

“The modification of DNA with indole-linked nucleotides induces BZ- and Z-conformation and alters its sensitivity to enzymatic cleavage”

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Abstract:

We report the synthesis of C-5 indole-tagged pyrimidine and C-8 indole-tagged purine nucleoside phosphoramidites and their incorporation into a fifteen-base antiparallel DNA duplex. The resulting modified duplexes adopt non-canonical conformations including modified B-DNA conformations, BZ junctions, and left-handed Z-DNA, under physiological conditions, bypassing the specific sequence requirements and high salt concentrations typically required for BZ or Z-DNA formation. Using a panel of twenty-three duplexes containing one to five indole-modified bases linked via either propyl or propargyl linkers, we demonstrate that overall duplex conformation is strongly influenced by propyl-linked indole modifications at dA/dU positions. Among the two linker types tested, the flexible propyl linker promoted conformational plasticity, enabling transitions to BZ or Z-like structures under physiological conditions. In contrast, duplexes containing the more rigid propargyl linkers retained canonical B-form conformations. Modifications placed within or near restriction enzyme recognition sites highlighted the importance of linker flexibility in modulating enzymatic recognition and cleavage. Duplexes with a high density of modifications, particularly those modified on both strands with propyl-linked indole, exhibited marked resistance to digestion by DNase I, EcoRI, SmaI, and XmaI. Termed “Z-inducing chimeras” (ZImeras), these duplexes represent a versatile platform for investigating the biological roles of non-canonical DNA structures, expanding the toolkit for exploring and controlling non-B DNA conformations in both basic research and therapeutic applications.