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Chemistry of nucleic acids: impacts in multiple fields

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Abstract

Research in nucleic acids has made major advances in the past decade in multiple fields of science and technology. Here we discuss some of the most important findings in DNA and RNA research in the fields of biology, chemistry, biotechnology, synthetic biology, nanostructures and optical materials, with emphasis on how chemistry has impacted, and is impacted by, these developments. Major challenges ahead include the development of new chemical strategies that allow synthetically modified nucleic acids to enter into, and function in, living systems.

The fields of research involving nucleic acids have been marked by amazing progress in the past decade. This recent work has been notable for both its diversity—covering many varied fields of research—and its breathtaking pace, with huge numbers of scientists and engineers diving into the pool.

Research and technology development involving DNA and RNA has been broadly attractive for many reasons. First is the relevance to biology and medicine; thus many of the developments have involved new basic findings in biology. Moreover, many of the technological developments are aimed at eventual application in medicine (either diagnostic or therapeutic). Second is the variety of predictable structures formed by DNA. This has encouraged not only chemists and biologists (who have a longer history with DNA) to make new tools, but also others in the fields of physics and engineering to enter the field as well. Third is the widespread availability of DNA: a large number of commercial sources now offer oligonucleotides of widely varied sequence and length and with a wide variety of modifications to be ordered at reasonable cost and shipped quickly. Moreover, high-throughput synthesizers have made large numbers of DNAs available at an attainable cost as well.

Natural discoveries inspire chemistry

Although nucleic acids have been studied for decades, there is room for surprising new discoveries in this field. The last ten years have uncovered several new and highly important fundamental aspects of the biology of nucleic acids, and many of these are inspiring chemically oriented research. One of the biggest findings in all of biology in the past decade

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has been the realization that there are many thousands of RNAs in the cell that are not classical messenger RNAs (mRNAs) or transfer RNAs (tRNAs) but which have biological functions nevertheless.[1] These RNAs range from very long (stretching thousands of nucleotides over multiple genes) to very short (20 nucleotides (nt) or less), and are encoded by either strand (i.e. sense or antisense) of the genomic DNA. The presence of the additional complexity afforded by cellular networks of interacting RNAs and proteins has helped explain how humans can be so complex with a relatively small genome (much smaller than some plants, for example).

Gaining a good deal of attention among chemists have been the various small noncoding RNAs (ncRNA) that are under study.[2] These RNAs are often as short as 20 nt and do not encode any polypeptide sequence (hence the name). The most important examples include miRNAs (micro RNAs) and siRNAs (short interfering RNAs). These latter RNAs have become the standard tool for downregulating genes in biological studies. They are most active as short RNA duplexes, and given the relative accessibility of synthetic RNA, they have been widely studied by chemists and biologists. Many examples of chemically modified siRNAs have been described over the past decade.[3] Modifications have been aimed at improved cellular uptake, enhanced stability against degradation, and altered activity in gene suppression. Chemically synthesized siRNAs are under intense study as drug candidates, and thus have entered the medicinal chemistry realm.[4]

Another fascinating class of small non-coding RNA is the riboswitches, which started as designed oligoribonucleotides that could switch activity (such as ribozyme activity) in response to this binding.[5] Subsequently, searches were carried out for small-molecule binding sequences within the genomes of organisms, and they were found in bacteria (and later in a wide variety of organisms). Their function as genetic switches have been explored in recent years.

Developments in synthesis and modification

The chemistry of DNA modification, which blossomed in the 1980s, has undergone some important new advances in the past ten years or so. A number of new conjugation methodologies have been developed recently that have supplanted some of the earlier approaches by offering greater simplicity, milder conditions, and higher yields. These allow the researcher to add fluorescent tags, affnity tags, electrochemical reporters, and groups to aid cellular uptake. For example, metal-mediated carbon-carbon bond forming chemistries have shown real utility in recent years.[6]

