Biophysical Chemistry 23 (1986) 251–259
Elsevier

BPC 01045

THEORETICAL STUDIES ON THE INTERACTION OF PROTEINS AND NUCLEIC ACIDS

I. THE BINDING OF β-PLEATED SHEETS TO A- AND B-DNA

Krystyna ZAKRZEWSKA and Bernard PULLMAN

Institut de Biologie Physico-Chimique, Laboratoire de Biochimie Théorique associé au CNRS, 13, rue Pierre et Marie Curie, 75005 Paris, France

Received 27th August 1985
Accepted 23rd December 1985

Key words: Protein-nucleic acid interaction; DNA; β-pleated sheet

A theoretical investigation of the interaction between a β-ribbon consisting of two glycine hexapeptides and DNA in its A and B conformations is presented. A refined semi-empirical energy formula and a sophisticated energy minimization technique are used to optimize the complex, taking into account the DNA-β-ribbon interaction, the full flexibility of the oligopeptide chains and of the positions of the DNA screening counterions. A considerable flexibility of the β-ribbon is demonstrated, which allows the polypeptide fragment to interact comfortably with both forms of DNA considered and with different base-pair sequences. The results are discussed in connection with the general problem of DNA-protein recognition.

1. Introduction

Recognition between nucleic acids and proteins is one of the central problems in molecular biology. Until a few years ago, however, little was known about the way in which these important biopolymers interact, the only structural data available being those on small systems. Recently, a number of regulatory proteins have been crystallized and their structures resolved, notably the 'cro', 'cap' and 'lambda' repressors (see, for instance, refs. 1–3). These studies provided useful hints for the construction of models which attempt to explain nucleic acid-protein specific recognition.

However, if we wish to gain a fundamental understanding of these recognition processes it seems reasonable to explore first how the basic structural motifs of proteins might interact with nucleic acid double helices. The two most important polypeptide structures to be considered are clearly the β-sheet and the α-helix. Simple models have been proposed, in both these cases, for possible binding configurations [4–6] by model-building studies and evidence of their interaction with DNA has been detected experimentally [7]. However, no thorough theoretical study of the energetics of these processes has been performed, this being the aim of our present investigation.

We are interested, in particular, in the adaptability of these peptide backbone conformations to different DNA conformers. Although our study concerns oligopeptide fragments in isolation the results obtained should provide insight into the possibilities of interaction which occur when these structural motifs are incorporated into a more complicated protein architecture, for example, in the case of the CRO protein, where, according to present models [8.9] the main recognition is governed by α-helices, located in successive major grooves of DNA, but where a β-ribbon fragment is also present, located in the intervening minor groove.

We begin our series of studies by considering the possible role of β-sheets which are common to

many globular proteins [10].

Any nucleic acid-protein interaction may be subdivided into two phases: firstly, the formation of a non-specific interaction between the two components of the complex and, secondly, specific recognition involving, presumably, the particular amino acid side chains present. In the present study we are interested primarily in the first phase of this problem: the geometrical adaptability of the protein fragment to the nucleic acids. As mentioned above, this problem has already been treated by the technique of model building, fitting the parameters of the nucleic acids and polypeptide chains to produce a coaxial complex. In this way, Carter and Kraut [4] proposed a model in which the antiparallel β-sheet was helically wrapped around the minor groove of A-RNA. This complex was stabilized by hydrogen bonds between the O1′ and O2′ oxygens of the ribose sugars and the amide hydrogens of the β-ribbon. The authors argued against formation of a complex with A-DNA due to the absence of the 2′-hydroxyl group, and also with B-DNA, considering the minor groove of the latter to be too narrow. However, the possibility of binding to the major groove of B-DNA was not excluded. These conclusions were contradicted by Church et al. [5] who performed a study fitting the parameters of an antiparallel β-ribbon to the minor groove of B-DNA. They found such an interaction quite plausible, necessitating only small modifications in the parameters of the standard B-DNA conformation. In their model, the complex was stabilized by a set of hydrogen bonds involving the O3′ oxygen of the phosphate groups and the amide hydrogens of the polypeptide.

