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Supplementary Information

Simulation of the Interactions between Tröger Bases and DNA

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Intercalation Complex of Asymmetric Troger Base (ASYM-INT)

During the simulation of this complex, the phenanthroline moiety remained intercalated in the gap while the proflavine kept interactions with DNA minor groove, as schematized in Figure S1A. According to the distances (Figure S1B), both the diazocin bridge (C) and the Np group were stably equidistant from the base-pairs contaning the gap, which confirms the intercalation (see cyan and green lines in Figure S1B).

Structures extracted from the simulation show that DNA double helix was relatively well conserved, with less zigzag distortions in backbone as compared to those observed in the intercalation complex of symmetric Troger base (see Figure 5C). Eventually, a slight bending towards the major groove can be observed (see structures at 5 and 18 ns in Figure S1C). As with SYM-INT complex, it was observed a decrease in the twist angle, which can be clearly observed at 10, 15, and 20 ns. In this case, however, unwinding was restricted to the base-pairs flanking the intercalation gap, without propagation to the terminal regions of the oligomer.

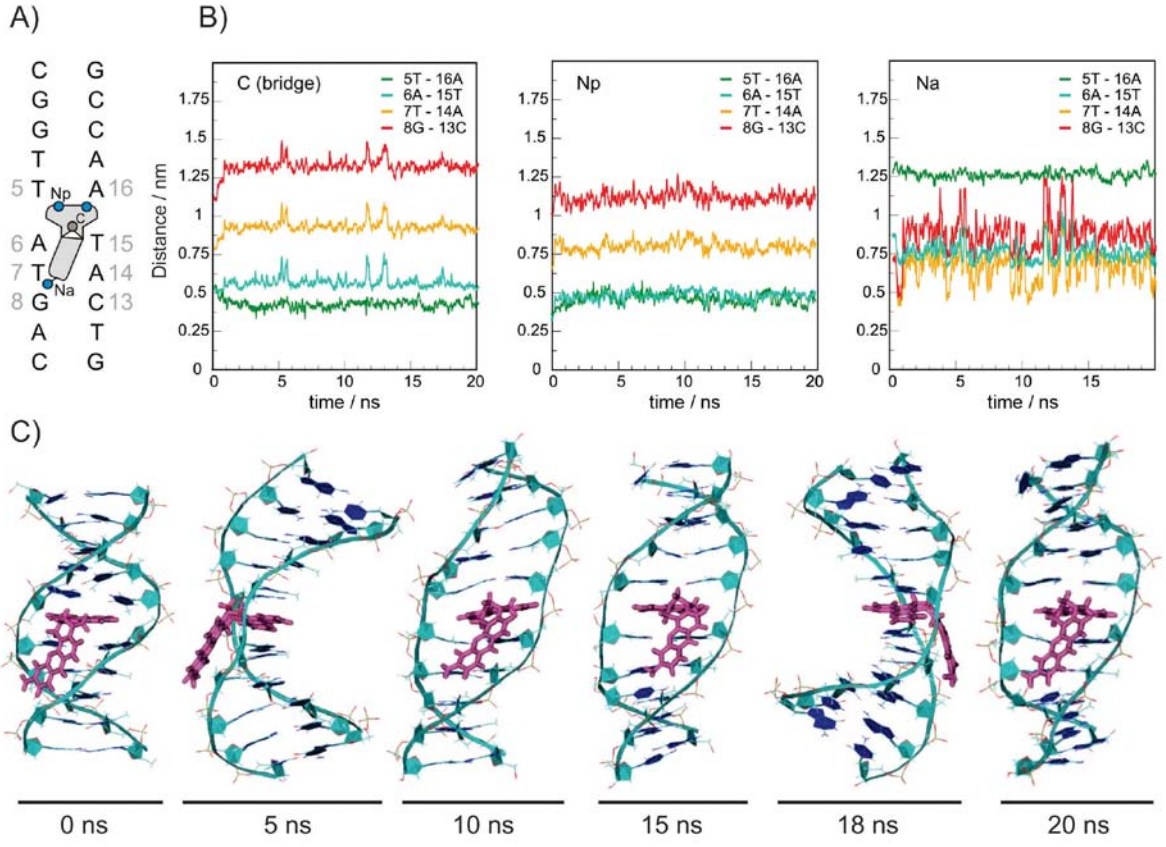

Figure S1. Time evolution of ASYM-INT complex. A) Schematic representation of binding site and binding mode. B) Distances of diazocine bridge (C), amino group (NA) and phenanthroline nitrogen (NP) from the center of mass of 4 base-pairs belonging to the binding site. C) Structures extracted from simulated trajectories.