One of the most important new chemistries for synthesis of DNA conjugates has been the [3+2] alkyne-azide cyclization (Huisgen-Sharpless ‘‘click’’ chemistry).[7] The reaction is mild and proceeds readily in water. Importantly, the reaction is strongly ‘‘bioorthogonal’’—that is, the reacting groups do not react with typical functional groups found in biological systems. The development of this chemistry for DNA and RNA conjugation has led to the availability of ‘‘clickable’’ reagents (for example, fluorophores with azides or alkynes attached) that can be readily attached to an oligonucleotide with the proper functional group.[8] The reaction is typically carried out with Cu[I] catalysis, although recent application

of strained alkynes has opened the possibility of carrying out the reaction without this metal as well.[9]

Useful chemically modified nucleotide monomers were explored widely this past decade. One example is designed monomers that allow one to generate unstable reactive intermediates in DNA, for the purpose of studying their biochemistry and biology. Examples include precursors for photochemical generation of free radicals on deoxyribose[10] and monomer nucleotides of putative damaged nucleotides.[11] Marx has shown that C-4′ alkylated nucleotides can be highly effcient polymerase substrates that can enhance fidelity of replication.[12] Hocek has demonstrated methods for rapidly introducing aldehydes on DNA bases, which yields a ready site for addition of labels.[6c]

Another important chemical advance in nucleic acids research has been the development of improved chemistry for the synthesis of RNA. The chemistry of Scaringe, who developed a new set of protecting groups for RNA in the late ‘90s (Fig. 1),[13] was especially important in the past ten years because of the strong demand for siRNAs among biologists.

The last decade has also seen vigorous development of DNA analogs having useful or unusual properties. Notable examples studied most in the past ten years include conformationally locked analogs LNA (locked nucleic acids),[14] BNA (bicyclo-DNA),[15] TNA (threose nucleic acids),[16] GNA (glycerol nucleic acids),[17] and xDNA.[18] The first two, LNAs and BNAs (Fig. 2), bind very strongly to DNA/RNA complements, due largely to rigidification of the otherwise relatively flexible ribose ring. Although developed prior to this decade, LNAs in particular have seen much study recently, with many biological applications reported, and derivatization with fluorophores and other moieties.[19] TNA, having a smaller sugar than natural nucleic acids, is of special interest from the molecular evolution standpoint; despite its simplicity, it hybridizes well to complements and can even be a substrate for polymerase enzymes.[20] And speaking of simplicity, one of these modifications, GNA, is remarkable because it hybridizes exceptionally strongly given its lack of a ribose (or indeed, any) ring. It is also quite simple to synthesize from simple chiral starting materials, allowing modified bases to be installed easily.[21] Finally, a different kind of DNA analog that has a natural phosphodiester backbone but with an entirely non-natural base pairing scaffold was developed during this decade, namely expanded DNA (xDNA); it is described in more detail below (see Synthetic Biology).

Nucleic acid biotechnologies

Of all the technologies built around DNA in this past decade, perhaps the highest impact came (and is continuing to come) from the new generation of high-throughput sequencing methodologies, most of which required substantial chemical innovation. Venter made a groundbreaking demonstration during the human genome project that ‘‘shotgun’’ sequencing approaches (combining many short reads and sorting them out computationally) could work to yield complex genomes quickly.[22]

This realization rapidly led to the development during this past decade of several high-throughput strategies for sequencing genomes more rapidly and cheaply. Examples of some of these approaches include the pyrosequencing approach; sequencing by synthesis (SBS)

and by hybridization (SBH) approaches in which chemically blocked nucleotides are added (with their signal) by polymerase, then chemically deblocked to allow the next step (Fig. 3); and the SOLiD approach, which involves ligation of nucleotide dimers.[23] Even more effcient methodologies are under continuing development by chemists, biologists, physicists, materials scientists and engineers.

