Conformational flexibility of DNA: an extension of the stereochemical guidelines

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1. INTRODUCTION

Following a stereochemical guideline, it was possible to obtain both right and left double-helical models of DNA [1–3]. When a nucleotide unit is used as a repeat, uniform helices are obtained and they can be classified into two categories; right-handed (RU) and left-handed (LU) uniform helices [4]. The stereochemical guideline for molecular model building using a nucleotide repeat was as follows. A correlation should always be maintained between the sugar conformation and the P–O torsions to obtain stereochemically satisfactory RU and LU helices [1–4]. In this way, 5 conformations of the nucleotide repeat were obtained which gave rise to RU and LU helices [4]. This deals with the extension of the stereochemical guideline and this results in two additional nucleotide conformations which again give rise to RU and LU helices.

2. A BRIEF SUMMARY OF THE STEREOCHEMICAL GUIDELINE AND THE PRESENT EXTENSION

It is well known that a base-paired dinucleoside monophosphate embodies the smallest fragment of a polynucleotide duplex because the former contains the major sources of flexibility and the essential stabilizing forces present in the latter. A base-paired dinucleoside monophosphate can be generated from a nucleotide repeat with 6 backbone torsion angles and a glycosidic torsion (fig. 1). Out of these torsion angles, two (ζ' and ϵ) define the sugar conformation. The angle ζ' denotes the puckering of the furanose ring which is found to fall in two broad regions: C3′-*endo*, $E^3(70 \leqslant \zeta' \leqslant 100)$; C2′-*endo*, $E^2(110 \leqslant \zeta' \leqslant 160)$ [5]. The angle ϵ describes the orientation of the C5′–O5′ bond with respect to the furanose ring and ϵ can take up 3 staggered orientations: $g^+(30 \leqslant \epsilon \leqslant 75)$; $t(150 \leqslant \zeta' \leqslant 210)$; $g^-(280 \leqslant \epsilon \leqslant 320)$. Thus, combining ζ' and ϵ, there can be 6

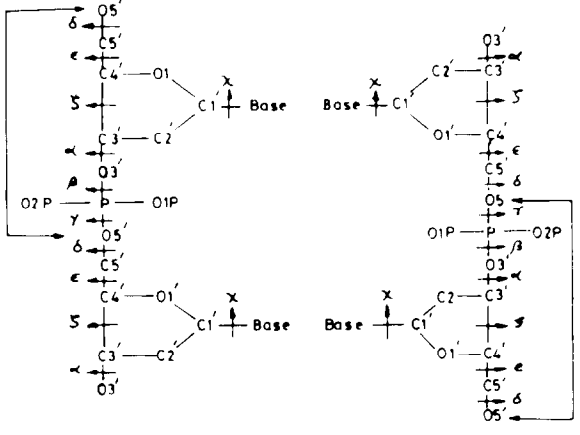

Fig. 1. Schematic representation of a base-paired dinucleoside monophosphate. Note that the true repeat is a nucleotide unit with 6 backbone torsions and 1 glycosyl torsion.

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possible conformations of the sugar residue in the nucleotide unit:

$\zeta \rightarrow$ / $\downarrow \epsilon$	Pucker E^3	E^2
g^+	1	2
t	3	4
g^-	5	6

The angle δ which defines the orientation of the phosphate group at the 5′-end of the sugar takes up *trans* [5] conformation ($140 \leqslant \delta \leqslant 215$). However, the angle α which defines the orientation of the phosphate group at the 3′-end can take either *trans* ($180 \leqslant \alpha \leqslant 225$) or *gauche*, g^- ($270 \leqslant \alpha \leqslant 295$) conformation; both the conformations have been observed in the single crystals of the nucleic acid components [6] and shown to be energetically favourable [7]. The torsions (β, γ) describe the orientations of the 2 neighbouring nucleotide units joined by the P–O bonds. Both β and γ can take up 3 staggered orientations such that there exist 9 combinations as shown below:

