Biophysical Chemistry 25 (1986) 201–213
Elsevier

BPC 01105

THEORETICAL STUDIES ON THE INTERACTION OF PROTEINS AND NUCLEIC ACID

II. THE BINDING OF α-HELIX TO B-DNA

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Received 19th June 1986
Accepted 22nd September 1986

Key words: Protein-nucleic acid interaction; α-Helix; B-DNA

Interactions between B-DNA and homopolymeric α-helices of glycine, alanine, serine, asparagine and aspartic acid have been studied theoretically. The complexation energy has been minimised taking into account the interactions between DNA and the polypeptides as well as the internal energy of the α-helix and the interaction energy of counterions with the complex. The results obtained indicate the important role of strong hydrogen bonds between the peptide side chains and nucleic acid phosphate groups, these bonds being much stronger than specific interactions with the base-pairs. The formation of these structural bonds depends on the size of the α-helix, which in turn determines whether bridging across the major groove is possible. The steric role of the methyl group of thymine in orienting the peptide helix and the role of DNA screening cations in complex stabilization are also significant.

1. Introduction

The problem of recognition between nucleic acids and proteins has long been a fundamental occupation of molecular biologists. It is generally agreed that this recognition should involve hydrogen-bond formation between nucleic acid bases and polypeptide side chains. Because of this, the major groove of DNA has been proposed as the recognition site since this side of the AT and GC base-pairs offers more possibilities of distinction through hydrogen bonding than the minor groove [1]. In order to establish a precise recognition pattern, many systems of differing complexity have been studied [2,3]: interactions between isolated bases and amino acids, fiber studies of complexes of DNA with polypeptides of different sequence or conformation [4], up to the determination of the structure of co-crystals between the DNA and phage 434 repressor or with the enzyme *Eco*RI [5,6]. The most recent studies seem to point unambiguously to the important role played in the interactions with nucleic acids by α-helical fragments of proteins. In the DNA-protein co-crystals mentioned above, an α-helix from each protein lies in the DNA major groove. Similarly, α-helices located in the DNA major groove have been proposed as structural recognition elements for three site-specific DNA-binding proteins: Cro and cI repressors of bacteriophage λ and the CAP protein of *E. coli* (for reviews see refs. 7 and 8). In these studies the implication of the importance of protein α-helices for the process of DNA-protein recognition rejoins older predictions based on theoretical modeling [9,11]. In addition, it has been shown that many polypeptides or protamines, which exist as coils in solution, assume α-helical conformations when interacting with DNA or RNA [11,12].

Thus, at present, there seems to be no doubt about the importance of this protein structural motif. The rules governing the molecular mecha-

nism of the recognition remain, however, unclear. In the case of Cro and λ repressor, both proteins bind to the same sites on DNA, but the amino acid sequences of their recognition helices are substantially different and they use different sets of amino acid side chains, organised somewhat differently in space, to interact with the nucleic acid bases. This suggests that there is no simple one-to-one code between amino acids and bases. It seems rather that the totality of the interaction between a segment of a protein and a segment of DNA and all of the energy terms (van der Waals, hydrogen bonding and electrostatic) play a role, and that a 'lock and key' analogy, similar to the case of the enzyme-substrate fit, is most appropriate [8].

In view of this situation, we have decided to investigate the problem of the interaction of proteins with nucleic acids by means of theoretical calculations, beginning by a study of homopolymeric peptide oligomers, in a regular α-helix conformation, interacting with B-DNA. Since there are many arguments [13,15] that DNA does not significantly change its structure upon such interaction, we use a rigid model DNA, with homopolymeric AT or GC base-pair sequences.

The questions that we try to answer by our explicit calculations are: firstly, what are the dominant energetic factors in these types of interaction; secondly, do the specific amino-acid helices show a pronounced preference for either base-pair sequence; and, thirdly, what is the importance of the interactions between base-pair atoms and peptide side chains with respect to interactions with the sugar-phosphate backbones of DNA.

We chose five homopolymeric dodecapeptides, composed of glycine, alanine, serine, asparagine or aspartic acid. In this way we have tried to cover a relatively wide range of amino acids, whose helices differ both in size and in hydrogen-bonding properties.

2. Methodology

The interaction energy of the complexes studied is calculated with an energy formula identical to that used in our previous investigations [16,18]:

$$E = \sum \left(-A_{ij}/r_{ij}^6 + B_{ij}/r_{ij}^{12} \right) + \sum_{HB} \left[\left(\cos\theta \left(-A_{ij}^{HB}/r_{ij}^6 + B_{ij}^{HB}/r_{ij}^{12} \right) + (1 - \cos\theta)\left(-A_{ij}/r_{ij}^6 + B_{ij}/r_{ij}^{12} \right) \right] + \sum q_i q_j / \left(\epsilon(r) r_{ij} \right) - \tfrac{1}{2} \sum \alpha_i \vec{F}_i^2 + \sum v_T (1 + \cos 3\tau) + \sum V_G / 2 (1 + \cos 2\tau)$$