In recent years there has been an increase in interest in not only the genome, but also epigenetics, and in particular, the state of CpG methylation, as specific methylation sites in the genome have become linked with cancer.[24] Chemists have reported a number of methods for detection of methylation of cytosine, including a bisulfite assay[25] and osmium oxidation.[26] Approaches to identifying methylation state at particular sites have also become commercialized recently. In addition, although it has been known for decades that 5′-hydroxymethylC exists as a common base in some bacteriophages, recent work has shown that it occurs to some extent even in mammalian tissues,[27] and the oxidative mechanism of its synthesis is being uncovered.[28]

In addition to full sequencing methodologies, this was the decade of massive development of methods for detecting and identifying short nucleic acid sequences in solution. Hundreds of new types of probes were developed; indeed, it seems now that every chemical journal issue offers one or two more papers describing new DNA detection methods. The majority of these have made use of fluorescence, either in labels directly attached to probes or associated with the DNAs otherwise.[29] It is clear that most of the hundreds of probes are unlikely to be developed for widespread use, and there are far too many to describe here. However, we will mention four approaches, either because they employed a dominating concept or offered real novelty in approach. These are molecular beacons (MBs), electronic DNA detection, nanoparticles, and templated chemistry. Although MBs were initially developed nearly two decades ago,[30] their simplicity of design (based on a stem-loop structure) has remained appealing. This past decade saw many dozens of reports of variations of the beacon design, and uses in detecting not just nucleic acids but also proteins.[31] Electronic DNA detection involves generating a change in an electron current signal upon hybridization; usually this involved attachment of a redox-active group (such as ferrocene) to a structured DNA.[32] The approach is appealing not only because it can offer high sensitivity, but also because it marries well with the ongoing rapid development in solid-state electronics.

Nanoparticle-based DNA detection methods also came into their own in the last few years;[33] the particles offered unusual fluorescence or optical reporting activities and high sensitivities in some applications (Fig. 4). This of course required substantial development of chemical methods for conjugating DNAs to such inorganic particles.

Finally, nucleic acid templated chemistry underwent major developments this decade. The approach commonly involves the use of two modified DNA (or PNA) probes that carry reactants; hybridization of these adjacent to one another on a complementary DNA (the analyte) results in a reaction that can yield a fluorescent signal. Several labs (including ours) demonstrated the use of templated fluorogenic reactions for highly sensitive and selective identification of DNAs in solution (Fig. 5),[29b,34] and recently, researchers have shown the

approach to function in intact bacterial and human cells (where RNA is the template) as well.[35] DNA-templated chemistry has also moved beyond uses in DNA detection, by offering a way to encode chemical libraries and allow them to undergo selection and amplification.[36] Moreover, Liu demonstrated the use of DNA templated chemistry in the discovery of new aqueous bond-forming reactions.[37]

Synthetic biology

The field of Synthetic Biology has exploded as the need for modified cells and organisms in medicine, environmental sciences and energy fields has become widely recognized. As a whole, the field is defined by biologically functioning systems that have synthetic (designed) components.[38]

For biologists, who take a top-down approach starting with already-functioning cells, this field entails adding, subtracting and mixing existing proteins and pathways to alter phenotypic function. For chemists, who like to work from the bottom up, the field (‘‘chemical synthetic biology’’) means designing the basic chemical components from scratch—new amino acids, new nucleotides, altered carbohydrates, modified metabolites, substrates and cofactors. These new components can then be inserted into live pathways for either basic science study or for technological utility. Necessarily this field has focused to a major degree on nucleic acids.

One of the biggest breakthroughs in this area was the demonstration of assembly of a functioning genome by Venter.[39] Venter extended the known methodologies of synthetic gene assembly (which prepares DNAs of ca. 1000 bp) on a massive scale, making a 1 megabase bacterial genome that was shown to function correctly. This required important developments in chemical DNA synthesis, gene synthesis, enzymatic repair methods, artificial chromosomes, and others, and required a large team of biologists to complete.

On the more chemical side, there has been a good deal of development of new functional base pairs and augmented genetic alphabets for DNA. Benner has continued the development of base pairs that utilize rearranged hydrogen bonding patterns.[40] Several groups described base pairs consisting of two ligands, with a metal acting as a bridge between the two.[41] Kool, Romesberg and Hirao, among others, demonstrated dozens of examples of replicable base pairs that lack hydrogen bonding and even many that lack purine and pyrimidine architectures.[42] Some examples have shown impressive abilities to be functional in PCR reactions alongside natural DNA pairs.[43] The work has culminated recently in examples of unnatural bases that function to encode information in cells, by being read correctly by the cellular replication machinery.[44] One of the future uses of new genetic alphabets will be the biological encoding of many new designer amino acids into protein.

