The Detection of B-Form/A-Form Junction in a Deoxyribonucleotide Duplex

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ABSTRACT The transition of the 14-meric deoxyoligonucleotide duplex d-(ACCCCCTTTTTTTG)·d-(CAAAAAAAGGGGGT) from the B- to the A-conformation in water/trifluorethanol (TFE) solution was studied with the use of circular dichroism. An increase in the fraction of TFE induces a two-step B-A transition. In the first step, up to 73% TFE, the A-form is generated from the GC-rich part; in the second step, 73–82% TFE, the AT-rich part shifts to the A-form. By this we suggest the existence of a B/A junction near 73% TFE. Emergence of the B/A junction has been directly confirmed with the use of distamycin A and netropsin, ligands known to selectively bind to AT stretches of B-DNA. It can be shown that both ligands suppress formation of the A-form in the B-philic part. The free energy value for the B/A junction was estimated to be 2.1 kcal/mol, which agrees well with known data for polymeric DNAs. The obtained results may have biological relevance in connection with recently published x-ray data about the occurrence of the B/A junction in the complex of DNA with reverse transcriptase of HIV.

INTRODUCTION

Since the first x-ray studies with oriented DNA fibers it has been known that the double helix may adopt two different conformations: B-forms and A-forms. B-DNA is stable at high humidity, whereas A-DNA is stable at low humidity; in calf thymus DNA the transition occurs at approximately 82% relative humidity (Franklin and Gosling, 1953; Pohle et al., 1984).

It is now well established that

1) In addition to fibers, the B-A conformational transition in DNA can be effected in solution by an increase in the fraction of a nonelectrolyte miscible in water, like ethanol or trifluorethanol (Brahms and Mommaerts, 1964; Malenkov et al., 1975; Ivanov and Krylov, 1992).

2) The B-A transition proceeds within individual DNA molecules in a narrow interval of the changing conditions, i.e., it is an intramolecular cooperative transition (Ivanov et al., 1983).

3) The B-A transition depends on nucleotide sequence. The capability of a DNA site to shift to the A-form is controlled mainly by the relation between CC/GG and AA/TT steps (contacts). The CC/GG contact is called A-philic and requires low energy to acquire the A-form; the B-philic AA/TT contact requires high energy (Minchenkova et al., 1986; Becker and Wang, 1989). This last-mentioned property of the B-to-A transition has prompted us to study the B-A transition in a deoxyoligonucleotide duplex, one-half of which is built from A-philic contacts, whereas the other one consists of B-philic contacts.

The main purpose of the present study is to detect experimentally a stable (fixed) B/A junction and to estimate its free energy. This purpose is even more interesting because of the recently established fact (by x-ray analysis) that the B/A junction occurs in a DNA complex with HIV reverse transcriptase (Jacobo-Molina et al., 1993).

The data on the B/A junctions in the course of the B-A transition of free DNA in water/nonelectrolyte solutions can be found in numerous publications (Ivanov et al., 1974, 1985; Zavriev et al., 1978; Minchenkova and Zimmer, 1980; Krylov et al., 1989; Becker and Wang, 1989). For the atomic models of the B/A junction, cf. Selsing et al. (1979) and Zhurkin et al. (1988).

MATERIALS AND METHODS

Synthesis of oligonucleotides

Sample preparation

The following oligonucleotides have been used:
d-ACCCCCTTTTTTTG (1)
d-CAAAAAAAGGGGGT (2)

d-ACTACCCGAAATGA (3)
d-TGATGGGCTTTACT (4)

Formation of the two duplexes (1)·(2) and (3)·(4) was done by mixing equimolar amounts of (1) and (2) as well as of (3) and (4), respectively, heating to 90°C, and subsequent slow cooling.