Yet another model has been proposed by Gurskii et al. [11] in a study concerning, more directly, the second of the problems mentioned above, namely, the specificity of base sequence recognition. Based on their work on the interaction between nucleic acids and groove-binding antibiotics of the distamycin family, they proposed a mechanism for the specific binding of regulatory proteins in which the antiparallel β-ribbons of the protein bind in the minor groove of the nucleic acid and undergo major structural modifications. Half of the total number of hydrogen bonds in the β-ribbon fragment are broken during such an interaction and new hydrogen bonds are formed between the amide groups of the polypeptide chain and the DNA bases, the amide groups acting as hydrogen bond acceptors in one polypeptide chain and as donors in the other.

Overall, these model-building studies cannot be considered as providing more than general indications of the sterical feasibility of complex formation. We have therefore undertaken an energy-minimization study in which a flexible β-ribbon fragment was allowed to interact with DNA in both its A and B conformations and to form complexes with both grooves of the DNA double helix. We also consider two different base-pair sequences: G-C and A-T. The question we attempt to answer is whether there is a clear energetic preference for certain interaction sites and conformations and, concomitantly, whether certain binding sites can be excluded as being structurally impossible.

Since there are a number of indications that DNA does not change its conformation profoundly during its interaction with regulatory protein [12–14], we have used a rigid DNA model. Our β-ribbon fragment is formed from two glycine chains, each constructed of six peptides. This fragment was allowed full flexibility.

It should be mentioned that for an antiparallel β-ribbon there are two possible binding orientations with respect to a nucleic acid double helix. A complex is termed 'parallel' when the direction of the $N \rightarrow C'$ bond of the peptide chain is aligned with the $3' \rightarrow 5'$ direction of the polynucleotide chain. The complex with the opposite orientation of the chains is termed 'antiparallel'. In this connection it can be mentioned that Carter and Kraut [4] found that the formation of a parallel complex necessitated much less distortion of both RNA and β-ribbon parameters than that of he antiparallel one. A similar conclusion was reached by Church et al. [5] in the case of B-DNA. In contrast, Gurskii et al. [11] assumed an antiparallel orientation of the two macromolecules. In our calculations we will consequently attempt to verify whether there is indeed a clear difference, as concerns polypeptide adaptability or interaction with nucleic acids, between these two orientations.

2. Methodology

The interaction energy of the complexes studied is calculated with an energy formula identical to that used in our previous investigations on groove-binding ligand-DNA interactions [15–17]:

$$E = \sum \left(-A_{ij}/r_{ij}^6 + B_{ij}/r_{ij}^{12} \right) + \sum_{\mathrm{HB}} \left[\left(\cos\theta \left(-A_{ij}^{\mathrm{H}}/r_{ij}^6 + B_{ij}^{\mathrm{H}}/r_{ij}^{12} \right) + (1 - \cos\theta)\left(-A_{ij}/r_{ij}^6 + B_{ij}/r_{ij}^{12} \right) \right) \right] + \sum q_i q_j / \left(r_{ij} \cdot \epsilon(r) \right) + 1/2 \sum \alpha_i F_i^2 + \sum V_{\mathrm{T}}/2(1 + \cos 3\tau) + \sum V_{\mathrm{G}}/2(1 + \cos 2\tau)$$

The first term describes the Lennard-Jones energy calculated with 6–12 potential functions in the parameterization from ref. 18, the second term denoting the angle-dependent hydrogen bond energy, where θ is the angle between the vectors $\overrightarrow{AH}$ and $\overrightarrow{HB}$ of a hydrogen bond A–H $\cdots$ B. The electrostatic energy is calculated with our optimized atomic monopoles [19,20] derived from a specially parameterized Hückel-Del Re calculation. The fourth term describes the polarization energy in terms of the mean atomic polarizabilities, 'α', taken from Kang and John [21], and $\vec{F}$, the total electrostatic field acting on each atom. The field calculation involved a short-range correction, following the work of Gresh et al. [22], and is given by the formula:

$$\vec{F}_i = \sum q_j \vec{r}_{ij} / r_{ij}'^3 \qquad r_{ij}' = r_{ij} + D(w_i + w_j)$$

where w_i is the van der Waals radius of atom i.

The final two terms correspond to the bond torsion and anomeric (or *gauche*) energies, respectively, where τ denotes the bond torsion angle, and V_{T} and V_{G} the torsion and anomeric energy barriers. In the calculations of the electrostatic and polarization energies we employ a distance-dependent dielectric constant with a sigmoidal form proposed by Hingerty et al. [23] (for details see ref. 24).