The first term describes the Lennard-Jones energy calculated with the so-called '6-12' potential functions in the parametrisation of ref. 19, and the second term relates to the angle-dependent hydrogen-bond energy, where θ denotes the angle between the vectors $\vec{AH}$ and $\vec{HB}$ of a hydrogen bond A–B · · · · B. The electrostatic energy (third term) is calculated with our optimised atomic monopoles [20,21] derived from a specially parameterised Huckel-Del Re calculation. The fourth term describes the polarization energy in terms of mean atomic polarisabilities. α_i, taken from ref. 22, and $\vec{F}_i$ the total electrostatic field acting on each atom. The field term involved a short-range correction, following the work of ref. 23 and is given by the formula:

$$\vec{F}_i = \sum q_j \vec{r}_{ij} / \left(\epsilon(r) r_{ij}^3 \right) \quad r_{ij} = r_{ij} + 0.225(\omega_i + \omega_j)$$

where ω_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 calculation of the electrostatic and polarization energies we employ a distance-dependent dielectric constant with a sigmoidal form proposed by Hingerty et al. [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 either poly(dA) · poly(dT) or poly(dG) · poly(dC), with the geometry proposed for B-DNA by Arnott et al. [25]. The nucleic acids were screened by 22 Na^+, 11 on each sugar-phosphate chain.

The calculations of the complexation energies were performed keeping the geometry of the nucleic acid constant, but allowing for variations in the counterion positions. These positions were optimised during the complex formation, maintaining however, the helical symmetry of the cation locations within each chain of the double helix.

The α-helices were modelled by dodecamers of the amino acids glycine, alanine, serine, asparagine and aspartic acid, with standard bond lengths and angles and α-helix parameters taken from Arnott et al. [26]. During complex formation the ψ and ϕ angles of the α-helices were kept constant, but all single bonds of the peptide side chains were free to rotate.

The total energy of the optimised complex is expressed as a sum of the counterion screened nucleic acid-polypeptide interaction energy, the nucleic acid internal energy (the interaction energy between the double-helical segment of DNA and the mobile counterions) and the internal energy of the α-helix, calculated as a sum of atom pair interactions for all pairs of atoms separated by at least three bonds. Minimisation was performed using a sophisticated conjugate gradient technique with the BFGS algorithm [27,28]. 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 each atom within the complex, using the formulae given in detail in an earlier publication [29]. For each complex studied many starting positions were used, of the order of 20, obtained with the help of studies on a high-resolution interactive graphics system.

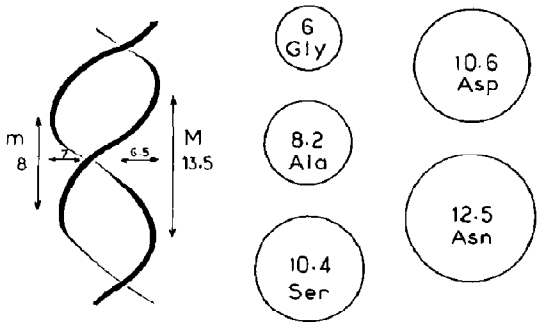

Fig. 1. The dimensions of the major and minor grooves of B-DNA and the dimensions of the proteins α-helices studied.

3. Results

In the present study we obtained the energy-minimised complexes of B-DNA with five homopolymeric peptide α-helices. We are therefore dealing with α-helices of a rather regular cylindrical shape and roughly constant diameters. The smallest diameter of the helix (6 Å) is that of

Table 1

Specific interactions of the polypeptide α-helices with the B-DNA major groove (kcal/mol)

Amino acid side chain	Base-pair sequence	E_{inter}				E_{intra}^{DNA}	E_{intra}^{α}	E^{tot}
		Lennard-Jones	Electrostatic	Polarization	Total			
Gly	AT	−22.4	−10.8	−0.7	−33.9	0.9	0.8	−32.2
	GC	−22.8	−12.0	0.9	−35.7	0.8	1.0	−34.0
Ala	AT	−20.9	−11.8	−0.7	−33.5	0.4	1.8	−31.3
	GC	−18.4	−12.8	−0.9	−32.0	0.2	0.3	−31.6
Ser	AT	−16.0	−45.6	−3.8	−65.5	1.7	10.1	−53.7
	GC	−18.2	−46.0	−4.2	−68.4	0.2	18.1	−50.1
Asn	AT	−32.0	−16.1	−1.6	−49.7	0.1	15.2	−34.4
	GC	−31.8	−23.2	−2.4	−57.3	0.1	18.3	−39.0
Asp	AT	0.0	−105.0	−13.6	−118.7	1.7	19.4	−97.5
	GC	1.3	−107.1	−14.1	−119.1	1.9	13.0	−104.1

polyglucine, while the largest is that of asparagine (12.5 Å). It is interesting to compare these values with the dimensions of the minor and major grooves of B-DNA used in our calculations. This is shown schematically in fig. 1.