The duplex d-ACCCCCTTTTTTTG·d-CAAAAAAAGGGGGT formed by (1) and (2) will be termed "the 14-mer duplex." For comparison, a second duplex d-ACTACCCGAAATGA·d-TGATGGGCTTTACT formed by (3) and (4) has been used. This second 14-mer duplex has the same number of AT and GC base pairs, but arranged in a more random sequence ("random" = 14-mer duplex).

The 14-mer duplexes were dissolved in deionized water. TFE was added stepwise accompanied by careful stirring until 82% (v/v) TFE was achieved. The final solutions contained 8.4×10^{-3} M DNA (in nucleotides), 2 mM NaCl, and 0.4 mM EDTA.

Concentrations of the ligands were determined from the molar extinction coefficients at 303 nm for distamycin A ($\epsilon = 31,500$) and at 296 nm for netropsin ($\epsilon = 23,133$ M^{-1} cm^{-1}), respectively (Zimmer and Wähnert, 1986). All UV absorption measurements were done on a Cary 1E spectrophotometer (Varian, Darmstadt, Germany) equipped with a thermostatted cell holder.

B-A transition curves

The A-to-B transition was obtained by the stepwise addition of water to the 82% TFE solution of the DNA samples and measuring the corresponding CD magnitudes at the selected wavelengths (see Figs. 3, 5, 6). The relative humidity (RH) values rather than TFE percentages were used in the B-A transition plots. Because we do not know the relation between TFE percentages and the relative humidity, we used the corresponding values of ethanol (Fig. 1; Ivanov and Krylov, 1992). We have shown recently that the TFE values may not differ significantly from those for ethanol.

Circular dichroism experiments

Circular dichroism (CD) spectra were recorded on a Jasco model 720 dichrograph using a quartz cell with 0.1-cm optical path length at 2°C; in particular, we checked that the 14 mers exist in duplex forms at this temperature, independently of the TFE content.

RESULTS AND DISCUSSION

CD spectra and the B-A transition curves

Drug-free system

The terms "A-DNA" and "B-DNA" will be used in the following by implying forms from the corresponding A- or B-families (Ivanov et al., 1979; Ivanov et al., 1983) rather than the specific conformations known from x-ray data.

In Fig. 2 are given the CD spectra for 14-mer in water/TFE solutions of different TFE content. The CD spectrum in 50% TFE (Fig. 2 A) is similar to that in water (shown by dots), which reflects the B-family form of the duplex. For the highest TFE content of 82%, the positive CD magnitude at 270 nm is almost threefold that of the B-form. At this high TFE content, the magnitude of the negative CD band at 210 nm is also enhanced (cf. Fig. 2, A and B). These features are typical for the A-family. Many proofs that DNA is in the A-form in solution with a high nonelectrolyte content have been published previously (Ivanov et al., 1974; Minchenkova and Zimmer, 1980; Ivanov et al., 1985; Krylov et al., 1989).

