Mimicking the Structure and Function of DNA

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I will describe the design, synthesis, and properties of three classes of nucleoside mimics in which the DNA bases are replaced by unnatural aromatic groups. They are studied both as components of DNA, and as nucleotide monomers. Surprisingly, some of these analogs retain full biochemical and cellular function, despite their large differences from the natural compounds.

Three approaches to this chemical mimicry of DNA will be discussed: first, nonpolar nucleoside shape mimics, which are designed as probes of electrostatic and steric effects in DNA polymerase enzymes. The compounds retain similar shapes as the natural compounds but have varied size, and some are found to have surprising biological activities. The second approach involves the discovery of new composite fluorescent labels and sensors by assembly of fluorescent monomer nucleosides into DNA-like oligomers. Finally, a molecular strategy for design of new genetic systems based on expanded-size base pairs ("xDNA") will be described.

The synthesis of new, biologically-inspired molecules that reproduce some of the structures and activities of their natural counterparts can lead to useful information about how biological systems function. Such work can also lead to new biotechnological tools and to biomedically useful compounds.