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α/γ Analysis of ASYM-INT and ASYM-GROOVE

As occurred with SYM-INT complex, intercalation of asymmetric Troger base also induces several α/γ transitions to the t/t region, confirming this low-twist conformation is important during small-molecule intercalative binding. In the minor groove binding, a contrary effect was observed, since the Troger base seems to inhibit α/γ transitions into non-canonical conformations and DNA remains mainly in the g–/g+ ground state during the entire simulation.

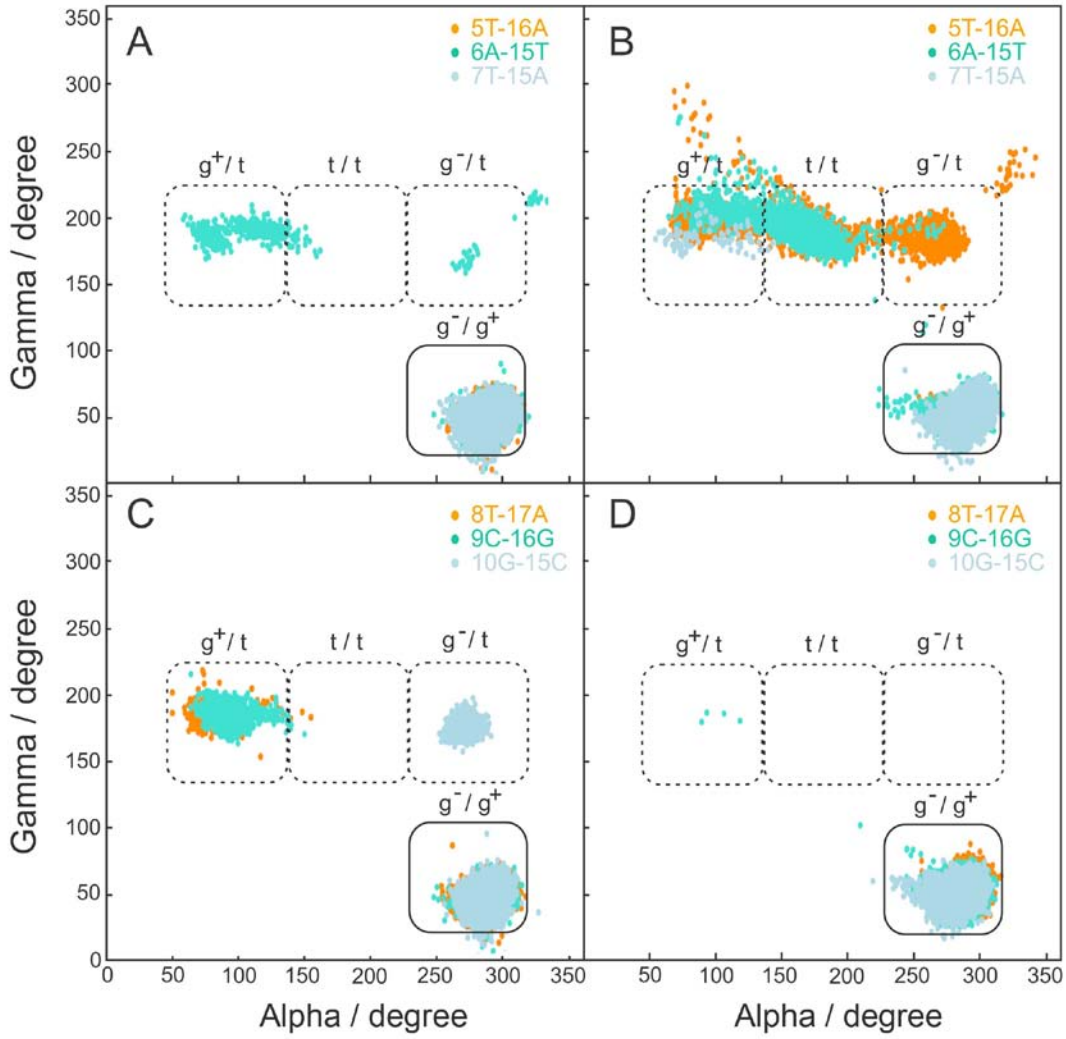

Figure S2. α/γ sampling for the nucleotides belonging to the assymetric Tröger binding site. A) DNA-GAP; B) ASYM-INT; C) DNA-NOGAP; D) ASYM-GROOVE. The global (solid line) and local (dashed line) minima are indicated.