Let us consider in more detail the peculiarities of the CD spectra (Fig. 2) for the 14-mer duplex d-(ACCCCCTTT TTTTG)·d-(CAAAAAAAGGGGGT). One may see that a transition starts with the lowest TFE content of 50%. This is because the CD spectra at 50% and 58% scarcely differ, so that a plateau in this region is attained. We were not able to examine the whole interval from 0% to 50% TFE because of denaturation of the sample in low TFE content at the given low ionic strength. Although some drop in CD magnitude within the B-family does occur at increasing nonelectrolyte content (Ivanov et al., 1973), it has a gentle slope, unlike the B-A cooperative steep transition. Therefore it could affect the B-A transition curve only slightly. This suggestion is supported by the similarity of the CD spectra at 50% TFE and 0% TFE (Fig. 2 A), though to prevent denaturation of the 14-mer duplex at 0% TFE we had to increase ionic strength (i.e., it is not a perfect reference sample). As shown in Fig. 2 A (50–73% TFE), only the positive CD band at 270 nm changes its magnitude at this low TFE content, but the negative CD band at 246 nm remains unchanged. However, at high TFE content (74–82% TFE), both CD bands change their magnitude (Fig. 2 B). Therefore, we suggest that two B-A transitions are involved: the first one, up to 73% TFE, occurs in the GC-rich A-philic zone of the 14-mer, and the second one, proceeding in the interval 74–82% TFE, emerges in the AT-rich B-philic zone. This would imply the coexistence of A- and B-forms in
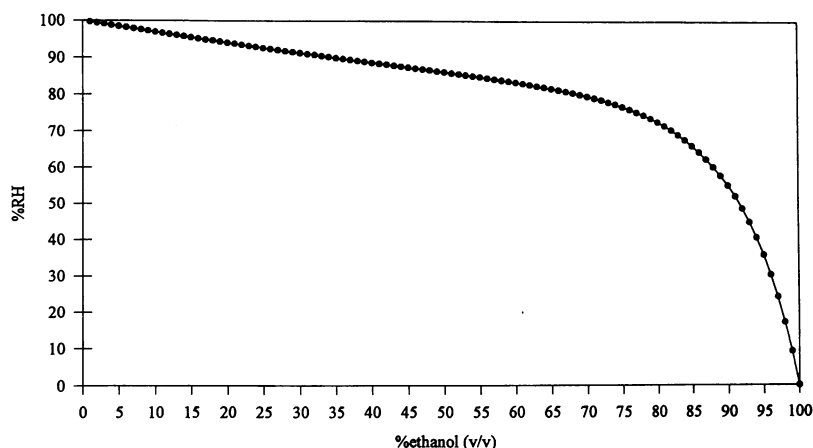

FIGURE 1   Relation between relative humidity (RH) and ethanol percentage of ethanol/water mixtures (v/v). Data from Ivanov and Krylov (1992).
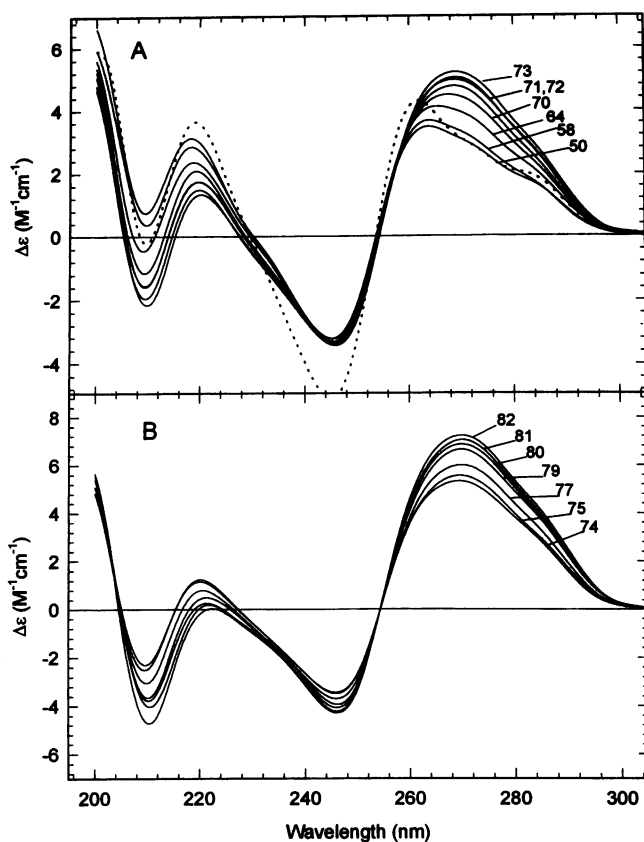
FIGURE 2   CD spectra of the 14-mer duplex, 0.84 mM in nucleotides, at 4°C in water-TFE solutions containing 2 mM NaCl and 0.4 mM EDTA. (A) TFE, 50–73% (v/v), 0% TFE with 100 mM NaCl (dotted line). (B) TFE, 74–82% (v/v). $\Delta\epsilon$ is given per mole of nucleotides.
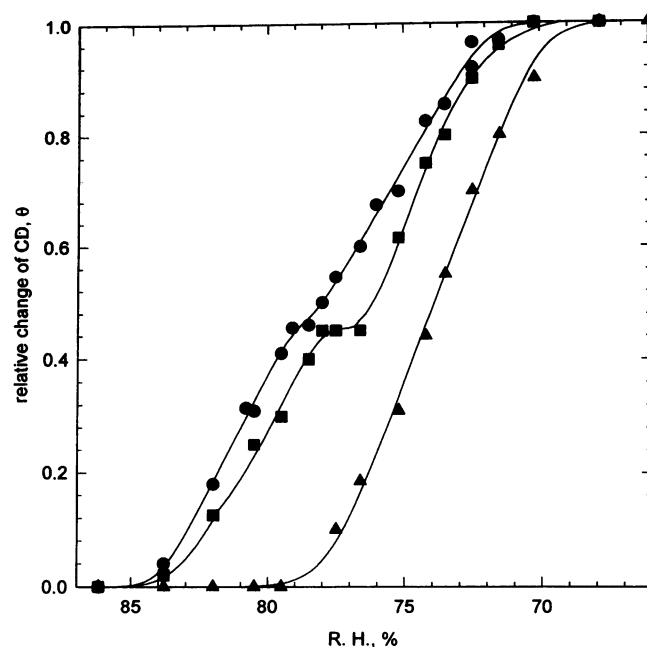