Some chemists have been inspired to go beyond the purine-pyrimidine architecture to avoid natural DNA base pair structure altogether. This has produced base pairing designs—new genetic sets—that yield full helices that are larger than the natural one. The first of these was xDNA, which is analogous to DNA but with bases enlarged by benzo-homologation.[18,45] It is composed of eight letters rather than Nature’s four, and is not only more stable than

natural DNA, but is inherently fluorescent. Other examples of new DNA-like genetic architectures have been described, including base pairs with four hydrogen bonds[46] and bases with ethynyl homologation.[47] Although such fully unnatural designs might generally be expected to interact with natural enzymes poorly, experiments show that this might not always be the case. For example, our laboratory demonstrated that xDNA can be replicated in vitro by some DNA polymerases.[48] Even more surprising was the recent observation that xDNA bases can correctly encode genetic information in a living cell.[49]

Nanostructures and materials

A growing trend recently, followed by chemists and materials scientists, has been the building of functioning nano-structures from DNA. The field was seeded almost entirely from the early work of Seeman,[50] and has branched and blossomed in many directions recently. The early parts of the decade saw rapid development of strategies for formation of tiled 2-D DNA structures,[51] which yielded important insights into how to build complex structures from simple repeatable helical units and crossover junctions. Seeman also showed how to build 3D closed structures (such as polyhedrons) from DNA by developing strategies for corners and edges.[52] More chemists have recently entered the design arena and have made chimeric structures containing DNA and small molecules,[53] DNA and metal complexes[54] and DNA and inorganic nanoparticles.[55] Over time, designs for forming an impressive array of structures, such as tubes[56] and buckyballs,[57] from DNA have been demonstrated.

One of the most influential recent developments has been the ‘‘DNA origami’’ designs of Rothemund, who used single-stranded phage DNA combined with hundreds of different oligonucleotides to make an impressive array of closed structures (Fig. 6).[58] One highly appealing aspect of this approach is that half of the DNA is easy and cheap to obtain (circular phage DNA), and the closed nature of that DNA makes the ultimate structures more stable. Many new examples and applications following this approach have emerged and no doubt will continue to appear.[59] Synthetic DNA can be used not only to build static structures, but also mobile ones. This has led to the development of a number of robots that move or perform work in response to a stimulus or molecular fuel.[60]

Finally in the field of functional nanomaterials and devices has come the recent development of DNA as a scaffold for structures with useful optical properties. Several laboratories have demonstrated methods for incorporating several fluorophores into DNA oligonucleotides, and have explored the unusual fluorescence emission properties that result from photophysical interactions between them.[61] Researchers have reported ‘‘superquenching’’ emissive molecules,[62] white light-emitting molecules,[63] photonic wires,[64] polychromatic enzyme sensors,[65] multicolor biological dyes (Fig. 7),[66] and sensors of organic vapors built from these modified DNAs.[67]

The next decade

Extrapolating recent trends allows us to make some predictions about the coming decade of chemical research in the nucleic acids. One of the biggest trends among chemists has been the increasing interest in biology and medicine. In the next ten years we will see a move

toward biotechnological applications in vivo—that is, in cells and whole organisms. Intracellular applications allow researchers and clinicians to avoid removing the contents from the cell prior to analysis, saving time and cost. As a result, chemists are likely to spend more time thinking about issues such as biostability and intracellular delivery. Getting synthetic nucleic acids to pass through the cellular membrane is a long-standing problem; we suspect that the next ten years will see strong advances in that direction.

A second, and related, major trend for the next ten years will be the rapid development of synthetic biology. For chemists, this means increasing development of replacements for cellular components, and inserting them into functioning biological pathways. In the nucleic acids, we will see more studies of modified backbones and bases in vivo, and we will see tests of whether altered cells can take up nucleic acid components from the medium. Pathways involving synthetically altered ribozymes, riboswitches, and other biologically active RNAs will be explored. Many applications might arise, including the ability to encode many more amino acids than nature currently allows. The tools of chemistry will work intimately with those of molecular biology to make this happen.