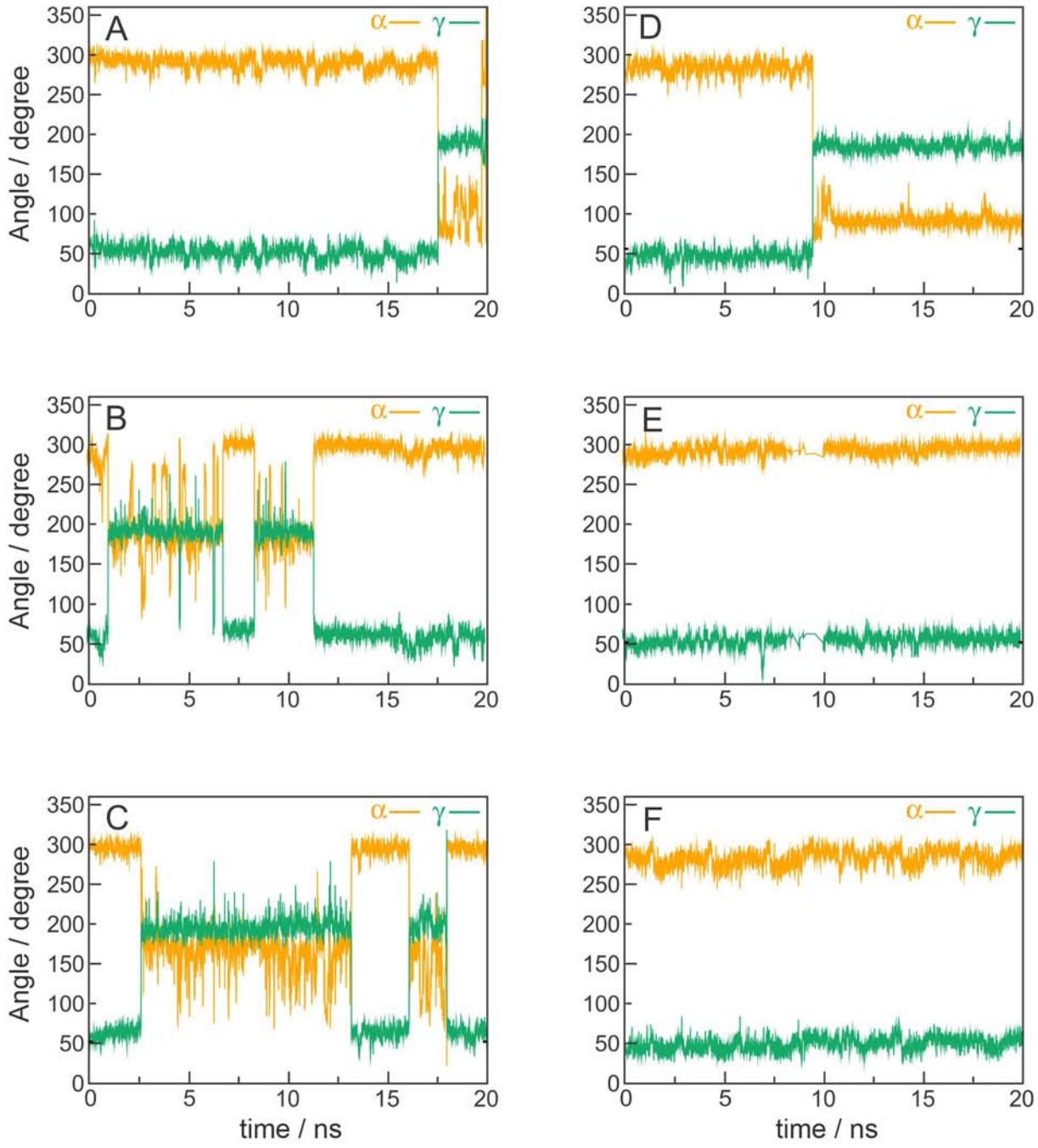

Figure S3. Temporal analysis of α (orange) and γ (green) transitions. The left column shows transitions for 6A nucleotide in DNA-GAP (A); SYM-INT (B); and ASYM-INT (C). The right column shows the transitions for 16G nucleotide in DNA-NOGAP (D); SYM-GROOVE (E); and ASYM-GROOVE (E).

