Table 23.3.4.1. *Sequence-dependent differential deformability in B-DNA. I. The Major Canon*

See Dickerson (1998*a*,*b*,*c*) and Dickerson & Chiu (1997).

(1) *Structural basis for helix bending in B-DNA*

Bending is nearly always the result of roll between successive base pairs, seldom tilt.

Positive roll, compressing the wide major groove, is more common than negative roll, in which the narrower minor groove is compressed.

Observed bends in B-DNA are of three main types: (*a*) *localized kinks* (large positive roll at one or two discrete base steps), (*b*) *three-dimensional writhe* (positive roll at a series of successive steps), or (*c*) *smooth curvature* (alternation of positive and negative roll every half turn, with side-to-side zigzagging at intermediate positions). (*a*) and (*b*) are easier to accomplish than (*c*), and hence are more common.

Local writhe in a DNA helix produces macroscopic curvature only when the extent of writhe does not match the natural rotational periodicity of the helix. Endless writhe results in a straight helix, and indeed A-DNA can be regarded as a continuously writhed variant of the B form. Conversely, the bending effect of writhe can be amplified if it is repeated with the periodicity of the helix itself – that is, repeated alternation of writhed and unwrithed segments every ten base pairs, as with A-tract B-DNA.

(2) *Pyrimidine-purine (Y-R) steps: C-A = T-G, T-A and C-G*

Little ring–ring stacking overlap.

Polar N or O stacked over polarizable aromatic rings.

Y-R steps are natural fracture points for the helix. They can show (but are not required in every case to show) large twist and slide deformations, and bending mainly *via* positive roll, compressing the major groove.

(3) *Purine-purine (R-R) steps: A-A = T-T, A-G = C-T, G-A = T-C and G-G = C-C*

Extensive ring–ring overlap.

Base pairs tend to pivot about stacked purines as a hinge, with greater ring–ring separation at pyrimidine ends.

Tight stacking, with only minor roll, slide and twist deformations.

(4) *Purine-pyrimidine (R-Y) steps: A-C = G-T, A-T and C-G*

Behaviour in general like R-R steps, with extensive ring–ring overlap and tight stacking, with again only minor roll, slide and twist deformations.

(5) *A-A and A-T steps, as contrasted with T-A*

Especially resistant to roll bending, probably because of sawhorse interlocking of highly propellered base pairs, supplemented by inter-base-pair hydrogen bonds within grooves. In contrast, T-A is particularly weak and subject to roll bending.

A-tracts, defined as four or more consecutive AT base pairs without the disruptive T-A step, are especially straight and resistant to bending. Natural selection has apparently chosen short A-tracts for regions of protein–DNA contacts where bending is not wanted.

resolvase (Yang & Steitz, 1995), *Eco*RV restriction enzyme (Winkler *et al.*, 1993; Kostrewa & Winkler, 1995), integration host factor or IHF (Rice *et al.*, 1996), and TBP or TATA-binding protein (Kim, Gerger *et al.*, 1993; Kim, Nikolov & Burley, 1993; Nikolov *et al.*, 1996; Juo *et al.*, 1996) are all sequence-specific DNA-binding proteins that bend or deform the nucleic acid duplex severely during the recognition process. IHF in Fig. 23.3.4.5 may be taken as representative of this class of DNA-binding proteins. The bend is produced by two localized rolls of *ca* 60° in a direction compressing the major groove and are additive, because they are spaced nine base pairs, or roughly one turn of helix, apart. In IHF, the two helix segments flanking the bend should be straight and unbent, and this is accomplished in one segment *via* a six-adenine A-tract: -C-A-A-A-A-A-A-G-.

The bending locus in IHF is C-A-A-T/A-T-T-G . It is C-G in *lacI* and *purR* repressors (Fig. 23.3.4.6), C-A = T-G in CAP (Fig. 10 of Dickerson, 1998*b*), and T-A in *Eco*RV, $\gamma\delta$-resolvase and TBP (Fig. 23.3.4.7). Pyrimidine-purine or Y-R steps appear to be especially suitable loci for roll bending. The dashed lines in Figs. 23.3.4.6 and 23.3.4.7 plot tilt, and demonstrate its insignificance in bending, compared with roll. (This is intuitively obvious. Imagine yourself standing near a tall stack of wooden planks in a lumberyard during an earthquake. Where would you prefer to stand: alongside the stack, or at one end?)

In summary, bending of the B-DNA helix nearly always involves roll, not tilt. The easier direction of bending is that which compresses the broad major groove, although examples of roll compression of the minor groove are known. Y-R steps are especially prone to roll bending. Again, the phenomenon is one of sequence-induced bendability, not mandatory bending. No one imagines that the IHF binding sequence of Fig. 23.3.4.5 is permanently kinked at its two C-A-A-T/A-T-T-G steps, wandering deformed through the nucleus, looking for an IHF molecule to bind to. Instead, this sequence has a potential bendability that other sequences, such as A-A-A-A-A-A, lack.

Table 23.3.4.1 summarizes the observed behaviour of Y-R, R-R and R-Y steps from a great many X-ray crystal structure analyses, with and without bound DNA. In the present context, these rules are termed the 'Major Canon', since they are well established and generally well understood. Some understanding of the proneness of Y-R steps to bend can be obtained by looking at stereo pairs of two successive base pairs viewed down the helix axis. Fig. 23.3.4.8 gives a few representative examples; many more can be found in Figs. 4–6 of Dickerson (1988*b*) and in the original literature. In brief, Y-R steps, especially C-A and T-A, tend to orient so that polar exocyclic N and O atoms stack against polarizable rings of the other base pair. This is the same type of polar-on-polarizable stacking stabilization mentioned earlier in connection with O4′ and guanine in Z-DNA (Bugg *et al.*, 1971; Thomas *et al.*, 1982; Hunter & Sanders, 1990; B32). Base pairs in T-A steps tend not to slide over one another along their long axes, keeping pyrimidine O2 stacked over the purine five-membered ring (Fig. 23.3.4.8*b*). C-A steps can adopt this same stacking, or the base pairs can slide until the pyrimidine O2 sits over the purine six-membered ring instead (Fig. 23.3.4.8*a*).

Purine-purine or R-R steps behave quite differently (Fig. 23.3.4.8*c*). They stack ring-on-ring, usually with greater overlap on the purine end than the pyrimidine. The net effect is that the pivot

references