A critical analysis of a left-handed double helix model for B-DNA fibers

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ABSTRACT

A search for a left-handed double helix model for B-DNA fibers has been undertaken. The model has to present good stereochemistry and also to be in agreement with X-ray and infrared data. Dihedral angles as well as atomic coordinates and calculated intensities curves are given for the best model obtained. Comparison with experimental results shows that this model must be rejected as a candidate for the representation of B-DNA fibers.

INTRODUCTION

It is a well known fact that X-ray on fibers of DNA can not give the handedness of DNA double helical conformations (1,2). The only evidence used by Watson and Crick for the proposal of a right-handed double helix for the B-DNA was based on stereochemistry (3). Indeed left-handed double helices were built but they presented poor interatomic contacts and thus were rejected. The same scheme of reasoning was used for the proposition of the A form of DNA (4). Even if crystals of nucleotides and t-RNA do present fragments of right-handed helices (5), it is not possible to generalize on the rotational sense of helices of DNA and RNA in fibers or in solutions. New proposed models for the B-DNA, called "side-by-side models" (6,7,8) and constituted from alternating right and left-handed sections of helices have restarted the controversy on this subject (9). The discovery of the left-handed helix (Z-DNA) (10) for crystals of short sequences of purine and pyrimidine nucleotides as well as that of a right-handed double helix of dodecanucleotides (11) demonstrate the polymorphism of DNA molecules.

Besides these experimental studies, theoretical approaches allow one to propose models of left-handed helices having good stereochemistry and parameters corresponding to DNA in its B-
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form (12,13,14,15) and even in its A and C forms (12). Moreover, it has been shown that transitions between Z and B forms are possible in solution (16,17) and fibers (18). As a right-handed double helix which agrees with infrared and X-ray measurements has been proposed for the B-DNA (19), it is interesting to know if a left-handed double helical model can also be accepted or rejected.

In the present work, we have searched for conformations of the DNA in left-handed double helices with a geometry in agreement with the experimental data from infrared spectroscopy (20) as well as from X-ray (2). Dihedral angles of a left-handed double helix conformation are presented together with atomic coordinates and curves of calculated intensities; comparison with X-ray data enables this kind of conformation as a model for the B-DNA to be rejected.

**METHOD**

A first step in the determination of a left-handed double helix is the building of a physical model which has the helical parameters of B-DNA, namely a pitch of 33.8 Å and 36° of rotation per base pair. One can also, on this model orientate the phosphate group in order to verify roughly the orientations given by infrared (20): the direction of the oxygen atoms 0\(1\)O\(2\) has to make an angle of 56° with the helix axis and the bisector of 0\(1\)PO\(2\) an angle of 70° with this axis. This model can hardly be a precise one but it permits the determination of a set of dihedral angles which allows one to compute a well defined conformation. The computational method used to get atomic coordinates of a double helix constrained to agree with geometrical parameters obtained from X-ray and infrared has been previously presented (19) and already used to obtain a right-handed double helical model for B-DNA.

The cylindrical coordinates of the atoms of the helix which give good geometrical parameters and also good stereochemistry are used to calculate the Fourier transform and theoretical diffracted intensities. The same procedure (21) as previously used is followed but the order n of the Bessel functions are now defined by \(n = -1 + 10m\) for the layer line 1 (with m an integer).
RESULTS

Table I gives values of the dihedral angles for the best left-handed double helical conformation now obtained (model I). The geometrical parameters of this helix are also given in this table; the orientation of the base plane is given by the tilt and twist and their position relative to the axis is defined by the distance of the line D joining the atom C₆ (pyrimidine) to C₈ (purine) (22). In table II the directions of O₁O₂ and the bisector of O₁PO₂ relative to the helix axis are presented. In table III atomic coordinates of a nucleotide are given for this model and figure I presents a schematic diagram showing a projection of the left-handed double helix. On figure II curves of the calculated intensities are given and compared with experimental values.

