We report the crystal structure of a complex in which CuTMPyP4 (copper (II) meso-tetra(N-methyl-4-pyridyl)porphyrin) flips a base out of the helical stack of duplex d(CGATCG). The porphyrin system is located within the helical stack, with the copper atom near the helical axis. The porphyrin binds by normal intercalation between the C and G of 5' TCG 3' and by extruding the C of 5' CGA 3'. The DNA hexamer forms a distorted right-handed helix with only four normal cross-strand Watson-Crick base pairs. Two pyridyl rings of the porphyrin are located in each groove of the DNA. The complex appears to be extensively stabilized by electrostatic interactions between positively-charged nitrogen atoms of the pyridyl rings and negatively-charged phosphate oxygen atoms of the DNA. Favorable electrostatic interactions appear to draw the porphyrin into the duplex interior. These favorable interactions offset unfavorable steric clashes between the pyridyl rings and the DNA backbone. We believe these pyridyl-backbone clashes extend the DNA along its axis and preclude formation of van der Waals stacking contacts in the interior of the complex. The unusual lack of van der Waals stacking contacts observed in the porphyrin complex destabilizes the DNA duplex and decreases the energetic cost of local melting. Thus extrusion of a base appears to be facilitated by pyridyl-DNA steric clashes.

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All known minor groove drugs bind DNA in the AT rich region. We recently demonstrated by X-ray crystallography that the alternating DNA octamer d(CICICIC) binds two distamycin drugs side-by-side simultaneously (Xin Chen, B. Ramakrishnan, S. T. Rao and M. Sundaralingam, Nature Structural Biology, 1, 167, 1994). This binding involves a significant widening of the DNA minor groove. We have also successfully replaced the I's and C's by A's and T's and obtained similar drug DNA complexes (Xin Chen, B. Ramakrishnan and M. Sundaralingam, unpublished results), which indicate that inosine resembles adenine in the minor groove. In our continuing study of the binding of minor groove drugs to other related DNA sequences, we have obtained crystals of the complex between the DNA decamer d(CCCCCI I I I I) and netropsin. The asymmetric unit contains two DNA duplexes each with two netropsin molecules bound. Interestingly, the structure reveals that the two netropsin molecules are bound in an end-to-end fashion. The details of the binding and the comparison with the side-by-side binding mode will be presented.

The crystals are in space group P1 with cell dimensions a=32.56Å, b=32.90Å, c=37.63Å and α=86.30°, β=84.30°, γ=68.58°. The structure was solved by molecular replacement and refined by X-PLOR to a final R-factor of 0.22 using 3688 reflections (78% complete) at 2.8Å resolution. Supported by NIH Grant GM-17378.