FIGURE 3   Curves of the B-to-A transitions of the 14-mer duplex, plotted from the data of Fig. 2, A and B, at the wavelengths 270 nm (●), 262 nm (■), and 246 nm (▲). The vertical axis is the relative change of the CD magnitude, Θ, at the indicated wavelengths. The horizontal axis is the relative humidity, RH, recalculated from TFE contents (see Materials and Methods).

the same duplex linked by a stable B/A junction at about 73% TFE. Fig. 3 provides support for this idea. Depending on the selected wavelength, both the position and the width of the transition profile vary dramatically (compare the profiles at 270 nm and 245 nm); a step (or at least an irregularity) is perceptible in the plot of CD amplitude changes at 262 nm. (In Figs. 3, 5, and 6, the relative humidity values, RH, are plotted as the horizontal axis rather than TFE percentage, as described in Materials and Methods.)

However, of even greater importance is the fact that the transition profiles observed at 270 and 262 nm are unusually broad in comparison with the profile of the "random" 14-mer duplex used as a control (Fig. 6, curve 4). As discussed further, the width of the transition profile of the reference "random" 14-mer duplex corresponds perfectly to that for a one-step transition. Hence the hypothesis on the two-step transition in the 14-mer duplex looks very probable. Therefore, we have performed experiments with minor-groove binding ligands to directly confirm the hypothesis. We want to emphasize that the B-A transition means the cooperative transition between a form of the B-family (i.e., having S-type sugar pucker) and a form of the A-family (having N-type sugar pucker) rather than the models constructed from x-ray analysis. In this respect the specific conformation of the dAdT tract belongs to the B-

family forms at high water activity. So we suppose that the observed dramatic increase in CD at 270 nm at low RH reflects the B-to-A transition of the B-philic AT moiety of the 14-mer duplex, no matter what kind of B-family form was present. The final decision can be made by NMR experiments, which are in progress.