The minor groove of B-DNA is rather narrow and deep, with a width of about 8 Å and a depth of about 7 Å. The major groove is much wider (13.5 Å) and slightly shallower (6.5 Å). From this comparison it becomes clear that there is no possibility of interaction of the homopolymeric peptide helices with the bases in the minor groove of B-DNA. In fact, in all the complexes studied by us the peptide helix stayed outside, or (in the case of polyglycine) at the entrance to this groove. However, we performed energy minimisation for the minor groove complexes in order to obtain an estimate of the importance of the nonspecific in-

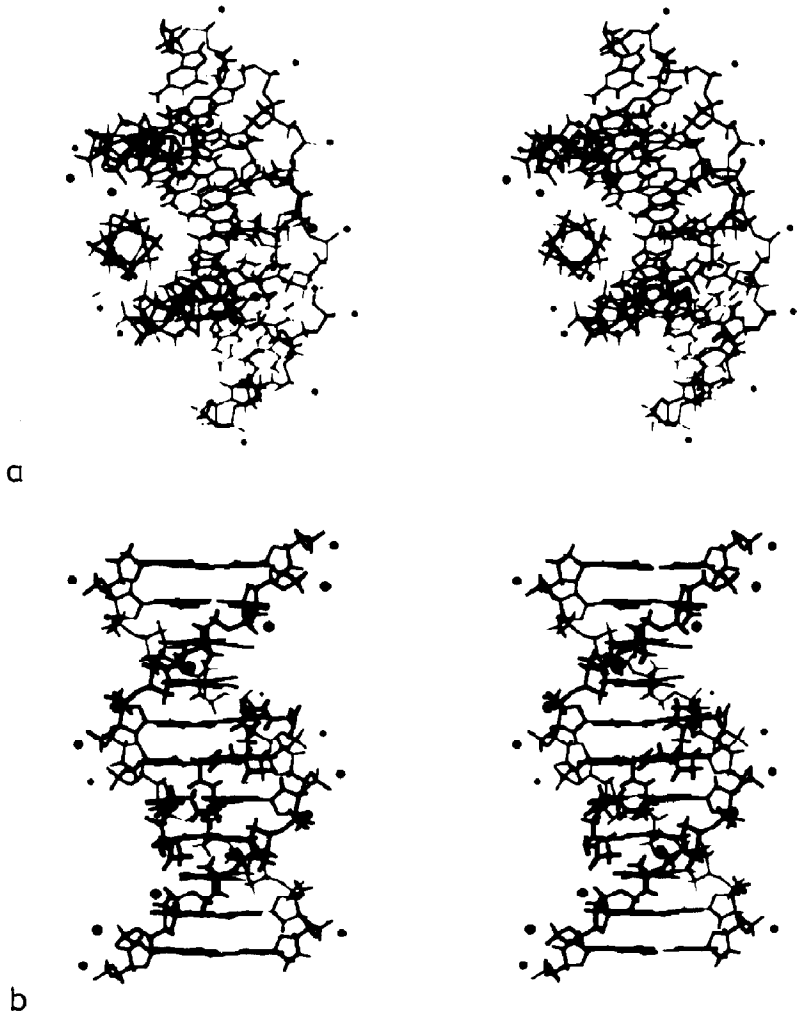

Fig. 2. Optimal complex of polyglycine in the major groove of B-DNA (GC sequence). (In figs. 2–8, panel a shows the complex when looking along the polypeptide helix axis, and panel b shows the complex with the DNA helical axis vertical and the major (figs. 2–6) or minor groove (figs. 7 and 8) pointing towards the viewer.)

teractions which may nevertheless exist at this binding site. In the major groove, on the other hand, there is enough space to accommodate even the largest of the polypeptide α-helicies that we have considered and to produce specific interactions with the base-pairs.

3.1. 'Specific' major groove complexes

Let us start by discussing the major groove complexes, which we can term specific since base sequence dependence can be expected. The results of our energy-minimisation studies are given in table 1. In this table the energetics of the best complex obtained for each of the polypeptides studied and for both DNA base-pair sequences are presented. In each case we give the DNA-polypeptide interaction energy E_{inter} and its components, electrostatic, Lennard-Jones and polarisation, the change in the internal energy E_{intra}^{DNA} of DNA, which, in the case of our rigid DNA model comes from the displacement of the DNA screen-