The polynucleotide models used to represent DNA consisted of 22 5'-nucleotides forming double-stranded oligomers of 11 base-pairs. Two homopolymeric base sequences are considered $(dA)_{11} \cdot (dT)_{11}$ and $(dG)_{11} \cdot (dC)_{11}$, representing one helical turn of DNA, with the geometry of Arnott et al. [25]. The nucleic acids were screened by 22 Na^+, 11 on each sugar-phosphate chain. Calculations of the complexation energies were performed keeping the geometry of the nucleic acid constant, but allowing for the variations in the counterion positions. These positions were optimized during complex formation, maintaining however, the helical symmetry of the cation locations within each chain of the double helix.

The β-ribbon fragment consisted of two antiparallel glycine hexamers, with bond lengths and angles taken from Arnott et al. [26]. During complex formation all single bonds were free to rotate. The internal energy of this fragment was calculated as the sum of the interaction energy between the two oligopeptide strands and the intra-strand contributions, consisting of the sum of the atom-atom interactions for all the pairs of atoms separated by at least three bonds, bond lengths and bond angles being considered as fixed.

The total energy of the optimized complex is expressed as the sum of the screened nucleic acid-polypeptide interaction energy, the nucleic acid internal energy (presently described by the interaction energy between the oligonucleotide strands and the mobile counterions) and the internal energy of the β-ribbon. Minimization was performed using a conjugate gradient technique with the BFGS algorithm [27]. This required the calculation of analytical derivatives of the energy with respect to all the variables involved, these derivatives being obtained from the atomic forces acting on the atoms within the complex, with the formulae given in detail in ref. 28. For every binding site considered several (or the order of 10) starting positions and conformations were tried, including the sets of ϕ and ψ angles proposed by Carter and Kraut [4] and Church et al. [5].

3. Results

Fig. 1 shows the β-ribbon fragment built up from two antiparallel glycine hexapeptides. The fragment is illustrated in its energy-minimized

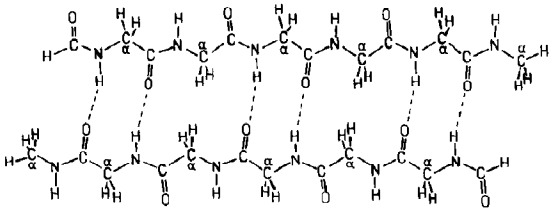

Fig. 1. The antiparallel β-ribbon studied in its energy-optimized conformation. The six interchain hydrogen bonds are denoted by dashed lines. The length of the hydrogen bonds is 1.98 Å, and their distortion from linearity 10.5°.

conformation with the six interchain hydrogen bonds between alternating peptide groups being represented by dotted lines.

In table 1 we present the results of our study of the interaction of this fragment with B-DNA, for the two homopolymeric base-pair sequences, AT and GC and, in each case in both the minor and major grooves. For each of the four resulting binding sites we give the best parallel and antiparallel complex (denoted as P and A, respectively) obtained with the ribbon. In the first four columns of table 1 are listed the interaction energy, E_{inter}, and its components (Lennard-Jones, electrostatic and polarization) for the interaction of the β-ribbon with the screened nucleic acid. These are followed by the interaction energy of DNA with the screening cations E_{intra}^{DNA}, calculated as the difference with respect to the energy obtained for an isolated DNA with its cations in their optimal positions. In the next column we tabulate the internal β-ribbon energy, E_{intra}^{β}, again calculated with respect to the minimized energy of the isolated β-ribbon. In the last column of this table the total energy of the complex E^{tot} is given as:

$$E^{tot} = E_{inter} + E_{intra}^{DNA} + E_{intra}^{\beta}$$

When the β-ribbon interacts with B-DNA the best complex for both AT and GC sequences is found to be in the DNA major groove. However, the binding energies in the minor groove are not very much weaker. In fact, the DNA-oligopeptide interaction energy E_{inter} (about −60 kcal/mol) is similar for all the binding positions with the exception of the antiparallel complexes in the minor groove, which are weaker by roughly 10 kcal/mol. The two main components of the interaction energy, the Lennard-Jones and electrostatic terms, are of similar importance in all the complexes, although, in most cases, the electrostatic contribution provides a slightly stronger stabilization. The final binding preference is obtained through a lower deformation energy within the polypeptide fragment in the case of the antiparallel complexes. The absence of a clearcut sequence dependence for this series of complexes is connected with the fact that the bound polypeptide sheet always remains towards the outside of the DNA double helix.