$\gamma \uparrow$ / $\beta \rightarrow$	g^+	t	g^-
g^-	1	2	3
t	4	5	6
g^+	7	8	9

For t orientation of α and δ, 6 conformations of the nucleotide unit gave rise to RU and LU helices and these are shown as helical domains in the $(\beta-\gamma)$ conformational space in fig. 2. It is seen that helical domains are obtained only when a strict correlation is maintained between the sugar conformation and the P–O torsions of the nucleotide repeat. For example, designating O5′–C5′–C4′–C3′–O3′–P–O5′ as the nucleotide repeat, $(t, g^+, E^3, t, g^-, g^-)$ conformation describes the helical domain I in fig. 2 while the (t, g^+, E^2, t, g^-) conformation describes the helical domain II. Thus, for (g^+, E^3) conformation of the sugar residue, only g^-g^- conformations of the P–O torsions lead to helical duplexes while for

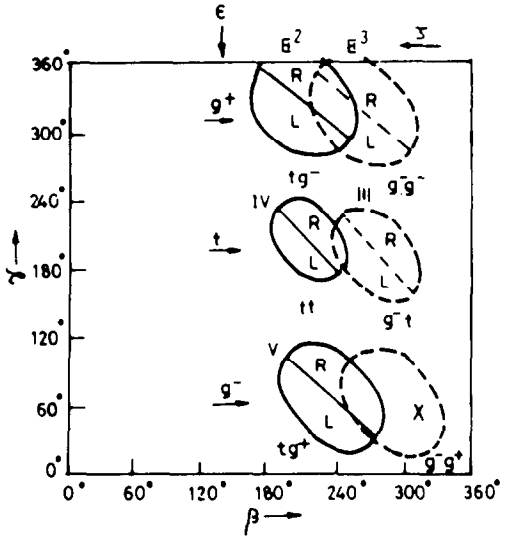

Fig. 2. Five helical domains (I–V) in the conformational space for a nucleotide repeat with α and δ in t orientation.

(g^+, E^2) sugar only tg^- conformations give rise to helical duplexes. Similarly, for each of the remaining 4 conformations of the sugar residue, only one combination of P–O torsions (i.e., β, γ) in each case results in helical structures. Thus, there are 6 nucleotide conformations (fig. 2). Out of these 6, $(t, g^-, E^3, t, g^-, g^+)$ conformation of the nucleotide unit is stereochemically inadmissible. Hence, there are only 5 conformations which lead to helical duplexes for t conformation of both α and δ.

However, when g^- conformation of α and t conformation of δ were considered, only 2 helical domains emerged which are described here (fig. 3) because:

For g^- conformation of α, E^3 sugars never lead to double helical structures and this leaves only 3 remaining (i.e., combinations of E^2 and ϵ) conformations for consideration of double-helical structures, out of which $(t^-, g^-, E^2, g^-, t, g^-)$ conformation of the nucleotide repeat gives rise to only LU (and never RU) helices. Thus, only in the two domains $(t, g^+, E^2, g^-, t, g^+)$ and $(t, g^-, E^2, g^-, t, g^-)$ conformations as shown in fig. 3, both RU and LU helices are possible for g^- conformation of α.

With these 2 helical domains, the 7 possible nucleo-

tide conformations exhaust all the helical domains in the conformational space. In all the 7 helical domains, the glycosylic torsion falls in the *anti* region ($-15 \leqslant \chi \leqslant 75$) and therefore both purines and pyrimidines can be accommodated in the RU and LU helices of these domains. It was found that stereochemically allowed B-DNA models could be constructed only when α is restricted to 275–300 in the g^- region. For the (t, g^+, E^2, g^-, t, t) conformation of the nucleotide repeat, it turned out that both RU and LU helices had $\alpha > 320$ in the E^2 region (E_1–E_3); this leads to steric compression between C4′---O1P. But it may be noted that RU and LU helices in this domain has appropriate r_p(~9.0 Å) and s_p(~13 Å) and bases perpendicular to the helix axis as required for the agreement with respect to the observed data. It was also observed that for $\alpha < 285°$, the P–O torsions reverted back to t, g^- conformations as in domain II of fig. 2.