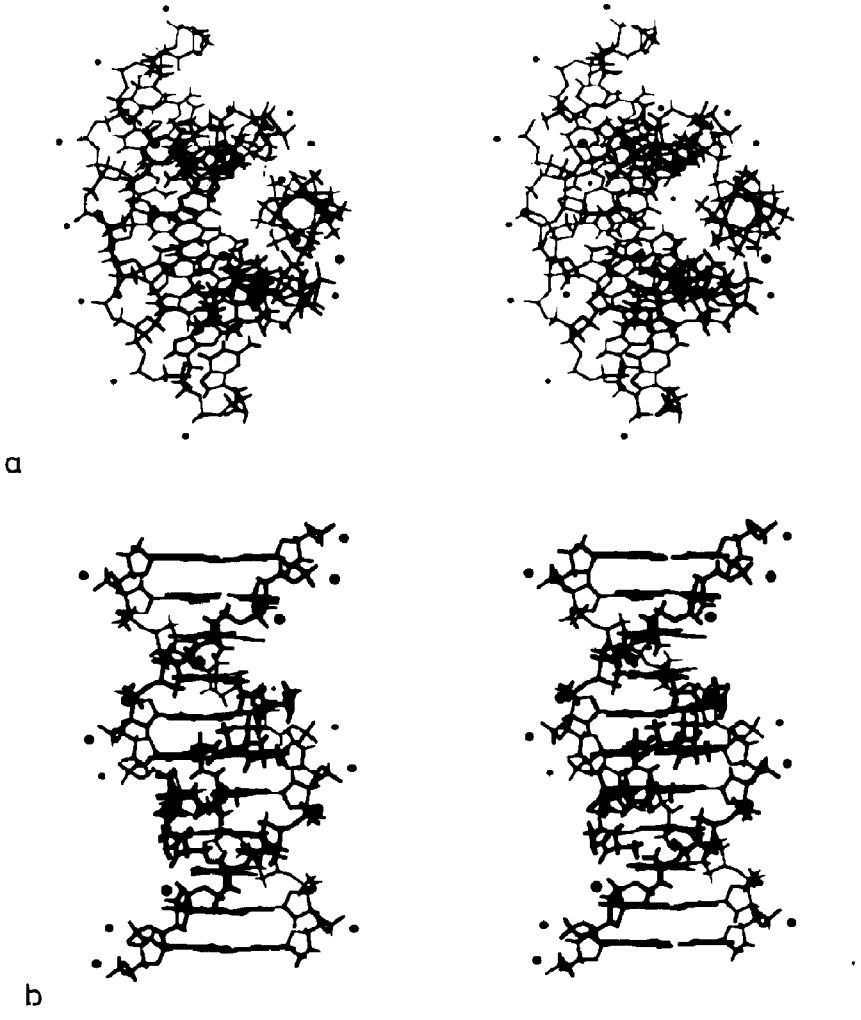

Fig. 3. Optimal complex of polyalanine in the major groove of B-DNA (GC sequence).

ing cations upon complex formation, the change of the internal energy of the polypeptide α-helix $E^{\alpha}_{\text{intra}}$ calculated with respect to an optimised isolated α-helix, and finally the total complexation energy, defined as a sum of these three contributions:

$$E^{\text{tot}} = E_{\text{inter}} + E^{\text{DNA}}_{\text{intra}} + E^{\alpha}_{\text{intra}}$$

The first two polypeptides we consider, polyglycine and polyalanine, have no possibility of forming hydrogen bonds. Their small size allows them to fit easily into the major groove of B-DNA, as can be seen in figs. 2 and 3 where the complexes are shown when looking on them along the polypeptide helical axis (figs. 2a and 3a) as well as in a more conventional view with the helical axis of DNA vertical and the major groove of the duplex pointing towards the viewer (figs. 2b and 3b). Similar conventions are adopted for viewing the remaining complexes shown in figs. 4–8 where the optimal complexes of the other α-helices are illustrated. In these complexes the main stabiliza-

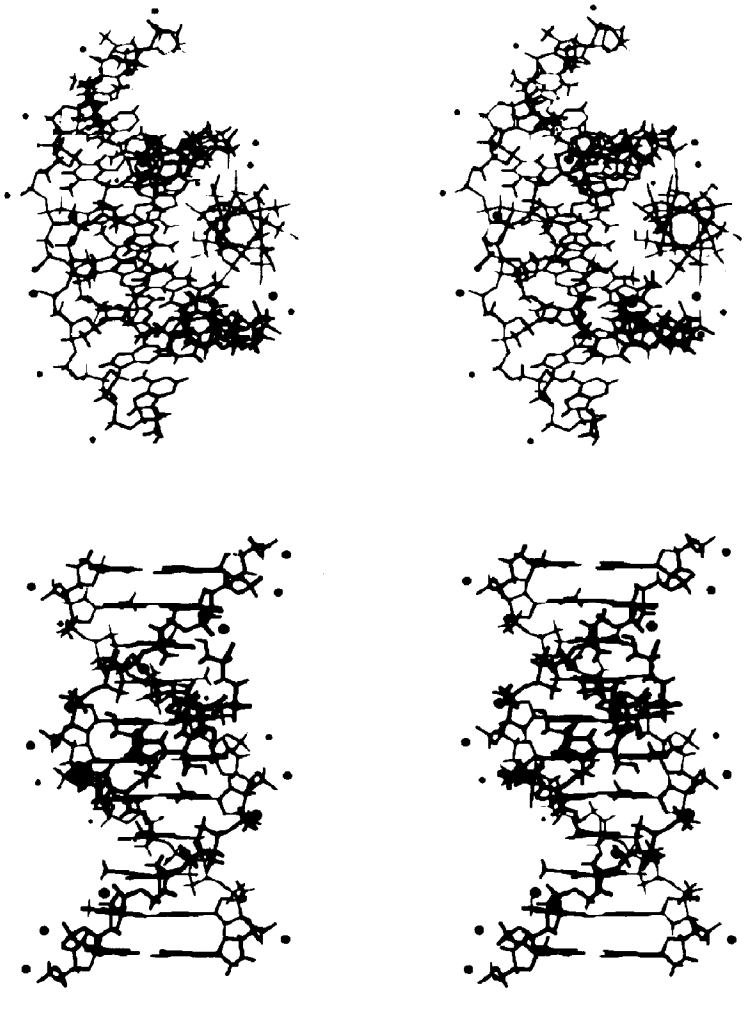

Fig. 4. Optimal complex of polyserine in the major groove of B-DNA (AT sequence).

tion energy is provided by the Lennard-Jones term with an additional stabilization given by a charge-dipole interaction between a DNA screening cation and the strong polypeptide α-helix dipole. This additional stabilization is possible since, due to the orientation of the phosphate anionic oxygens in B-DNA, the cations are located on the major groove side of the DNA helix, in both figs. 2a and 3a we can see a cation placed in the vicinity of the C′ end of the polypeptide helicies. It can be seen in table 1 that both glycine and alanine polypeptides slightly prefer the GC base-pair sequence.