Since no marked sequence dependence was found for the interaction of the β-ribbon with DNA we show only one molecular graphic for each DNA-binding site. The complex obtained with the minor groove is shown in fig. 2, that with the major groove in fig. 3.

Looking more closely at the complexes ob-

Table 1

Complexation energy (kcal/mol) of the antiparallel β-ribbon with B-DNA

Base-pair sequence	Groove	Ligand orientation	E_{inter}				E_{intra}^{DNA}	E_{intra}^{β}	E^{tot}
			Lennard-Jones	Electrostatic	Polarization	Total			
AT	Minor	P	−23.25	−34.20	−2.92	−60.38	0.33	14.07	−45.98
		A	−24.09	−26.61	−2.51	−53.21	0.08	7.82	−45.31
	Major	P	−30.65	−29.13	−2.71	−62.49	0.01	13.00	−49.48
		A	−20.03	−36.99	−2.72	−59.74	0.64	6.34	−52.76
GC	Minor	P	−23.67	−33.73	−2.89	−60.28	0.17	13.70	−46.41
		A	−18.13	−27.91	−2.03	−48.08	0.32	5.45	−42.31
	Major	P	−25.91	−31.09	−3.60	−60.60	0.04	13.64	−46.92
		A	−18.45	−39.05	−2.92	−60.42	0.46	6.30	−53.66

tained we can see that in the case of the minor groove there is a certain competition within the polypeptide sheet for the interaction with the nucleic acid or between the two strands. In the case of the parallel complex (fig. 2) six hydrogen bonds are formed between the peptide NH groups and the anionic oxygens of the phosphate groups. Thus, every second peptide is bound to DNA, alternating with the peptides forming the internal hydrogen bonds between the two strands of the β-ribbon. In order to improve the binding with DNA one of the internal hydrogen bonds of the β-ribbon breaks, giving rise to a relatively high internal energy for the fragment. In the case of the antiparallel complex all six internal hydrogen bonds are maintained but only three hydrogen bonds are formed with the phosphates of DNA. It is this difference that gives rise to a better internal peptide energy, but also to a less favorable energy of interaction between the two macromolecules.

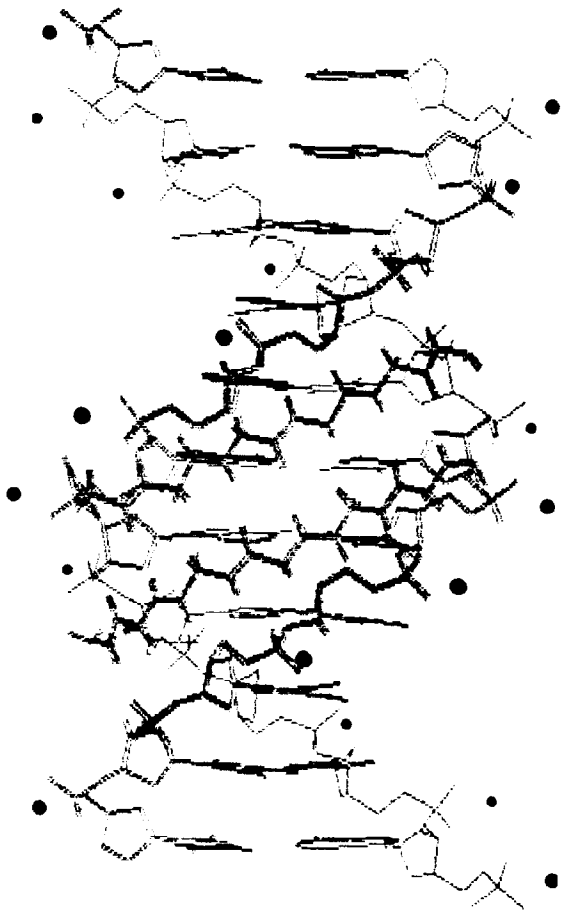

Fig. 2. The energy-minimized parallel complex formed between the β-ribbon and the minor groove of B-DNA. The example shown was obtained for the AT sequence, the complex with the GC sequence being very similar. In this figure and in figs. 3–5 the black dots indicate the positions of Na^+.