3. STEREOCHEMISTRY AND THE SCATTERING PROFILES OF THE RU AND LU HELICES IN THE ADDITIONAL HELICAL DOMAINS (fig. 3)

Possibility of a B-DNA model was judged based upon the following criteria:

(i) Allowed stereochemistry;

(ii) Favourable packing;

(iii) Agreement with the fibre diffraction data.

Only for the (t, t, E^2, g^-, t, g^+) conformation of the nucleotide repeat, it was possible to construct RU and LU helices which could be packed in the unit cell of the B-DNA. The conformational parameters of the RU and LU helices in this domain are given in table 2: in both models, bases could be brought close to the helix centre ($-0.4 \leqslant D \leqslant -0.8$ Å) and the gross structural parameters (i.e., r_p and s_p) could be made almost identical. However, in the process of doing so, the values of δ in all the RU models in this domain came close to 240 (an eclipsed conformation) while in the LU helices δ could be restricted to 225°. But it may be noted that there were hardly any differences in the relative stabilities of the two kinds of models as judged by computing the energy values based upon the classical potential functions [8].

Fig. 4 shows the scattering profiles of the RU and LU helices in the domains under consideration. The cylindrically averaged Fourier transfor-

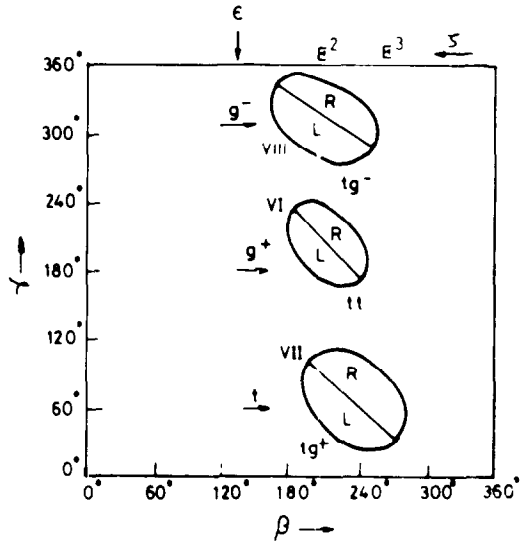

Fig. 3. Two helical domains (VI,VII) in the conformational space for a nucleotide repeat with α as g^- and δ as t. Note that inside the region VIII only left-handed (L) duplexes are possible; otherwise in domains I–VII of fig. 2 and 3 both right- (R) and left-handed (L) duplexes are possible.

Table 1

The conformational parameters of the RU and LU helices of B-DNA in the domain VII of fig. 3[a]

		RU helix	LU helix
Backbone torsion angles (deg.)	α	285	297
	β	199	176
	γ	72	54
	δ	238	225
	ϵ	176	160
	ζ	140	130
Glycosyltorsion (deg.)	χ	48	2
Base parameters (deg., D in Å)	θ_x	2	−2
	θ_y	−5	1
	D	−0.40	−0.8
Gross structural parameters (Å)	r_p	9.47	9.2
	S_p	13.00	12.8
R-factor		0.40	0.34