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Biographies

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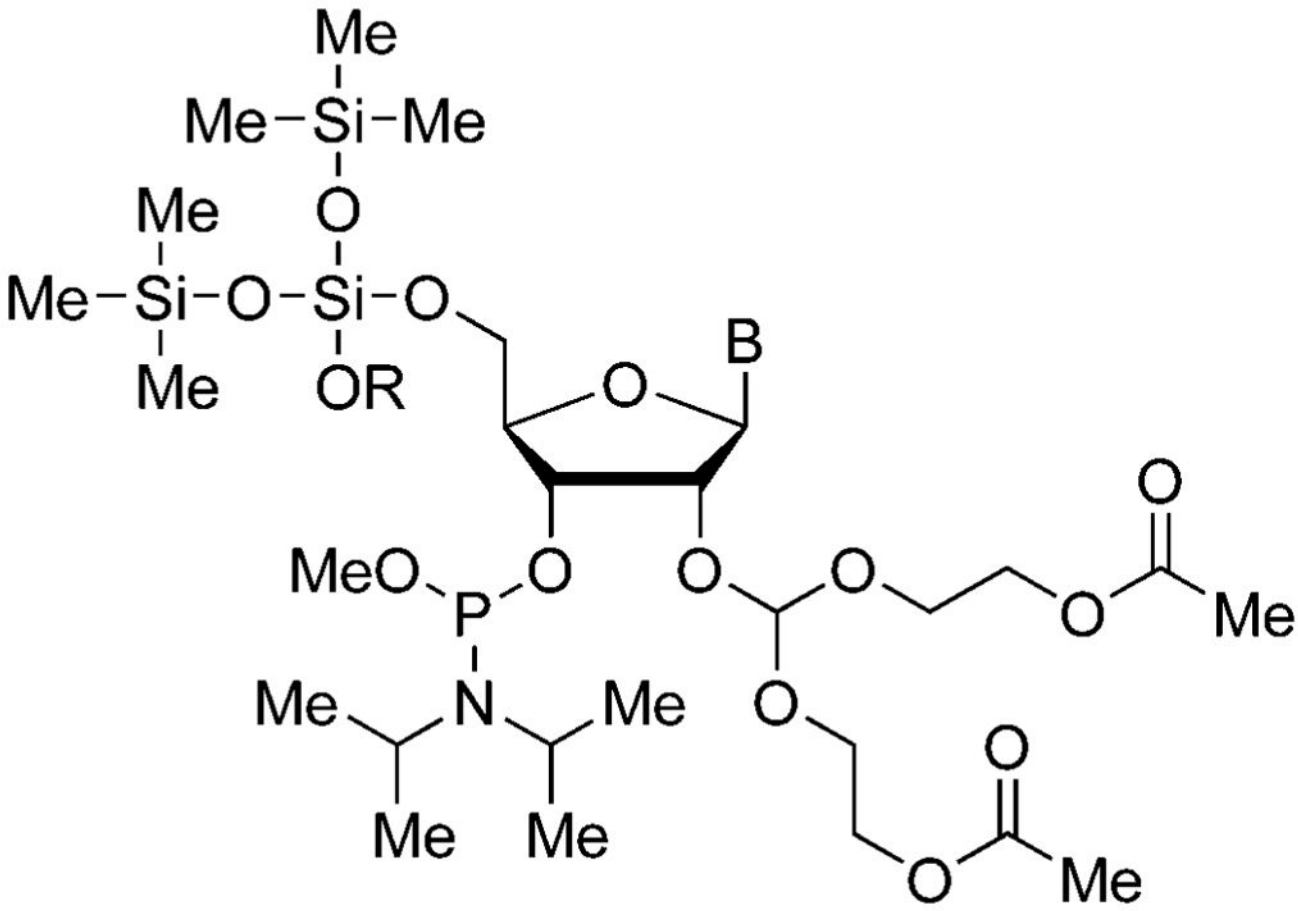

Fig. 1.
RNA synthesis building block developed by Scaringe.

