Deoxypseudoisocytidine (PidC) is an isostere of dC that offers an additional hydrogen-bond donor at the N3 position, compared with the natural dC base. Because of this property, PidC-modified oligonucleotides are primarily used to enhance triple-helix formation between single-stranded polypyrinmidine oligonucleotides and duplex DNA. Under standard conditions, protonation of the N3 position of the single (Hoogsteen) strand is required in order to stabilize triple-helix formation within the C-GC pyrimidine-purine-pyrimidine binding motif. Acidic conditions are required to convert C-GC into (C+)-GC, which drives the Hoogsteen base pairing between the N3-protonated cytidine and G (2). However, under physiological conditions (which are neutral/slightly basic), deprotonation of this cytidine occurs, and Hoogsteen base pairing is disrupted, destabilizing the triple helix. Substitution of PidC for dC in the polypyrinmidine single strand allows for the formation of PidC-dG Hoogsteen base pairs via hydrogen bonding between the N3 of PidC and dG at neutral pH. References