Complex formation with minor-groove binding drugs

We studied the effect of selected drugs to prove the occurrence of two B-A transitions within the 14-mer, which are related to its A-philic and B-philic halves. The idea was to use minor-groove binding ligands that are known to bind specifically to a stretch of AT pairs of DNA in the B-form (Zimmer, 1975; Zimmer and Wähnert, 1986), and by that to stabilize this conformation against a shift to the A-form (Fritzsche et al., 1984; Fritzsche, 1994). In these systems one could expect that TFE would induce the B-A shift within the GC-rich A-philic half, whereas the AT-rich half, complexed with the ligand, is left in the B-form. Fig. 4 shows the CD spectra for a complex of the 14-mer with the minor-groove binding ligand distamycin A (Dst A) at different TFE content. It is seen that an increase in TFE percentage increases the CD signal at 270 nm and decreases the CD magnitudes at 240 nm and at 330 nm. The CD signal at 330 nm reflects an induced Cotton effect related to an absorption band of Dst A. Plotting the changes in the CD magnitude at 270 nm as a function of RH, a profile is
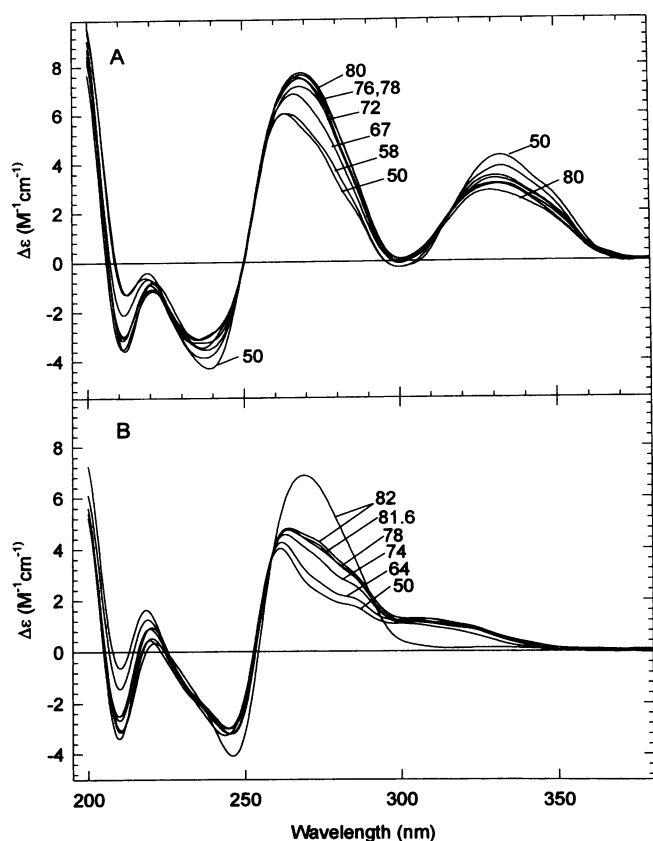
FIGURE 4   CD spectra of the 14-mer duplex in complexes with Dst A (*A*) and Nt (*B*) at different TFE contents. The ratios of the ligands to the 14-mer duplex were [Dst A]/[14-mer] = 8:1; [Nt]/[14-mer] = 2:1. The curves in *A* and *B* are labeled with the TFE content (v/v). The high-magnitude spectrum in *B* labeled 82% TFE is for a sample without Nt. All other conditions are as in Fig. 2.

FIGURE 5   The relative change of the CD magnitude at 270 nm, Θ, with the decrease in relative humidity, RH, of the free 14-mer duplex (*curve 1*, ▲), its Dst A complex (*curve 2*, ○), and its Nt complex (*curve 2*, ●). Curve 3 (■) is the normalized CD change of the free 14-mer duplex at 246 nm (Fig. 3). Note that curve 3 is close to the difference between curve 1 and curve 2. The CD values from Figs. 2 and 4 have been used.