[a] Atomic coordinates of the model can be obtained from the authors

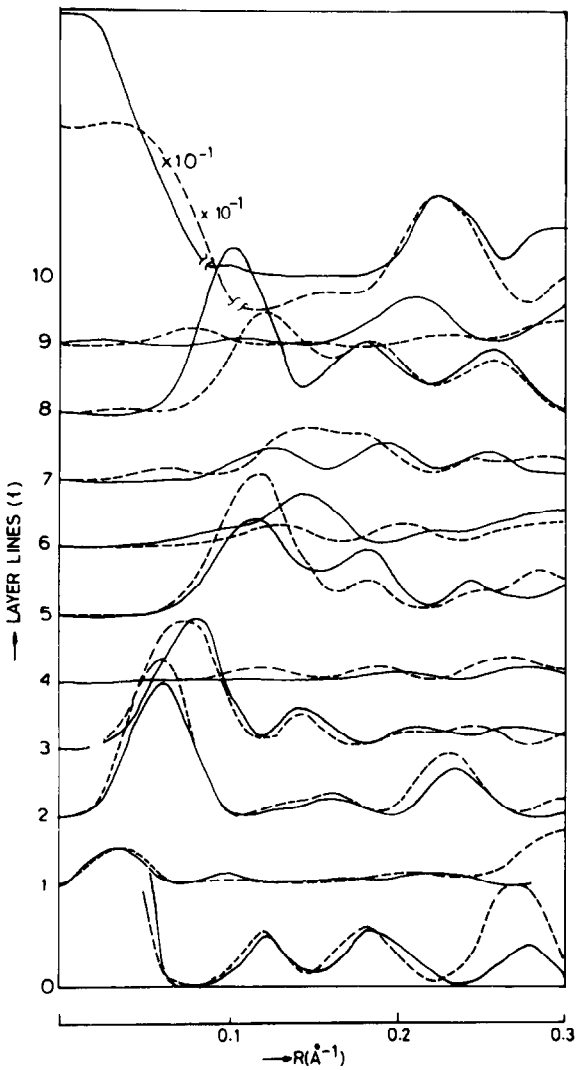

Fig. 4. The cylindrically averaged Fourier transform of the RU (– – –) and LU (——) helices discussed in table 1. Note that the LU helix shows a better agreement with the observed χ-pattern.

mations show that RU and LU helices agree equally well on the layer lines 0–5. The transforms of RU and LU helices have also another thing in common in that the intensity on the layer line 9 is weak in the range $R = 0$–0.2 Å^{-1} in the transforms due to both the models. Such a feature on the layer line 9 was never seen in transforms of the RU and LU helices reported in [2]. The discrepancy between the two transforms, arises on the layer lines

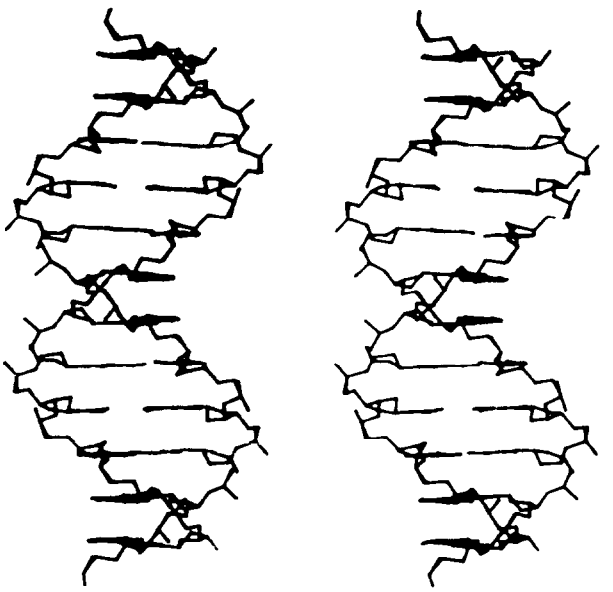

Fig. 5. A stereopair of the LU helix of B-DNA (table 1) along the helix axis.

6–8. When the structure factor amplitudes were computed using the procedure in [2] and compared with the observed structure factor amplitudes, the RU model gave an R-factor of 0.40 while the LU model gave 0.34. Thus, the LU helix in this domain is hereafter discussed in detail.

Fig. 5 shows the stereopair of the LU helix along the helix axis; from the figure it is clearly seen that the basepairs are flat and almost perpendicular to the helix axis.

4. CONCLUSION

This paper shows how the extension of the stereochemical guideline adds to the variability in the structural models of the B-DNA. However, the main aim of the paper is not to present yet another model for the B-DNA but to emphasise the conformational flexibility of DNA inherent in the nucleotide repeat. It is shown that the conformational flexibility when exploited following a stereochemical guideline results in the 7 helical domains in the conformational space (fig. 2,3). Structures in these domains exhaust all the possibilities of RU and LU helices that can be obtained using a nucleotide repeat in which all the bases can be accommodated.

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