ε/ζ Analysis of ASYM-INT and ASYM-GROOVE

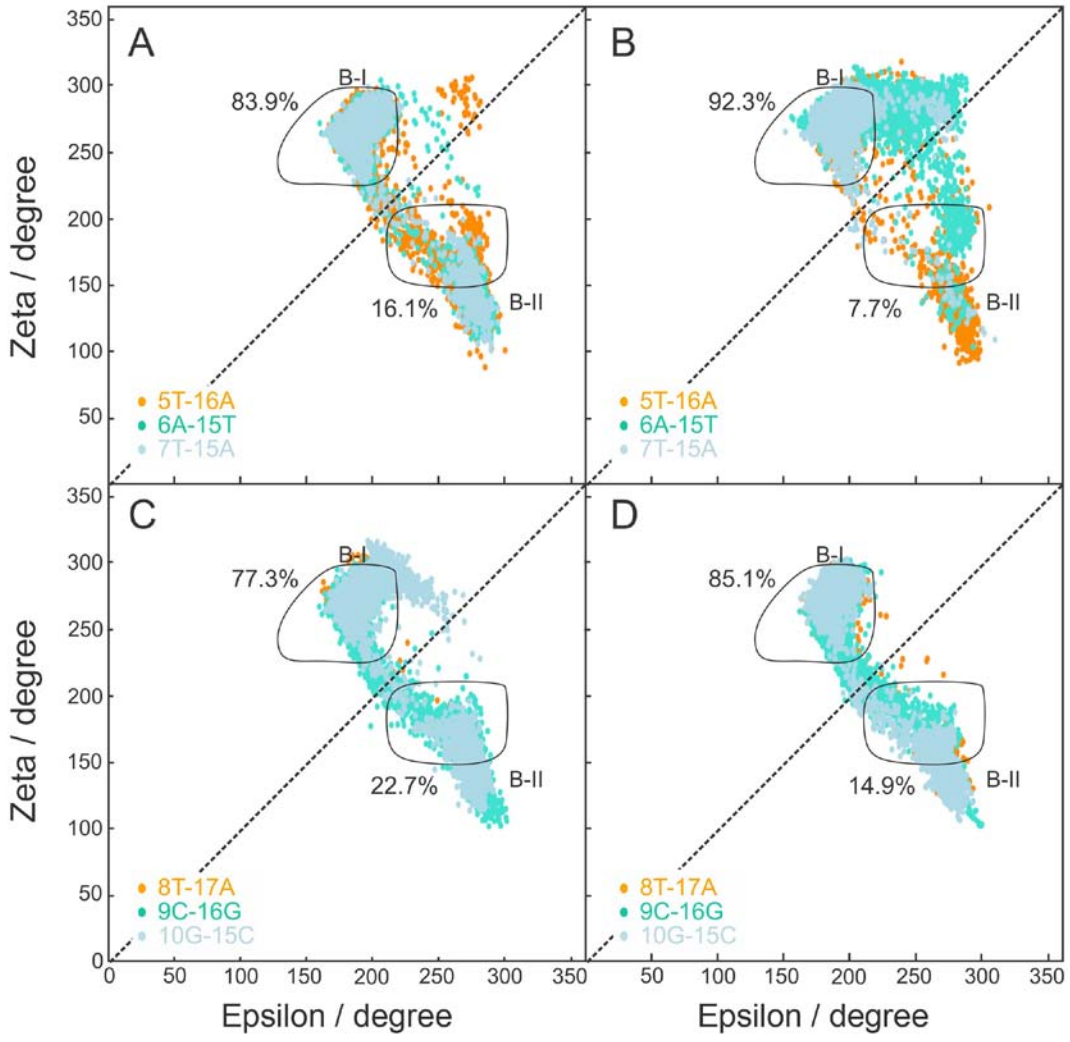

Figure S4. ε/ζ sampling for the nucleotides belonging to the asymmetric Tröger binding site. A) DNA-GAP; B) ASYM-INT; C) DNA-NOGAP; D) ASYM-GROOVE. The BI and BII regions are indicated, as well as the percentual occurrence of each canonical conformation during the simulation time.