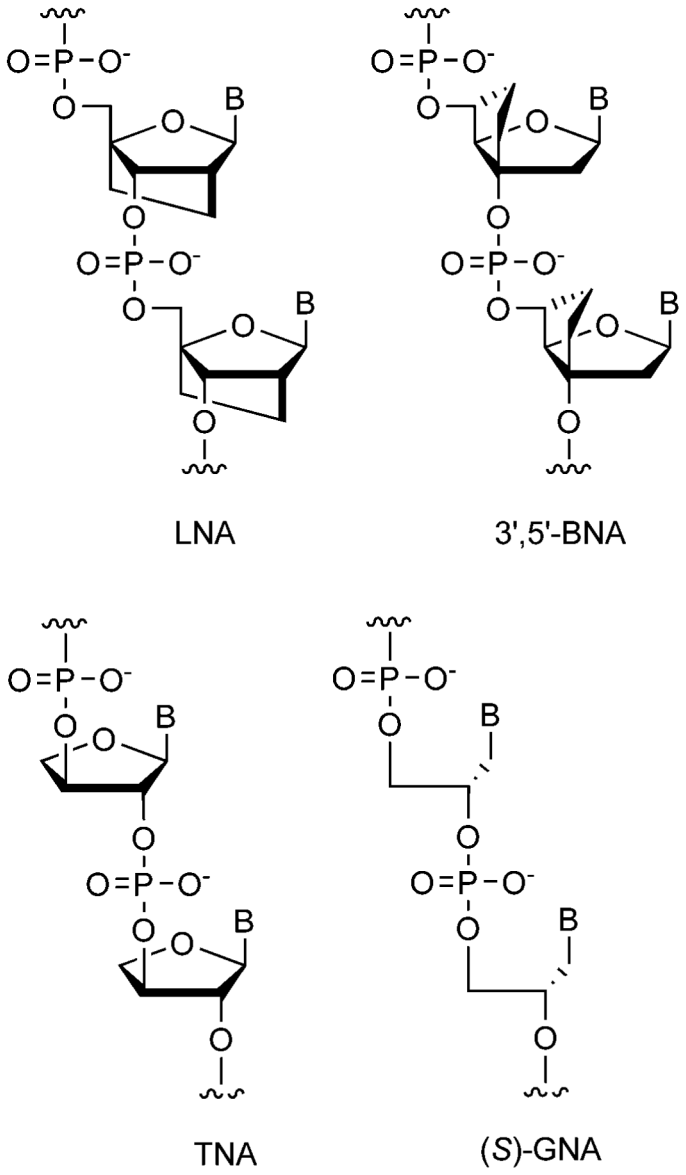

Fig. 2.
Structures of backbone analogs of DNA studied recently.

