Stable Synthesis of Modified DNA using Novel Protecting Groups

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Background

Chemically synthesized DNA has found usage in a large number of fields from diagnostics and therapeutics to sensors to construction of nanoscale structures. The phosphoramidite-based method for chemical synthesis of DNA has been instrumental in enabling these applications and is the most widely used procedure for DNA synthesis due to its high efficiency. This method requires the use of chemical groups, known as protecting groups (PG) that can be selectively installed and removed from the precursor molecules at various stages of the synthesis to allow the reactions sequence to occur only at the desired locations and thus produce the correct DNA structures. However, many of the most interesting applications require modification of the natural DNA structure, such as addition of fluorescent signaling groups or chemical reactive groups like the borane group that allows specific deposition of metals onto DNA for use in nano-electronics. But traditional PGs are often incompatible with these modifications, and can cause degradation of the modification, as well as undesired reactions and products. Therefore, there is a need for PGs that can be selectively installed and removed without adverse side effects.

Technology

A University of Colorado research team led by Marvin Caruthers has synthesized and used a new class of PG for phosphoramidite-based DNA synthesis that is stable to modifications, such as the borane group, with only minor modifications of the synthetic cycle. At the same time the removal of these PGs can be carried out under very mild conditions without the use of any chemical bases, which are well known to degrade many fluorescent groups and other useful modifications. Using this new class of PG resulted in successful synthesis of a greater number of nucleotides (between 15-24) with higher yields and purity than current methods.

Figure: Synthesis of protected phosphoramidites.

Such long-chain DNA oligonucleotides are useful in a wide variety of applications including, but not limited to, studying binding and biochemical properties, and therapeutic use.

This technology represents a significant departure from the established PGs, and presents unique properties that will allow for broad applicability in chemical synthesis of modified DNA oligomers.



Key Documents

Exocylic Nitrogen Atom Protected Nucleoside and Method For Producing and Using the Same. PCT filed August 3, 2013.

Reduction of metal ions by boranephosphonate DNA. Org Biomol Chem. 2012 Dec 14;10(46):9130-3. PDF available upon request.