Rise/twist analysis of ASYM-INT and ASYM-GROOVE

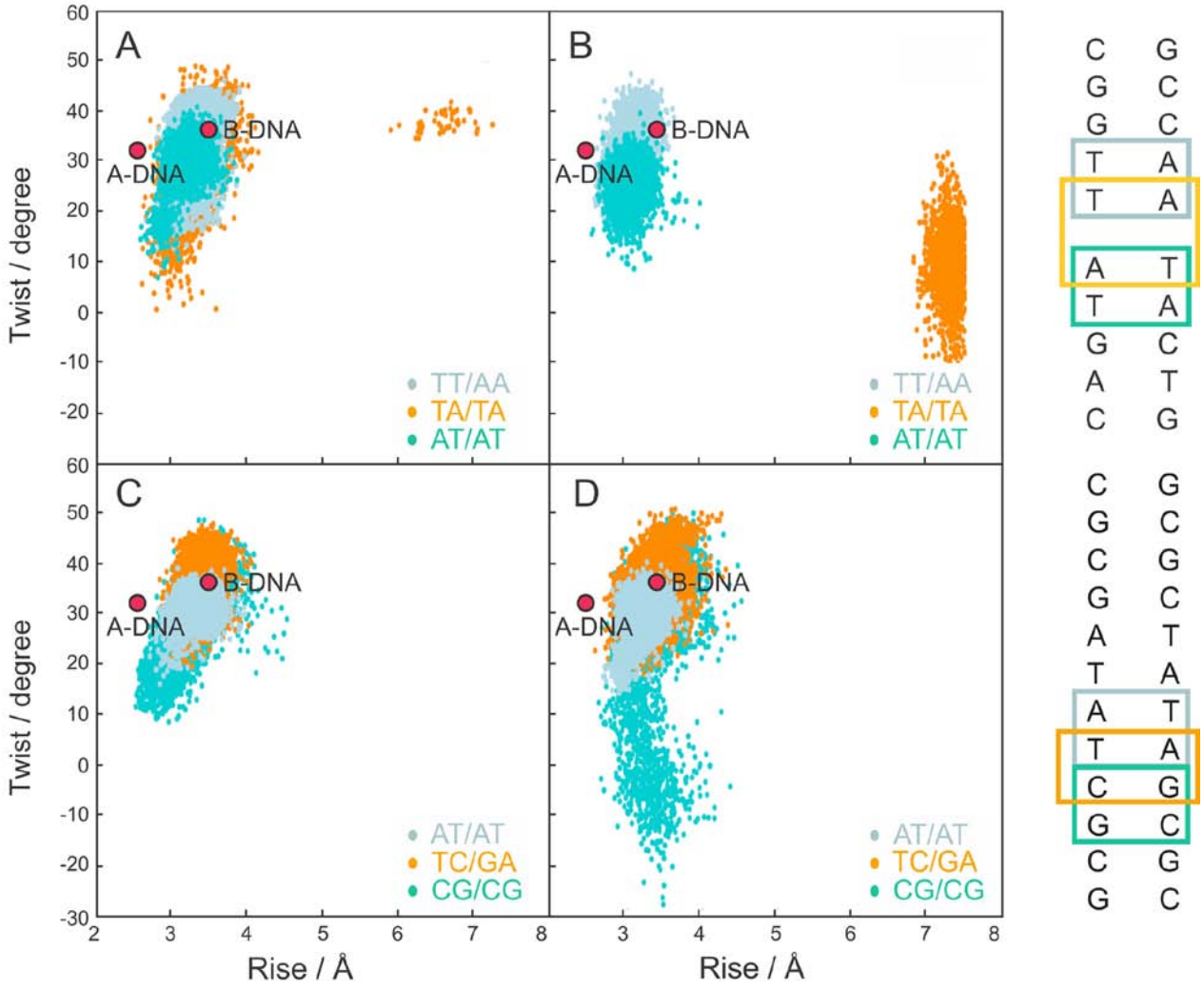

Figure S5. Rise/twist distribution for the base-pair steps belonging to the asymmetric Troger binding site. A) DNA-GAP; B) ASYM-INT; C) DNA-NOGAP; D) ASYM-GROOVE. The regions corresponding to canonical A- and B-DNA are indicated.