The third polypeptide studies, polyserine, presents quite a different picture. It has rather short side chains which nevertheless have the possibility to act either as hydrogen-bond donors or acceptors. The optimal complex with DNA was found for the AT sequence and is shown in fig. 4. In this complex polyserine forms hydrogen bonds with two phosphate oxygens belonging to the adenosine chain and two bonds with adenine atoms using, in

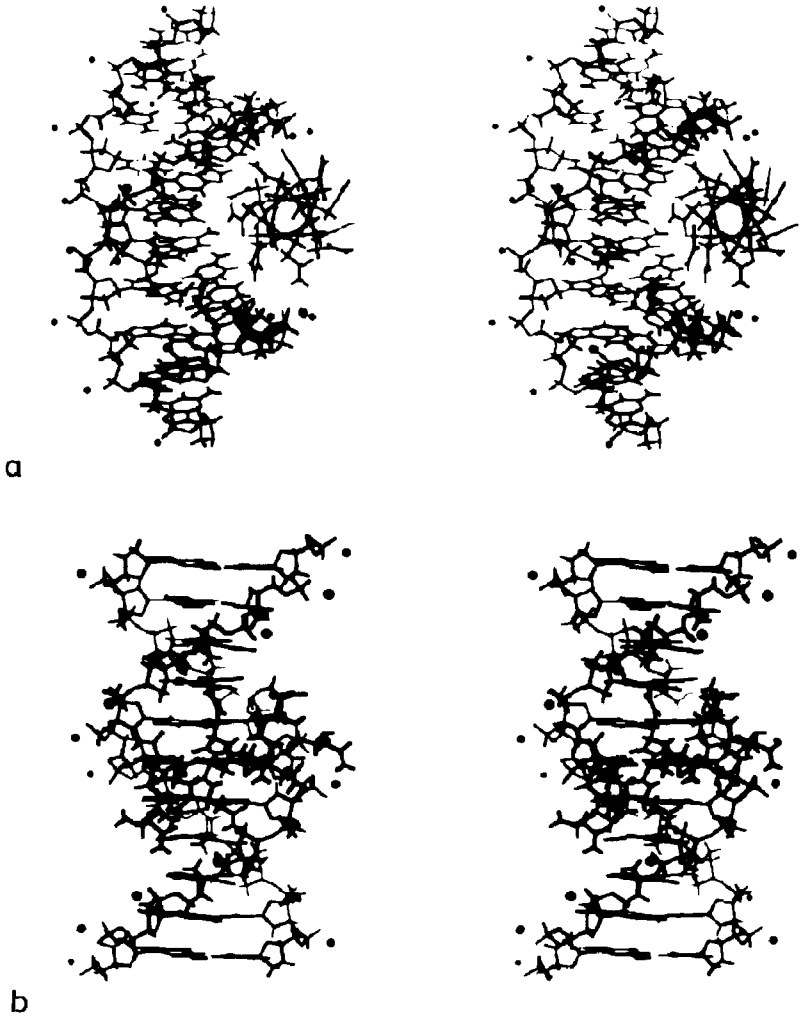

Fig. 5. Optimal complex of polyasparagine in the major groove of B-DNA (GC sequence).

one case, the amino group of adenine and the hydroxyl oxygen of the serine and, in the other case, adenine N7 and the serine hydroxyl proton. For the GC sequence there is one hydrogen bond formed with a phosphate group and one formed between guanine N7 and a serine hydroxyl proton. It is interesting to note that a serine side chain binding to adenine is proposed in the Cro-DNA complex, whereas binding to guanine is proposed in the λ repressor model. Discussion of these studies [8] concluded, in fact, that the involvement of a particular amino acid will depend on the conformation and orientation of the protein backbone. Our study agrees with this view and points to the steric effect of the thymine methyl group. In the case of the AT sequence polyserine is positioned asymmetrically in the DNA major groove, over the adenine strand, thus avoiding the bulky methyl groups of the thymines. In the GC sequence, where no such obstacle exists, polyserine is located more symmetrically in the groove which corresponds to a better interaction energy E_{inter}.