obtained which, after normalization (Fig. 5, *curve 2, open circles*), nearly coincides with that obtained by subtraction of the low humidity transition at 245 nm from the total profile at 270 nm in the absence of Dst A (Fig. 5, *curve 3*). The attendant changes in the CD band at 240 nm and at 330 nm between 50% and 80% TFE (Fig. 4 *A*) can be explained by the uptake of an excess of free Dst A present in solution by the B-DNA, arising from a GC-rich zone. Dst A is known to form a weak complex with GC zones of B-DNA reflected in the CD spectra at these wavelengths (Luck et al., 1977; Zimmer et al., 1983; Feigon et al., 1984). It is worthwhile to note that we had to use a significant excess of Dst A over the 14-mer (Dst A/duplex = 8:1) because of a decrease in the Dst A binding constant to DNA in the presence of high TFE content. The observed change in the CD of the long-wavelength Dst A band at 330 nm implies that there may well be concomitant changes in CD of the short-wavelength bands of Dst A, overlapping with DNA bands. This does not allow us to consider with certainty curve 2 of Fig. 5 (*open circles*) as the B-to-A transition profile of the GC A-philic half in the 14-mer duplex. These complications forced us to carry out similar experiments
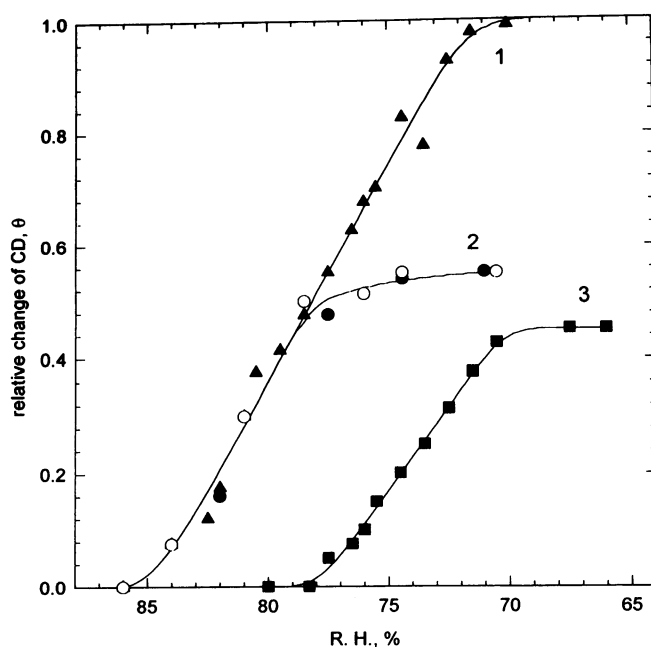
with another minor-groove binding ligand, netropsin (Nt), also specific to AT stretches in B-DNA. However, unlike Dst A with its single positive charge, Nt has two positive charges. Therefore, the binding of Nt to DNA in TFE solution is expected to be much stronger. Fig. 4 *B* supports this expectation. Even at a 1:1 ratio of Nt/14-mer, the CD magnitude of the band at 315 nm due to Nt is close to saturation. Therefore, we used a twofold excess of Nt only. In this case, in contrast to Dst A, no significant alterations of the CD magnitude were observed in the Nt–14-mer complex at 246 nm and 315 nm between 50% and 82% TFE; the only changes occur in the CD band near 260 nm (Fig. 4 *B*). One can see that the CD magnitude at 270 nm as a function of RH produces a profile that is coincident with that with Dst A (Fig. 5, *curve 2, filled circles*). This testifies a posteriori that the above-mentioned interference of the overlapping CD bands of Dst A and the 14-mer duplex, if it exists, should be small. Thus we can conclude that the 14-mer undergoes two successive B-A transitions when the RH decreases (or the TFE content increases). The first one, in the A-philic GC-rich half, takes place within the range from 86% to 78% RH. The second one, in the B-philic AT-rich region, occurs in the range from 78% to 68% RH. The transitions scarcely overlap, and near 78% RH (73% TFE) there must exist a stable B/A junction. In the presence of the ligands Dst A or Nt, the RH interval in which the B/A junction exists is much broader because of suppression of A-form emergence within the B-philic AT-rich zone. The interval is then expanded from 78% RH to a RH value

A   A/B

$F_S/2$
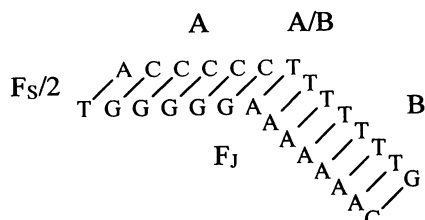
Scheme 1 $F_S/2$ and F_J are equivalent to $G°_S/2$ and $G°_J$, respectively, as given in the text.

defined by the solubility of the sample: not less than 66% RH (i.e., not more than 85% TFE).