Roll/Slide Analysis

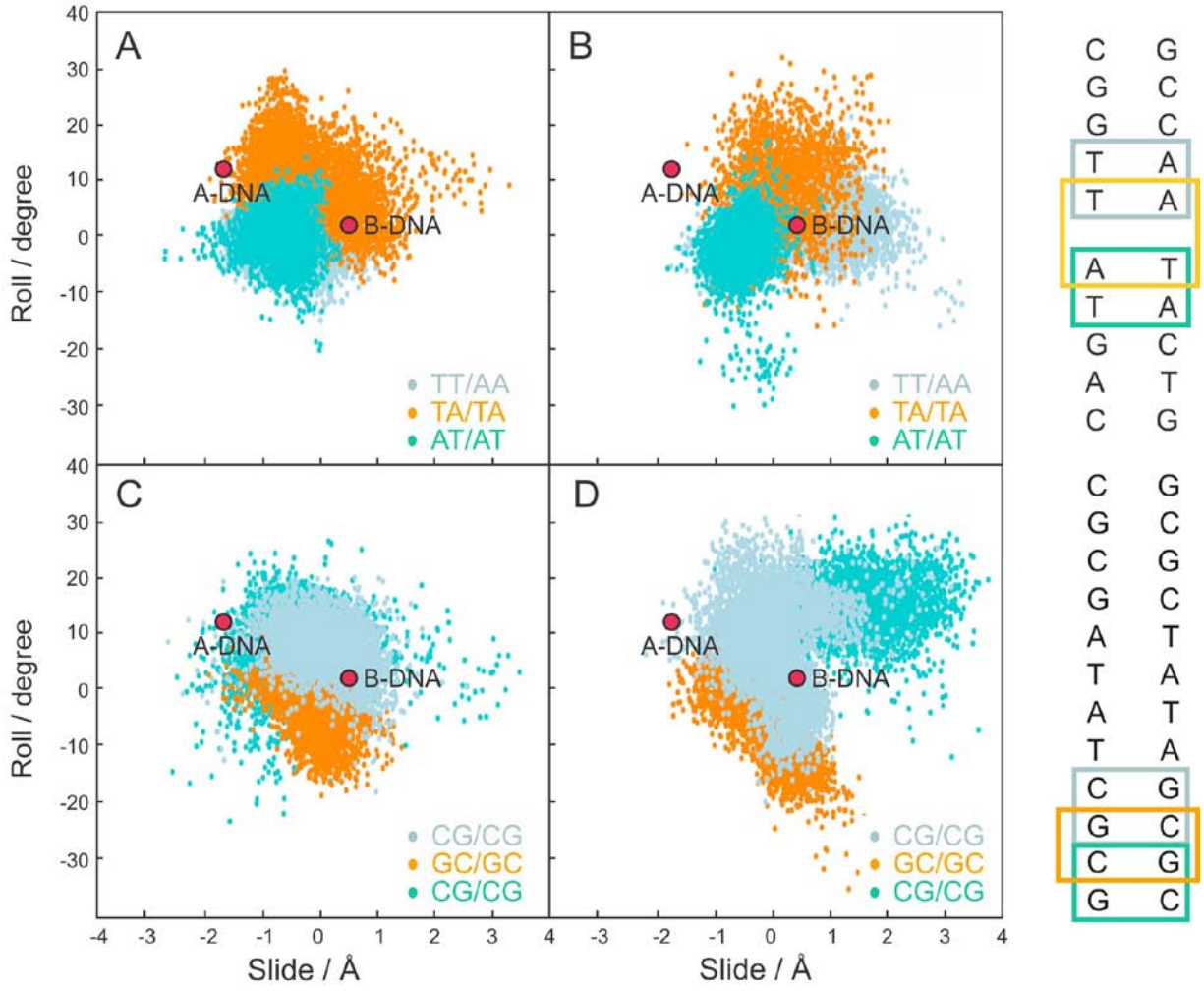

Figure S6. Slide/roll distribution for the base-pair steps belonging to the symmetric Tröger binding sites. A) DNA-GAP; B) SYM-INT; C) DNA-NOGAP; D) SYM-GROOVE. The regions corresponding to canonical A- and B-DNA are indicated.

