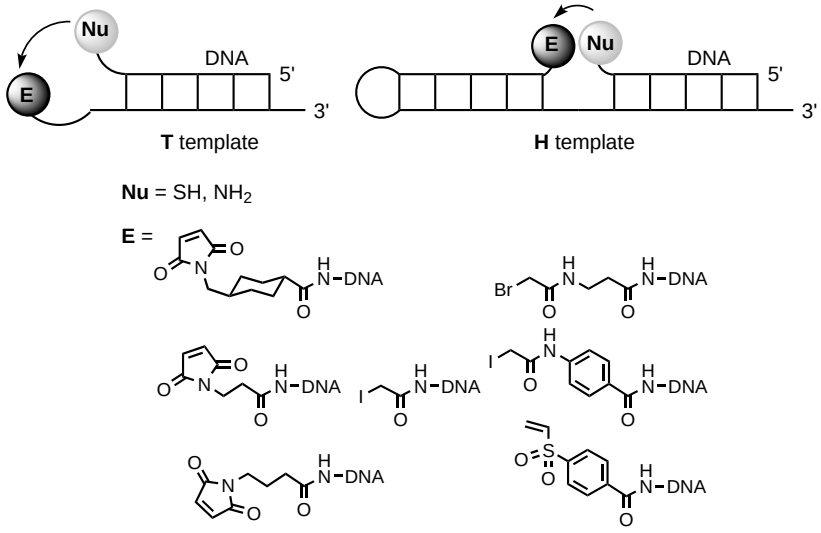


Figure 1. Synthesis directed by helix terminus (**T**) and hairpin (**H**) templates.[8] E = electrophile, Nu = nucleophile, DNA double stranded regions are represented as a ladder for simplicity.

the expected reaction products, whereas little non-templated intermolecular product formation was observed. Remarkably, the reported DNA-templated reactions include a variety of reaction types and reactant structures, despite considerable variations in their transition-state geometry, steric hindrance, and conformational flexibility.

Interestingly, it was found that single nucleobase mismatches introduced in the DNA duplex caused a more than hundred-fold decrease in the reaction rate. However, the origins for the almost ubiquitous sequence selectivity in the DNA-templated reactions remains to be fully elucidated. Gartner and Liu further investigated how the length and the nature of the linkers that bear the reactants influence product formation (Scheme 4). Reactants that were separated by only one base reacted with rates similar to those that were separated by up to 30 bases, while maintaining sequence specificity. Furthermore, templates in which the linking nucleotides were replaced with any of the alternatives shown in Scheme 4, had little effect on the rates of product formation, which indicates that structural elements of DNA are not responsible for the observed distance independence. The sequence specificity and distance independence suggest that mixtures of reagents may be able to react predictably with complementary mixtures of templates. In future, it should be possible to program chemical reactions in a ordered and predictable fashion by attachment of a DNA sequence as a specific reaction tag. Gartner and Liu have reported the first promising results along this line. Nevertheless, the general applicability of this approach remains to be established.

The described developments suggest that DNA-templated synthesis is a phenomenon that applies to a remarkable variety of chemical reactions and may be more general in nature. The ease of automated DNA synthesis, predictable binding, and established methods for nucleic acid amplification and sequence analysis render DNA a promising template for future developments and applications. DNA-templated synthesis is still an emerging field with a great potential for further advancements in organic and supramolecular synthesis, combinatorial chemistry, and biotechnology.

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