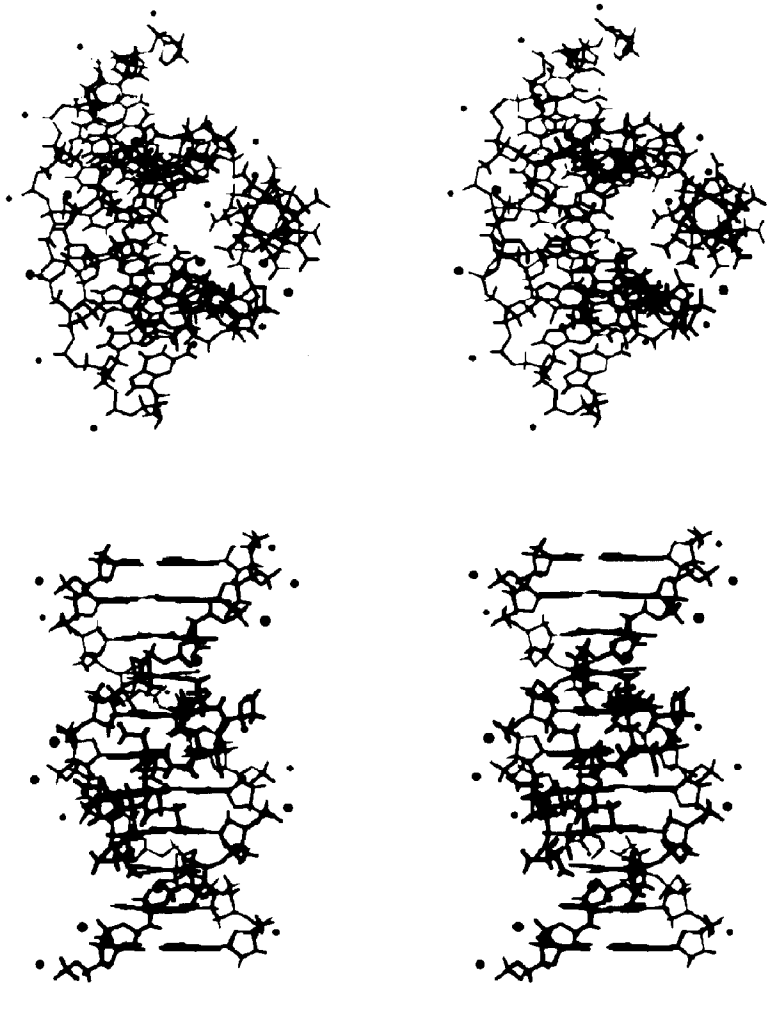

Fig. 6. Optimal complex of polyaspartic acid in the major groove of B-DNA (GC sequence).

However, the internal distortion of the α-helix is also much higher in this complex and the final complexation energy shows a preference for the AT sequence of the DNA.

The largest α-helix amongst the polypeptides treated in this study corresponds to polyasparagine. This polypeptide, like serine, also has both donor and acceptor hydrogen-bonding possibilities. In contrast to serine, it is big enough to bridge across the major groove of the nucleic acid, and to form direct interactions with the phosphate groups of both chains as well as to bind to nucleic acid base atoms located at the bottom of the groove. In the case of the AT base sequence there are hydrogen bonds formed between the amino groups of these asparagines and three phosphate anionic oxygens, two of them belonging to the adenine strand and one to the thymine strand. The sequence-specific interactions with the base atoms take place again only with the adenine chain, where there are bidentate hydrogen bonds formed by the carbonyl oxygen of asparagine interacting with the amino group of adenine and by the amino group of asparagine interacting with N7 of the same base in the center of the DNA fragment. It is interesting to note that this type of a double hydrogen bond has been proposed in ref. 1 as a mechanism for the specific recognition of the AT base-pair by the asparagine side chain. In addition to this interaction, we detect another hydrogen bond between the amino group of asparagine and the N7 of adenine distant by two base-pairs from the central one.

In the case of the GC sequence of DNA there are four hydrogen bonds formed with the phosphate anionic oxygens, two with the purine strand and two with the pyrimidine strand, and, in addition, two hydrogen bonds with base atoms (fig. 5). One of the latter is formed between guanine O6 and the amino group of asparagine, while the other occurs between the amino group of cytosine and the carbonyl oxygen of asparagine. An overall energetic preference for the GC sequence of DNA is again calculated, mainly due to the more favorable electrostatic interaction obtained with this sequence. The GC preference present in the E_{inter} term is reduced by the higher internal distortion of the polyasparagine α-helix forming the complex with the latter sequence. The final difference amounts to 4.5 kcal/mol. These complexes would suggest that for the interaction of asparagine with an α-helix having a rather large diameter there is no particular energetic preference for bidentate hydrogen bonds from individual peptide side chains. The overall complexation energy is determined by a more subtle balance involving all the contributing terms. This is not to say that bidentate hydrogen bonds with the nucleic acid bases will not be important in the case of interactions of smaller or more irregular helices.

Polyaspartic acid, whose diameter is only slightly greater than that of serine, is the only example of a charged polypeptide chain treated in this study. One could expect that because of its high negative charge no favorable interactions would be found with polyanionic DNA. Looking at table 1 we can see that, on the contrary, very strong binding energies are calculated, due to the strong electrostatic interactions between the DNA screening cations and the polypeptide side chains. These interactions were so strong that they dominated the steric repulsion, leading to small or slightly positive values for the Lennard-Jones term. The size of the polyaspartic acid α-helix is such that a very successful complex can be formed in which the counterions can stabilise both polyanionic helices simultaneously. The complex is shown in fig. 6 for the more energetically favorable GC sequence. For this sequence the polypeptide α-helix is positioned quite deeply in the major groove forming, however, only a single hydrogen bond between a cytosine amino group and an anionic oxygen of an aspartic acid side chain. In the case of the AT sequence a hydrogen bond is formed with the adenine amino group, but the bulky thymine methyl groups once again prevent the polypeptide helix from entering the groove deeply.