Calculation of free energy for B/A junction

Scheme 1 illustrates the structural transformation of the 14-mer with the B/A junction, where the A-philic, GC-rich half is in the A-form but the AT-rich, B-philic half is in the B-form. Previously we have shown experimentally that the free energy difference of A- and B-forms, $G°_A - G°_B$, varies linearly with the relative humidity (Malenkov et al., 1975; Minchenkova et al., 1986). (Because of this fact, all of the transition curves in Figs. 3, 5, 6 are plotted as a function of RH.) The free energy change when going from 100% RH to the RH corresponding to the transition point for the A-philic zone, a_0, will be

$$G°_A - G°_B = n(100 - a_0)RT/Q. \quad (1)$$

Herein n is the quantity of base pairs in the A-form of the fragment of the 14-mer in a state with a stable B/A junction (Scheme 1). This scheme displays a state of the 14-mer duplex with its A-philic, GC-rich zone in the A-conformation, whereas the B-philic AT-rich zone conserves the B-conformation. Indicated are the A/B junction, the free energy of the junction, $G°_J$, and the free energy difference between the B- and A-conformations of the terminal base pair, $G°_S/2$. Thus we can assume $n = 7$ or very close to it; $a = 81\%$ RH is the B-A transition point of the first transition (Figs. 5, 6); R is the gas constant; T is the absolute temperature; Q is a coefficient characterizing the steepness of the free energy change with RH. The coefficient Q can be estimated from the width of the B-A transition, Δa, for a short duplex, "jumping" to the A-form according to the "all-or-none" principle; for the B-A transition this length is determined by the cooperativity length, which is on the order of 10 base pairs (Ivanov and Krylov, 1992). In such a case (Minchenkova et al., 1986),

$$n - 1 = 4Q/\Delta a. \quad (2)$$

According to the study by Minchenkova et al. (1986), $Q = 14.5\%$ RH. Substituting the required values into Eq. 1, we obtain $G°_A - G°_B = 5.0$ kcal/mol, under the assumption of $n = 7$ base pairs. On the other hand, $G°_A - G°_B$ can be calculated from the decimal code of steps (contacts) controlling the B-A transition (Ivanov and Minchenkova, 1995). In this study the values $G°_A - G°_B$ at 100% RH have
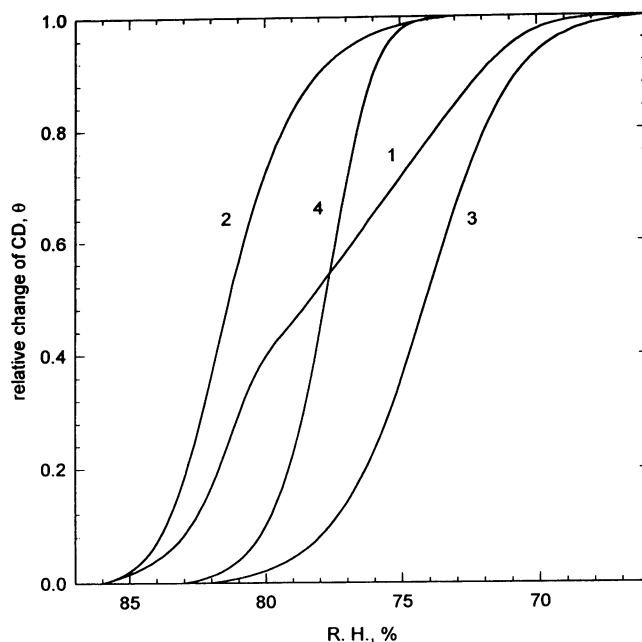
FIGURE 6 The normalized B-A transition profiles of the 14-mer duplex (curve 1) and its A-philic (curve 2) as revealed by relative CD changes at 270 nm, and B-philic (curve 3) moieties, at 245 nm. Curve 4 is the profile for the B-A transition of the "random" 14-mer duplex d-ACTACCCGA AATGA·d-TCATTTCGGGTAGT (which does not contain A-philic and B-philic halves), taken from the relative CD changes at 270 nm.