We may also remark that the total complexation energies of the parallel and antiparallel complexes in the minor groove are identical for the AT base-pair sequence, while for the GC sequence a slightly better energy is found with the parallel arrangement. However, this difference is very small. In the study by Church et al. [4] the parallel complex was suggested as being preferable while we find that, in fact, the β-ribbon can be arranged in the antiparallel sense without any loss of energy.

In the case of the major groove complexes, an example of which is given in fig. 3, the β-ribbon is found to lie deeper in the groove than for complexes involving the opposing groove, forming, in the parallel complex, hydrogen bonds not only to phosphate groups, but also to the nucleic acid base atoms (the amino group of adenine in the case of the AT sequence and the amino group of cytosine in the GC sequence). However, these interactions are formed at the cost of breaking one internal hydrogen bond of the β-ribbon and a slight lengthening of the remaining hydrogen bonds. In the antiparallel complex no binding was found to the base atoms. This weakens the resulting interaction energy only insignificantly but does improve the internal energy of the β-ribbon, giving rise to the final energetic preference for the latter complexes.

When the β-ribbon interacts with B-DNA, the cations screening the nucleic acid can remain very close to their optimum positions for uncomplexed DNA, namely, at the bridge position of the phosphates, in the OPO^- plane at a distance of 2.1 Å from the anionic oxygens. There are only very small modifications in these positions depending on the exact location of the bound peptide fragment and the variations in the DNA-cation interaction energy are less than 1 kcal/mol (table 1, column 5). Consequently, for this DNA allomorph

the distribution of the bound counterions does not appear to play a significant role in complex formation.

We now turn to studies involving the A conformation of DNA. The results obtained with this allomorph, given in table 2, show considerable differences with respect to those involving B-DNA and it is found that the final binding energies of the β-ribbon are the results of a delicate equilibrium between the three components of the complexation energy, namely, the screened DNA-oligopeptide interaction energy, the DNA-cation interaction energy and the internal energy of the β-ribbon.

If we consider firstly the complexes with β-ribbon located in the minor groove of A-DNA (an example of which is shown in fig. 4), the main contribution to their stabilization is provided by the Lennard-Jones component of the DNA-peptide interaction, which indicates a good steric fit of the β-ribbon at this binding site. The electrostatic energy is very strongly reduced (to about −4 kcal/mol) as compared to the complexes with B-DNA, with the accompanying reduction in the polarization energy. The best complexation energies are obtained with the β-ribbon located in the minor groove of the GC sequence in an antiparallel orientation. In this complex two hydrogen bonds are formed, between a guanine amino hydrogen and an amide carbonyl oxygen and between a sugar oxygen O1′ and an amide hydrogen. No hydrogen bonds were found with the phosphate groups of DNA, which may be due to the

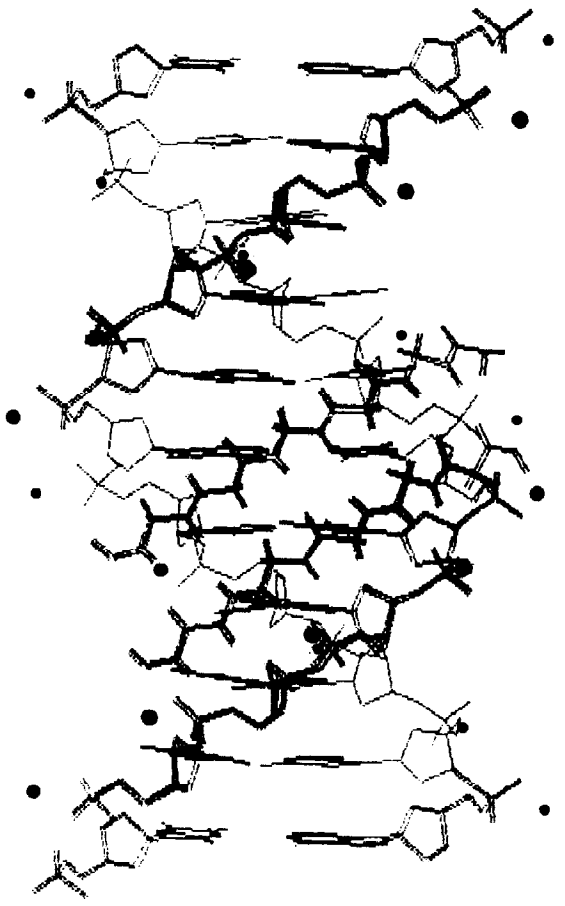

Fig. 3. The energy-minimized antiparallel complex formed between the β-ribbon and the major groove of B-DNA (only the AT sequence is shown).