In summary, we can point out several general features of these major groove complexes. The results obtained suggest that the formation of such interactions should be looked at as the interaction of two polyfunctional species in which the properties of their individual subunits can be attenuated or modified when these are incorporated into a macromolecular structure. The dominant role in

Table 2

Nonspecific interactions of the polypeptide α-helices with the B-DNA minor groove (kcal/mol)

Amino acid side chain	Base-pair sequence	E_{inter}				E_{intra}^{DNA}	E_{intra}^{α}	E^{tot}
		Lennard-Jones	Electrostatic	Polarization	Total			
Gly	AT	−23.5	−4.1	−0.4	−28.0	0.0	0.5	−27.5
	GC	−21.9	−4.1	−0.4	−26.4	0.0	0.4	−26.0
Ala	AT	−19.7	−0.4	−0.5	−20.6	0.0	0.7	−19.9
	GC	−19.9	−0.3	−0.5	−20.7	0.0	0.7	−20.0
Ser	AT	−11.1	−41.6	−3.8	−56.5	0.3	9.1	−47.0
	GC	−4.9	−47.7	−3.9	−56.6	0.2	8.9	−47.5
Asn	AT	−16.6	−37.7	−3.2	−57.4	0.1	14.2	−43.1
	GC	−16.6	−37.6	−3.2	−57.3	0.1	14.2	−43.0
Asp	AT	12.8	−108.9	−13.5	−109.6	0.5	5.8	−103.4
	GC	12.8	−109.2	−13.6	−109.9	0.5	5.8	−103.7

intermolecular binding is played by the structural properties of the system as a whole. Thus, the size of the α-helix as compared to the size of the major groove is very important, as is the possibility of forming hydrogen bonds between the peptide side chains and DNA phosphate groups. If the latter possibility exists, and if the α-helix can bridge the phosphates across the major groove, a very strong stabilisation can be achieved since the hydrogen bonds to the anionic oxygens of phosphates are much stronger than those to the bases.

Hydrogen bonds with the bases of DNA are, in this sense, of secondary importance, at least in energy terms, and they cannot always make use of the full bonding possibilities of the peptide side chains due to the conformational constraints imposed by the incorporation of the peptides into an α-helix.

In addition one should note the role of the thymine methyl group which turns out to be important in fixing the position adopted by the α-helix in the major groove.

3.2. Nonspecific minor groove complexes

We now pass to the complexes obtained for these same α-helices interacting with the minor groove of B-DNA. A summary of the energies associated with the best complex for each polypeptide and both nucleic acid sequences is given in table 2. The most striking feature of these results is the lack of any sequence dependence, which might have been anticipated from the geometrical considerations discussed previously. In all the cases studied the polypeptide helices stay outside the groove giving rise, when the peptide side chains permit it, to interactions with the phosphate anionic oxygens. Only in the case of the polyglycine helix, which has the smallest diameter of those studied, was the helix partly in the groove, contacting the sugar-phosphate backbone of the nucleic acid, but still without coming close to the base-pairs. This complex is shown in fig. 7. As table 2 indicates, due to this partly embedded position the polyglycine complexes have the strongest Lennard-Jones energy of all the polypeptides studied. In the case of the polyalanine helix the steric fit is less easy and the helix being larger has to be positioned further out which is also accompanied by a reduction in the electrostatic interaction energy.

A different situation exists for the α-helix of polyserine. In this case the possibility of hydrogen bonding with the phosphates of DNA exists and the helix is oriented slightly across the minor groove so as to make hydrogen bonds with the phosphate oxygens at both ends of the polypeptide helix. A very similar picture is obtained for polyasparagine. For both DNA base-pair sequences, four hydrogen bonds are formed between

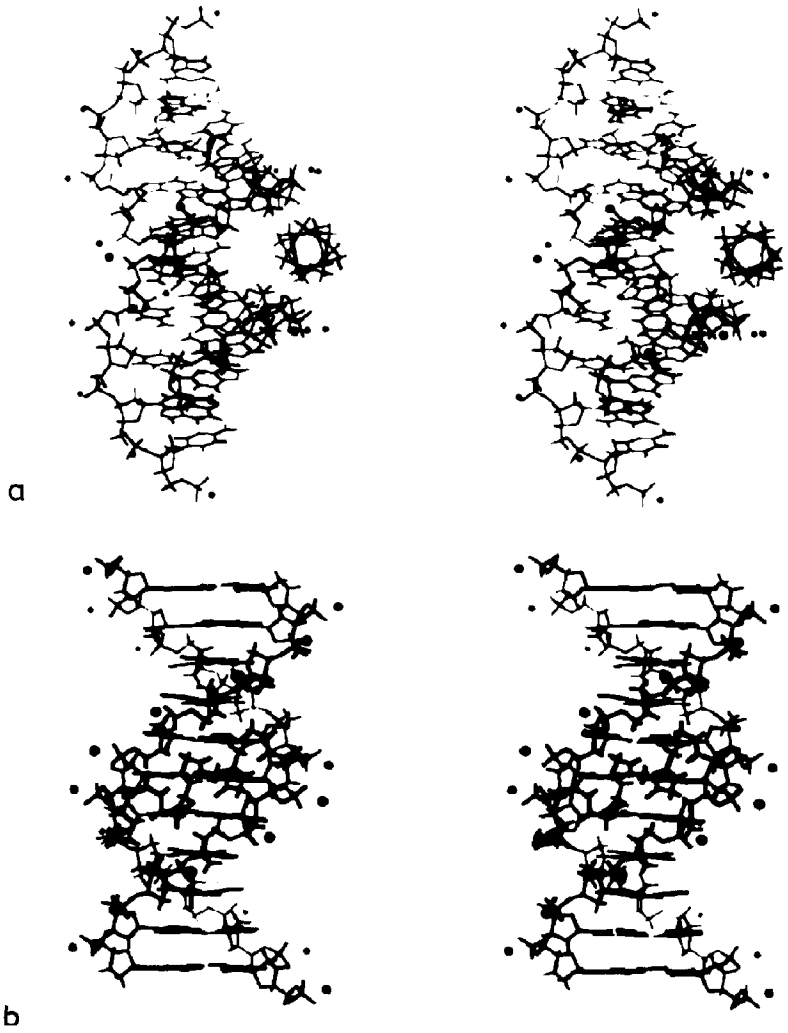

Fig. 7. Optimal complex of polyglycine in the minor groove of B-DNA (GC sequence).

the asparagine amino groups and the anionic oxygens of the phosphates, two belonging to each sugar-phosphate chain (the complex formed by polyasparagine with the AT base-pair sequence is shown in fig. 8).