been reported for each of the 10 possible contacts. Considering the situation that an A/B junction exists at 73% TFE, we have only three of the 10 possible contacts in the segment that is in the A-form. In the 14-mer duplex only three of those are involved: CC/GG, AC/GT, and AG/CT (Scheme 1). Besides these parameters it is necessary to add the energy of the terminal base pair exposed to solvent, $G°_S/2$ (Minchenkova et al., 1986), and the energy of the B/A junction, $G°_J$. Thus, for the A-philic part of the 14-mer, we have

$$G°_A - G°_B = G°_{AC/GT} + 4G°_{CC/GG}$$
$$+ G°_{AG/CT} + G°_S/2 + G°_J. \quad (3)$$

According to our estimation (Ivanov and Minchenkova, 1995), the corresponding free energy values are as follows (kcal/mol): $G°_{AC/GT} = 0.13$; $G°_{CC/GG} = 0.19$; $G°_{AG/CT} = 0.33$; $G°_S/2 = 1.65$. One gets as a result $G°_J = 2.1$ kcal/mol. This value for the free energy of the B/A junction can be compared with those found earlier with DNA polymers: $G°_J = 1.8$ (Ivanov et al., 1974); 1.4 (Minchenkova and Zimmer, 1980); 1.5–1.8 (Ivanov et al., 1985); 1.4 (Minyat et al., 1978); 2.0 for poly(dA-dT) (Ivanov et al., 1985). Taking into account some uncertainty in the position of the B/A junction in the 14-mer, the agreement with published data is quite good. It follows from Eq. 2 that, if our 14-mer could transit into the A-form in accord with a "one-or-none" mechanism, its B-A transition width would be equal to 4.5% RH. (It is this value that is observed for the other 14-mer oligonucleotide duplex d-ACTACCCGAAATGA

·dTGATGGGCTTTACT used as a control (Fig. 6, *curve 4*). This duplex has the same quantity of AT and GC pairs as the 14-mer in this study. However, AT and GC pairs are here mixed more randomly). It is pertinent to compare the B/A junction energy value with those known for other cooperative transitions in DNA: B-Z and helix-coil. It appears that the B-to-A transition with its junction free energy of 1.5–2.0 kcal/mol is less cooperative than the B-to-Z transition, with a B/Z junction free energy of 3.5–4.0 kcal/mol (Sheardy et al., 1993), and the helix-coil transition, at 4.0–5.0 kcal/mol (Lazurkin et al., 1970). However, this comparison is not quite correct because of the difference in the conditions inducing these transitions.

A discussion of other studies attempting to characterize sequence-dependent energetics of the B-A transition (Hunter, 1993; Basham et al., 1995) will be given in a separate publication on a decimal code controlling the B-to-A transition of DNA in solution (V. I. Ivanov et al., manuscript in preparation).

CONCLUSIONS

In this study we have shown the occurrence of a stable B/A junction at a defined value of relative humidity in DNA at the joint between A-philic and B-philic nucleotide sequences. Such sequence anomalies are met in natural DNAs. The B/A junctions in these DNAs, which could have been stabilized by proteins, could be of biological importance. For example, opening of the double helix may be facilitated because of the rather high free energy of the B/A junction.

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