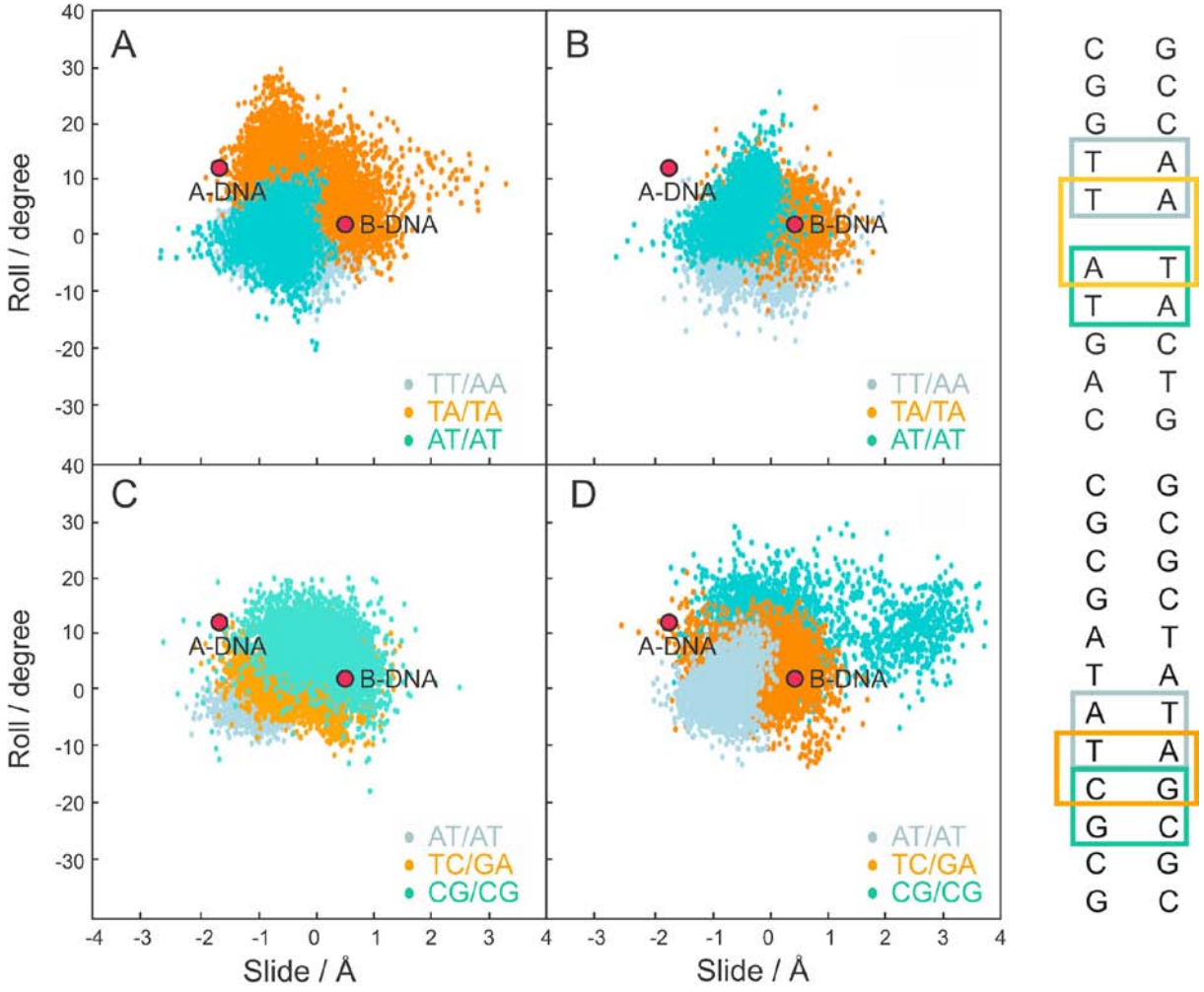

Figure S7. Slide/roll distribution for the base-pair steps belonging to the asymmetric Troger binding sites. A) DNA-GAP; B) ASYM-INT; C) DNA-NOGAP; D) ASYM-GROOVE. The regions corresponding to canonical A- and B-DNA are indicated.