Table 2

Complexation energy (kcal/mol) of the antiparallel β-ribbon with A-DNA

Base-pair sequence	Groove	Ligand orientation	E_{inter}				E_{intra}^{DNA}	E_{intra}^{β}	E^{tot}
			Lennard-Jones	Electrostatic	Polarization	Total			
AT	Minor	P	−32.35	−4.50	−0.44	−37.29	0.00	10.41	−26.88
		A	−33.47	−4.10	−0.40	−37.97	0.00	6.53	−31.44
	Major	P	−25.88	−26.14	−2.77	−54.79	11.66	16.42	−26.71
		A	−25.09	−22.28	−2.99	−50.36	11.53	9.60	−29.23
GC	Minor	P	−36.13	−4.71	−0.47	−41.31	0.00	10.22	−31.09
		A	−36.36	−3.81	−0.43	−40.60	0.00	7.23	−33.37
	Major	P	−26.59	−23.10	−2.44	−52.13	11.00	14.83	−26.30
		A	−24.96	−21.97	−2.98	−49.90	10.88	9.05	−29.97

considerable width of the minor groove in A-DNA. The existence of hydrogen bonding with the sugar oxygen is in line with the proposal of Kraut and Carter [4] concerning the interaction of β-ribbons. We have obtained similar hydrogen bonds for all the complexes in the minor groove, a slight binding preference being found for the GC sequence, due to an additional hydrogen bond with a guanine base. In all four complexes in the minor groove, the six internal hydrogen bonds of the β-ribbon are maintained. A slight energy preference can also be noted for the β-ribbon's internal energy within the antiparallel complexes. When the β-ribbon interacts with the minor groove, the DNA-screening cations remain effectively in their optimum position bridging the phosphate anionic oxygens.

A very different situation is found for the major groove complexes since the peptide fragment and counterions compete for the binding to DNA. In the energy-minimized complexes the counterions are found to be displaced from their optimal sites towards positions located between successive phosphate groups on each strand (see fig. 5). This is accompanied by a loss of about 11 kcal/mol in their interaction energy with DNA, but allows the β-ribbon to be accommodated better in the groove,

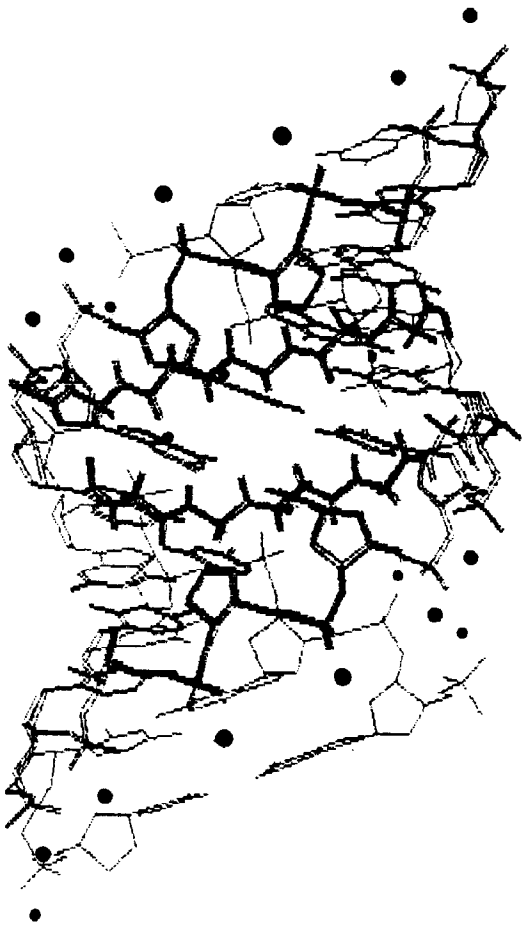

Fig. 4. The energy-minimized antiparallel complex formed between the β-ribbon and the minor groove of A-DNA (only the GC sequence is shown).