Table I
Chain dihedral angles and parameters of the left-handed double helices.

<table>
<thead>
<tr>
<th></th>
<th>model I</th>
<th>model I'</th>
</tr>
</thead>
<tbody>
<tr>
<td>α (°)</td>
<td>58.41</td>
<td>-160.04</td>
</tr>
<tr>
<td>β (°)</td>
<td>-132.88</td>
<td>115.82</td>
</tr>
<tr>
<td>γ (°)</td>
<td>159.93</td>
<td>24.48</td>
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<tr>
<td>δ (°)</td>
<td>138.29</td>
<td>135.88</td>
</tr>
<tr>
<td>ε (°)</td>
<td>-71.54</td>
<td>-7.87</td>
</tr>
<tr>
<td>ξ (°)</td>
<td>179.27</td>
<td>169.66</td>
</tr>
<tr>
<td>χ (°)</td>
<td>-190</td>
<td>-159</td>
</tr>
<tr>
<td>p (°)</td>
<td>33.8</td>
<td>34</td>
</tr>
<tr>
<td>θ (°)</td>
<td>-36</td>
<td>-36</td>
</tr>
<tr>
<td>p(A)</td>
<td>3.38</td>
<td>3.4</td>
</tr>
<tr>
<td>tilt (°)</td>
<td>18</td>
<td>-10</td>
</tr>
<tr>
<td>twist (°)</td>
<td>-4</td>
<td>-1</td>
</tr>
<tr>
<td>D(A)</td>
<td>-0.73</td>
<td>1.95</td>
</tr>
</tbody>
</table>

\[ O₅' \quad C₅' \quad Y \quad C₄' \quad δ \quad C₃' \quad ε \quad O₃' \quad ξ \quad p \]

α : 0₁' - C₁ - N₁ - C₂ for (C,T)
- C₄ for (G,A)
Table II
Geometry of the phosphate group compared with infrared results.

<table>
<thead>
<tr>
<th>Angle with the helical axis</th>
<th>Infra Red Ref (20)</th>
<th>Model I</th>
<th>Model I'</th>
</tr>
</thead>
<tbody>
<tr>
<td>of ((O_1O_2))</td>
<td>56°</td>
<td>55° 6</td>
<td>55°</td>
</tr>
<tr>
<td>of the bissector of ((O_1PO_2))</td>
<td>70°</td>
<td>69°58</td>
<td>68° 5</td>
</tr>
</tbody>
</table>

DISCUSSION
Many different left-handed double helices have already been proposed for B-DNA (12,13,14). Indeed it is not very difficult to obtain such conformations with good stereochemistry and helical parameters in agreement with X-ray data. But if one imposes constraints on the geometry in order to agree also with I.R. data, then almost all these conformations are eliminated. The model

Table III
Atomic cylindrical coordinates for one nucleotide of model I.