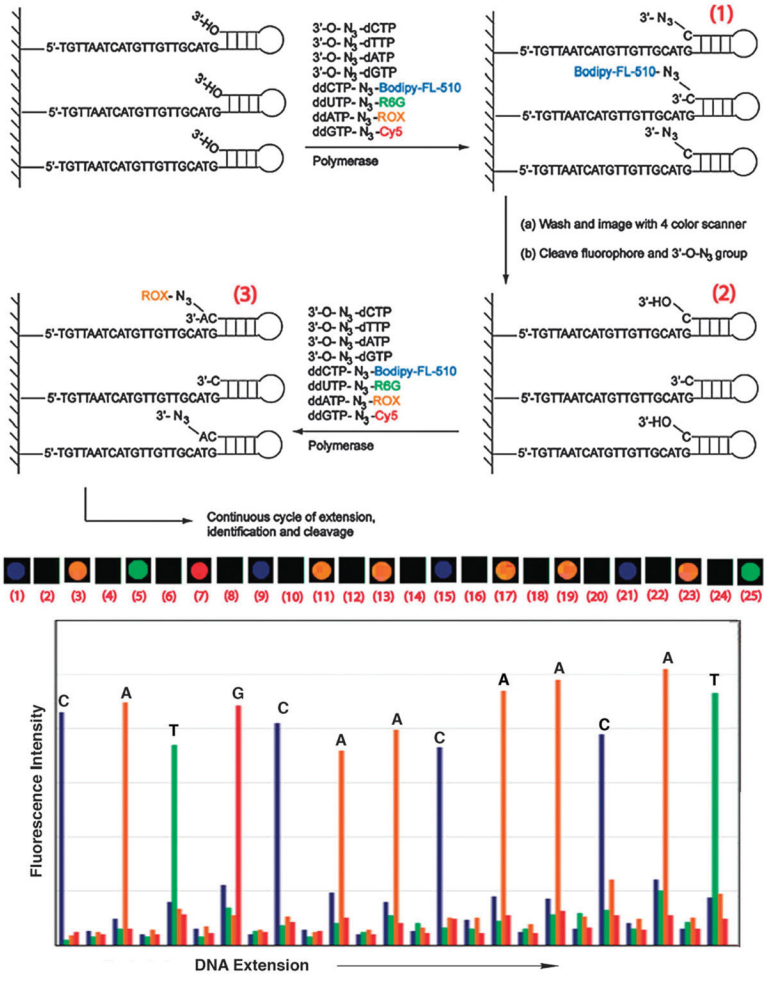

Fig. 3.

Example of sequencing by synthesis (SBS). Adapted with permission from PNAS, ref. 23a; Copyright 2006 National Academy of Sciences, USA

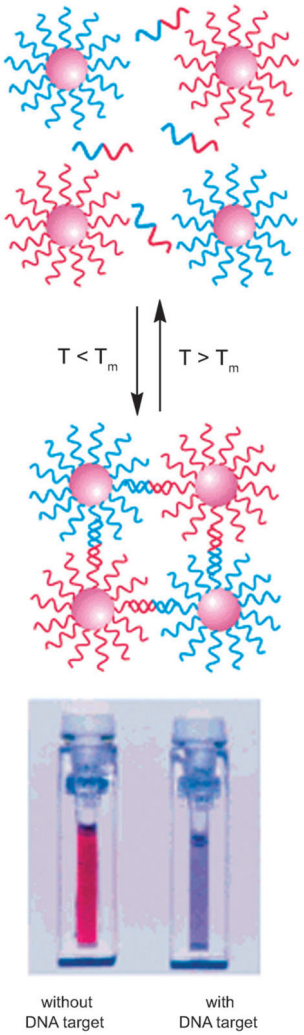

Fig. 4.

Detection of DNA with inorganic nanoparticles. Adapted with permission from ref. 33a. Copyright 2005 American Chemical Society.