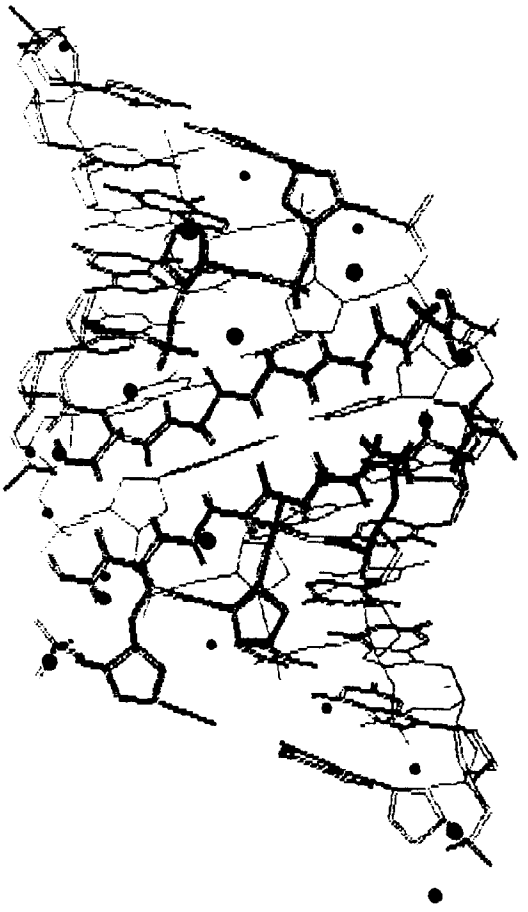

Fig. 5. The energy-minimized antiparallel complex formed between the β-ribbon and the major groove of B-DNA (only the GC sequence is shown). Note that the DNA-screening cations have shifted from the bridge position between the anionic oxygens to a position between successive phosphate groups.

improving its electrostatic interaction energy with the counterion-screened nucleic acid by almost 20 kcal/mol.

Since the major groove of A-DNA is quite narrow, the β-ribbon understandably stays rather on the outside of the nucleic acid helix. Three hydrogen bonds are formed between the amide hydrogens of the peptide fragment and the phosphate anionic oxygens. In the parallel complex, the three phosphate groups involved belong to both phosphodiester chains, while in the antiparallel arrangement they all belong to the same chain. This indicates that there is a certain misfit between the geometry of the A-DNA major groove and that of the β-ribbon, since not all possible hydrogen bonds are formed, as was observed in the minor groove of B-DNA.

Despite the very different energy contributions described above for the β-ribbon interacting with the two grooves of A-DNA, inspection of column 8 of table 2 shows that the final complexation energies are very close for all the complexes studied with A-DNA, and are, in general, weaker than those obtained for the interaction with B-DNA.

4. Conclusions

The results of our study show that the answer to the question posed in section 1, namely, whether there is any clear preference for a specific binding site for the interaction of a β-ribbon with DNA, seems to be rather negative. The polypeptide fragment turns out to be flexible enough to adapt its geometry to different forms and different grooves of DNA, and we cannot eliminate, on the basis of the calculated complexation energies, any of the binding sites examined.

One effect nevertheless appears rather systematically, namely, that the formation of the antiparallel complex requires less deformation energy than that of the parallel complex. This conclusion is in disagreement with the results of the model-building studies of Kraut and Carter [4] and Church et al. [5], but concurs with the hypothesis of stereospecific binding made by Gurskii et al. [10]. However, the parallel arrangement of the polypeptide and polynucleotide chains generally results in a better interaction energy between the two macromolecules. As a result of these two opposing factors, the final complexation energies for both arrangements are found to be rather close.

We may conclude that in the absence of amino acid side chains there is no evidence of a significant binding specificity for the β-ribbons, even when there are direct interactions with the nucleic acid bases: the flexibility of the β-ribbon allows it to adapt itself not only to the geometry of the DNA backbones but also to the available positions of base hydrogen bond donor and acceptor atoms. Any specific recognition must consequently be performed by the side chains. The interesting aspect of these results is that specific recognition by amino acid side chains need only involve small energy differences because the complex can be held together well by nonspecific interactions, irrespective of the conformation of base sequence of the nucleic acid. Conversely, the presence of any strong preference of binding exhibited by the peptide backbone without side chains would reduce the usefulness of this structural motif in recognition processes, as this preference would then have to be overcome by the amino acid side chains in order to induce specific binding in other locations.