<table>
<thead>
<tr>
<th>Atom</th>
<th>(R_j) (A)</th>
<th>(\phi_j) (°)</th>
<th>(Z_j) (A)</th>
<th>Atom</th>
<th>(R_j) (A)</th>
<th>(\phi_j) (°)</th>
<th>(Z_j) (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O3'</td>
<td>7.74</td>
<td>-122.88</td>
<td>2.62</td>
<td>N9</td>
<td>4.40</td>
<td>-96.58</td>
<td>1.44</td>
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<tr>
<td>P</td>
<td>9.2</td>
<td>-122.86</td>
<td>3.27</td>
<td>C8</td>
<td>4.72</td>
<td>-80.30</td>
<td>1.40</td>
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<tr>
<td>O1</td>
<td>9.67</td>
<td>-114.64</td>
<td>3.65</td>
<td>N7</td>
<td>3.89</td>
<td>-67.69</td>
<td>0.95</td>
</tr>
<tr>
<td>O2</td>
<td>10.20</td>
<td>-125.81</td>
<td>2.29</td>
<td>C5</td>
<td>2.65</td>
<td>-77.46</td>
<td>0.70</td>
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<tr>
<td>O5'</td>
<td>9.04</td>
<td>-128.98</td>
<td>4.53</td>
<td>C4</td>
<td>3.12</td>
<td>-102.55</td>
<td>1.00</td>
</tr>
<tr>
<td>Desoxyribose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C5'</td>
<td>8.84</td>
<td>-102.01</td>
<td>0.93</td>
<td>C2</td>
<td>2.07</td>
<td>-145.68</td>
<td>0.45</td>
</tr>
<tr>
<td>C4'</td>
<td>7.85</td>
<td>-106.31</td>
<td>1.89</td>
<td>N2</td>
<td>2.80</td>
<td>-172.33</td>
<td>0.29</td>
</tr>
<tr>
<td>C3'</td>
<td>7.55</td>
<td>-116.99</td>
<td>1.45</td>
<td>N1</td>
<td>0.80</td>
<td>-129.45</td>
<td>0.13</td>
</tr>
<tr>
<td>C2'</td>
<td>6.14</td>
<td>-116.63</td>
<td>0.89</td>
<td>C6</td>
<td>1.44</td>
<td>-60.46</td>
<td>0.22</td>
</tr>
<tr>
<td>C1'</td>
<td>5.51</td>
<td>-106.95</td>
<td>1.88</td>
<td>O6</td>
<td>1.87</td>
<td>-20.92</td>
<td>-0.10</td>
</tr>
<tr>
<td>O1'</td>
<td>6.68</td>
<td>99.52</td>
<td>2.04</td>
<td></td>
<td></td>
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</tbody>
</table>
proposed (model I) is the only one we obtained which fulfills all the geometrical conditions. It presents very good stereochemistry; the dihedral angles have values in domains commonly allowed for nucleotides (23). The sugar pucker is C2' endo, its plane is almost perpendicular to the helix axis while it is parallel for right-handed helices (2,19). This last feature induces an important tilt of 18° on the base plane but the small twist of 4° has no effect on their good pairing. The stacking of bases is good (the distance D is small (22) and the phosphorous atom is approximately 9 Å from the helix axis in agreement with X-ray data). The minor groove is narrower for this left-handed conformation than for the right-handed ones (2). When calculated intensities are compared with observed ones, many large disagreements can be seen such that calculated intensities on the layer lines 1, 3, 5, 7 and 10 are much too small when compared with experimental values. Layer lines 4 and 9 also present poor agreement with observed intensities as experimental values are small and the calcula-
Curves of the diffracted intensities, calculated with the model I (---), with the model I' (---), experimentally observed intensities (x •).

It was not possible to improve the calculated intensities because the bases cannot be put perpendicular to the axis while the rest of the conformation remains acceptable.

Nevertheless in order to verify that the large tilt of the bases is the main reason for the disagreement between calculated...
and observed intensities, another model (I') was determined. This conformation does present good helical parameters (table I) and a good orientation of the phosphate group (table II), the sugar is C2' endo but the base plane present a tilt of 10° in the opposite sense when compared with model I and near to the tilt found in right-handed helices (2,19,22). The stereochemistry of this conformation is not good; one can see in table I that many dihedral angles have values far from their permitted regions (23) and cannot be improved when geometrical constraints are maintained. Nevertheless the calculated intensities (fig. II) are better even if large disagreements remain on layer lines 7, 8 and 9.

Thus it seems that the large tilt of bases in the model I is the main reason for the disagreement between the calculated and observed intensities. This geometrical characteristic cannot be modified when one tries to produce a left-handed double helical model of B-DNA which must fit all the geometrical constraints related to X-ray and infrared and also present good stereochemistry. As such a good model has been established for a right-handed double helix of DNA in the B form (19) it appears that a choice can be proposed in favour of this last sense of rotation.

REFERENCES
20. Pilet, J. & Brahms, J. (1973), Biopolymers 12, 387-403