The complexes, formed by polyaspartic acid, have the strongest complexation energy, due to an extremely strong electrostatic contribution. This interaction is in turn due to interactions between the charged aspartic acid anionic groups and Na^+.

It should be remarked that although minor groove complexes are unlikely to be involved directly in 'recognition' processes, they are nevertheless not unimportant energetically. While the major groove complexes are clearly favored for glycine, alanine and serine, the minor and major groove complexes of aspartic acid are of a similar stability and for asparagine, the minor groove complexes are clearly favored.

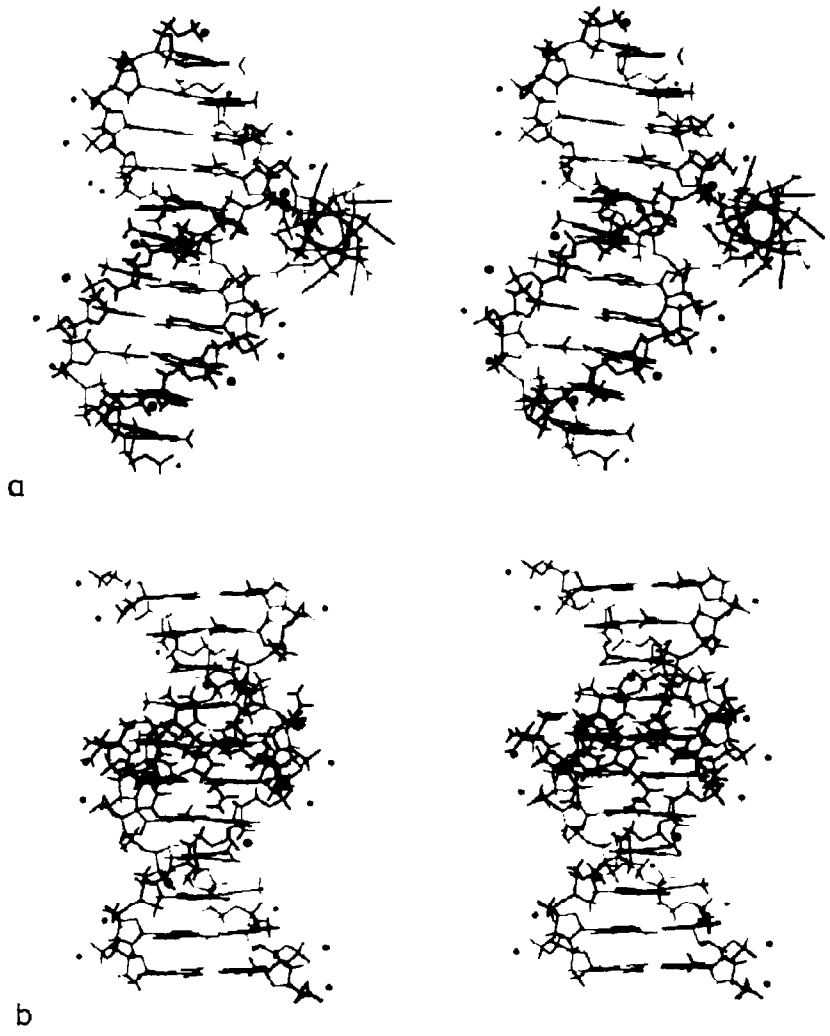

Fig. 8. Optimal complex of polyasparagine in the minor groove of B-DNA (AT sequence).

4. Conclusions

The results obtained in this study can be summarised in seven general remarks:

(1) With B-DNA, the major groove appears to be the only site for which sequence-specific interactions of regular α-helical polypeptides can occur.

(2) When no peptide hydrogen-bonding possibilities exist, the deeper GC major groove is preferred.

(3) If the peptide can act as a hydrogen-bond donor, strong 'structural' hydrogen bonds will be formed with the phosphate anionic oxygens of DNA. These hydrogen bonds can be more important energetically than the specific interactions with nucleic acid base atoms.

(4) The DNA screening cations are important.

They can provide a significant stabilization of complexes by charge-charge, or charge-dipole interactions, the latter even in the case of an α-helix with nonpolar side chains.

(5) The presence of thymine is an important factor in fixing the positioning of the peptide backbone through steric hindrance caused by its methyl group.

(6) The possibility of the formation of multidentate hydrogen bonds between polypeptide side chains and the nucleic acid bases does not appear to be a determining factor in the sequence-specific preference of α-helix binding.

(7) In the minor groove, strong interactions can exist whenever the peptide has hydrogen-bond donor possibilities enabling it to interact with phosphate anionic oxygens or can form charge-charge interactions with phosphate counterions. These complexes do not involve interaction with the bases, but they can equal or surpass the equivalent major groove complexes in binding energy.

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. They also wish to thank CIRCE (Orsay, France) for computational facilities.

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