The next question to arise clearly concerns what happens when specific amino acid side chains are present on the β-ribbon. In the complexes we have obtained, the β-ribbon fragment stayed largely on the outside of the nucleic acid double helix. In the case of the B-DNA minor groove and A-DNA major groove the peptide chains interacted directly only with the phosphate groups of DNA, leaving plenty of space around the nucleic acid bases to accommodate side chains responsible for subsequent nucleic acid-peptide sequence recognition. In the case of the major groove of B-DNA and minor groove of A-DNA some direct interactions were found between peptides and nucleic acid bases. This might indicate some advantage for binding to the two former grooves if the side chains present are rather bulky, but a detailed answer to this question can only be found by specific conformational energy calculations which will be the subject of future studies in our laboratory.

Acknowledgment

This work was supported by the National Foundation for Cancer Research (Bethesda, MD, U.S.A.) to which the authors wish to express their thanks.

References

1 Y. Takeda, D.H. Ohlendorf, W.F. Anderson and B.W. Matthews, Science 221 (1983) 1020.
2 D.H. Ohlendorf and B.W. Matthews, Annu. Rev. Biophys. Bioenerg. 12 (1983) 259.
3 C.O. Pabo and R.T. Sauer, Annu. Rev. Biochem. 53 (1984) 291.
4 C.W. Carter and J. Kraut, Proc. Natl. Acad. Sci. U.S.A. 71 (1974) 283.
5 G.M. Church, J. Sussman and S.H. Kim, Proc. Natl. Acad. Sci. U.S.A. 74 (1977) 1458.
6 P. De Santis, E. Forni and R. Rizzo, Biopolymers 13 (1974) 313.
7 W. Saenger, in: Specificity in biological interaction, eds. C. Chagas and B. Pullman, Ponticiae Acad. Sci. Scr. Varia 55 (1984) 99.
8 D.H. Ohlendorf, W.F. Anderson, R.G. Fisher, Y. Takeda and B.W. Matthews, Nature 298 (1982) 718.
9 B.W. Matthews, D.H. Ohlendorf, W.F. Anderson, R.G. Fisher and Y. Takeda, Cold Spring Harbor Symp. Quant. Biol. 47 (1982) 427.
10 C.J. Chothia, J. Mol. Biol. 75 (1973) 295.
11 G.V. Gurskii, V.G. Tumanyan, A.S. Zasedatelev, A.L. Zhuze, S.L. Grokhovsky and B.P. Gottikh, Nucleic Acid-Protein Recog, ed. H.J. Vogel (Academic Press, New York, 1977) 189.
12 A. Kolb and H. Buc, Nucleic Acids Res. 10 (1982) 473.
13 J.C. Wang, M.D. Barkley and S. Bourgeois, Nature 251 (1974) 247.
14 T. Maniatis and M. Ptashne, Proc. Natl. Acad. Sci. U.S.A. 70 (1973) 1531.
15 K. Zakrzewska and B. Pullman, J. Biomol. Struct. Dyn. 2 (1985) 737.
16 R. Lavery, H. Sklenar and B. Pullman, Stud. Biophys. 104 (1984) 285.
17 K. Zakrzewska and B. Pullman, Biopolymers (1985) in the press.
18 V.B. Zhurkin, V.I. Poltiev and V.I. Florent'ev, Mol. Biol. USA 14 (1980) 882.
19 R. Lavery, K. Zakrzewska and A. Pullman, J. Comput. Chem. 5 (1984) 363.
20 K. Zakrzewska and A. Pullman 6 (1985) J. Comput. Chem. 265.
21 Y.K. Kang and M.S. John, Theor. Chim. Acta 61 (1982) 41.
22 N. Gresh, P. Claverie and A. Pullman, Int. J. Quant. Chem. Quant. Biol. Symp. 13 (1973) 243.
23 B. Hingerty, R.H. Richie, T.L. Ferrel and J.E. Turner, Biopolymers 24 (1985) 427.
24 R. Lavery and B. Pullman, J. Biol. Struct. Dyn. 2 (1985) 1021.
25 S. Arnott, R. Chandrasekaran, D.L. Birdsall, A.G.W. Lesline and R.L. Ratliff, Nature 283 (1980) 743.
26 S. Arnott, S.D. Dover and A. Elliott, J. Mol. Biol. 30 (1967) 201.
27 M.Y.D. Powel, Report C.S.S. 15 A.E.R.E., Harwell, Harwell Library, Routine VA13A (1975).
28 R. Lavery, H. Sklenar, K. Zakrzewska and B. Pullman, J. Biomol. Struct. Dyn. in the press.