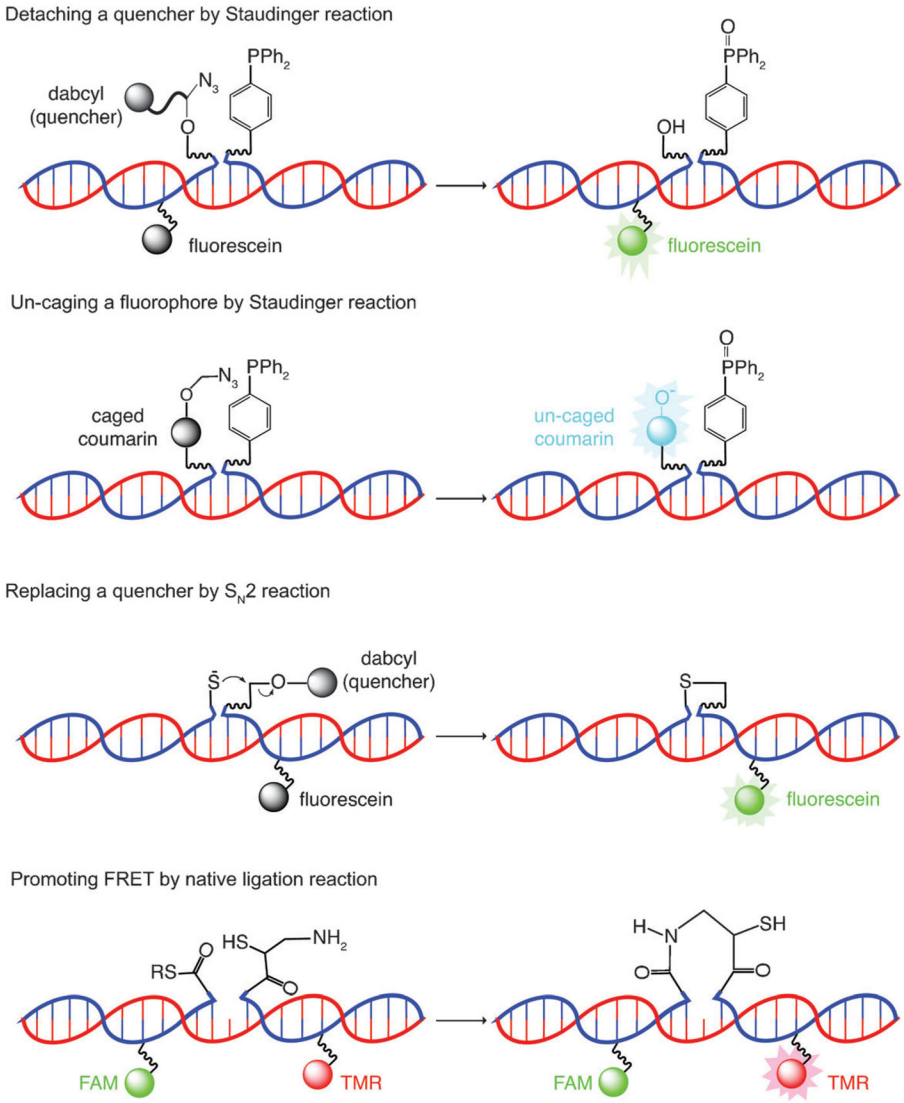

Fig. 5.
Examples of DNA detection with templated chemical reactions.

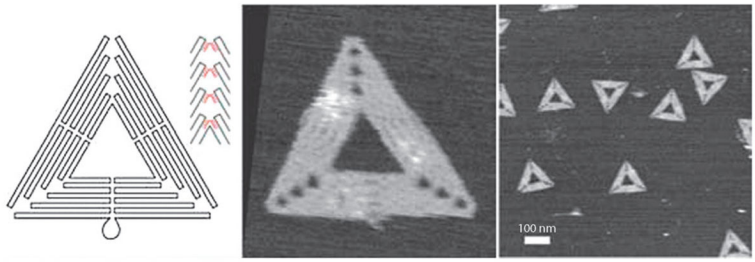

Fig. 6.

DNA origami shapes: folding path and AFM images. Adapted with permission from Macmillan Publishers Ltd: Nature, ref. 58, Copyright 2006.

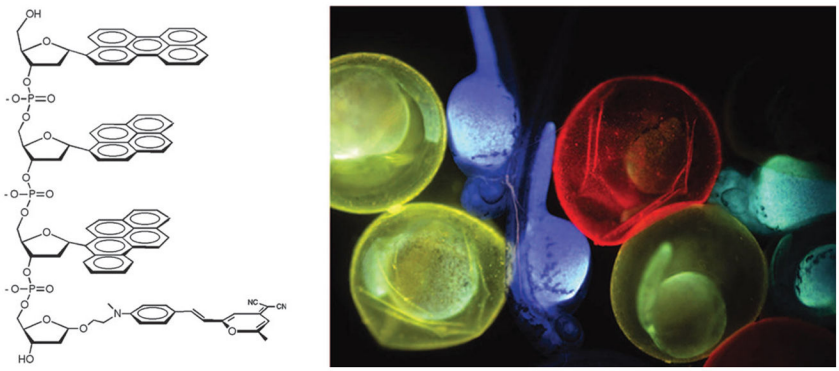

Fig. 7.

Example of DNA oligomer bearing multiple fluorophores and application in imaging biological systems. Adapted with permission from ref. 66. Copyright 2009 American Chemical Society.