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Kinetics of the salt-induced B- to Z-DNA transition

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Abstract The salt-induced B- to Z-DNA conformational transition is a cooperative- and time-dependent process. From a modified form of the logistic equation which describes an equilibrium between two states we have deduced a kinetic function to quantify the degree of the B to Z transition of a synthetic (dG-dC) · (dG-dC) polynucleotide. This function was obtained by introduction of time as a variable in the logistic function so that the equilibrium constant, K, is replaced by a new constant K_s, characteristic of the type of salt used. This constant is defined as the salt concentration needed to reach the B-Z transition-midpoint in the time unit. The equation fits the data obtained by circular dichroism (CD) for changes in molecular ellipticity of poly(dG-m^{5}dC) · poly(dG-m^{5}dC) and poly(dG-dC) · poly(dG-dC) incubated with various concentrations of mono-, di-, and trivalent salts at a constant temperature. The derived expression may be a very useful tool for studying the kinetics of the B- to Z-DNA transition.

Key words Z-DNA · Kinetics · Circular dichroism · Salt-dependence

Introduction

It is now well established that DNA sequences that are in the Z conformation or that have the potential to adopt the Z-DNA form can be found in biological systems (Herbert and Rich 1996). Evidence for the existence of Z-DNA in vivo has been reported in recent years. Thus, it has been shown that B and Z forms coexist in equilibrium in plasmids in *Escherichia coli* (Zacharias et al. 1988) and they have been detected in metabolically-active mammalian cells (Wittig et al. 1991) and in polytene chromosomes from Drosophila (Nordheim et al. 1981). Moreover, sequences that may adopt the Z conformation are found between two transcriptional domains alternatively expressed during the development of *Drosophila hydei* (Jiménez-Ruiz et al. 1991) and in the enhancer regions of the SV 40 minichromosome (Casasnovas et al. 1989). A possible role for Z-DNA in gene regulation has been proposed, making the biology of Z-DNA a field of current research (Chaires and Sturtevant 1986).

By analysis of the properties of poly(dG-dC) · poly(dG-dC) in solution, Pohl and Jovin (1972) showed that at high salt concentration (2.50 M NaCl or 0.70 M $MgCl_2$) the polynucleotide undergoes, in a cooperative manner, a conformational transition from B-DNA to a new conformation. This alternative DNA form was termed Z-DNA, being a left handed double helix which exhibits a CD spectrum that is the inverse of that shown by the B form (Pohl and Jovin 1972; Wang et al. 1979). Behe and Felsenfeld (1981) observed that the methylated polymer, poly(dG-m^{5}dC) · poly(dG-m^{5}dC), undergoes a transition from the B to the Z form, but at a lower salt concentrations (0.70 M NaCl and 0.60 mM $MgCl_2$).

In spite of the considerable amount of data collected about the salt-induced B- to Z-DNA transition in polynucleotides, there is not, at present, any detailed study of the kinetics of the process. In the present paper, we define an equation which describes the kinetics of the salt-induced B-Z transition of synthetic methylated and non-methylated poly(dG-dC) · poly(dG-dC) at a constant temperature. This equation fits the experimental data we have obtained from CD measurements and may be useful to quantify the degree of Z-DNA formation. A methylated polynucleotide was chosen as a model system since the dinucleotide sequence m^{5}dC-dG appears frequently in eukaryotic DNA. In fact, it has been shown that the dinucleotide sequency may account for more than half of all "d(CpG)" sequences and that the degree of methylation of cytosine residues within a structural gene may be correlated with the tran-

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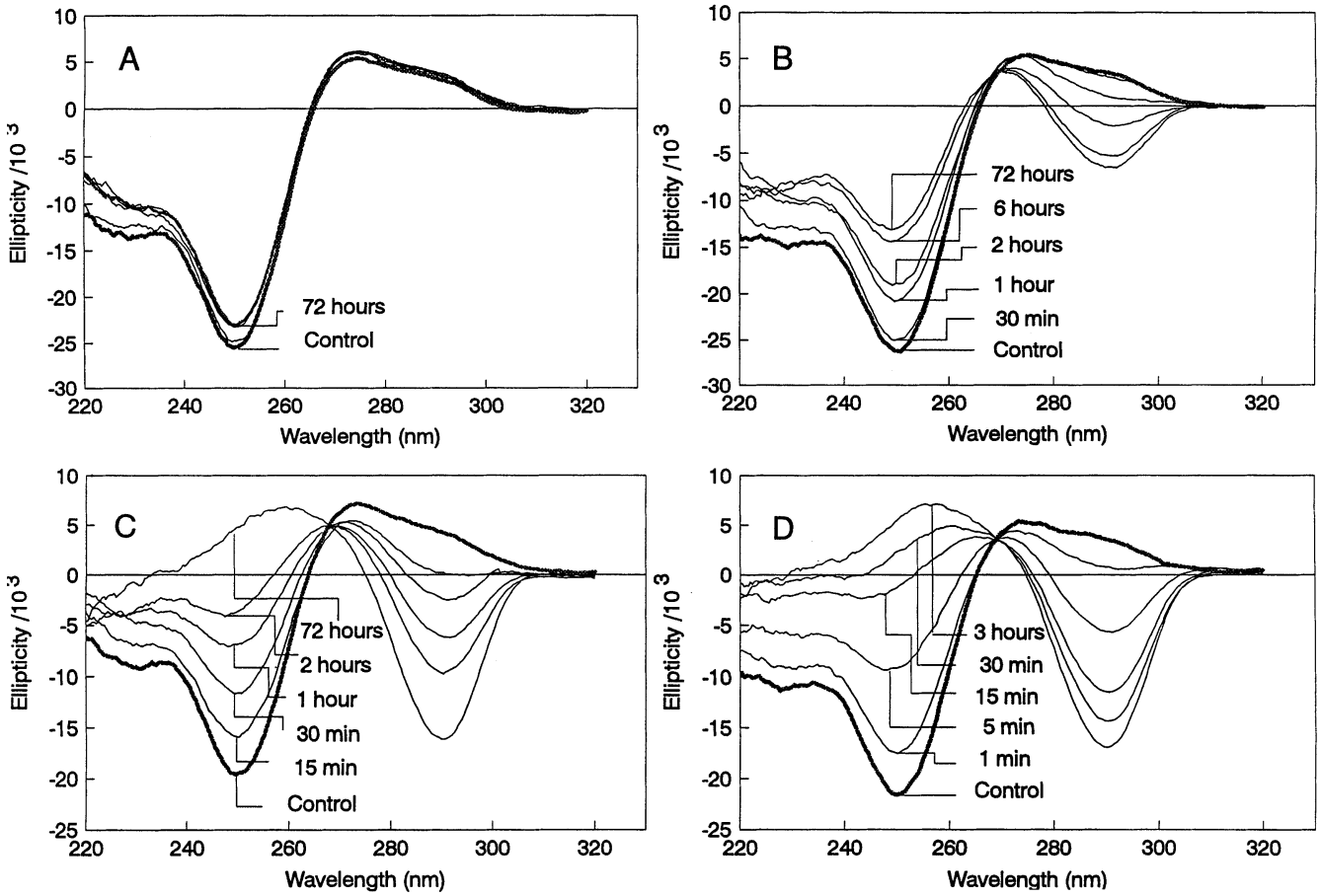

Fig. 1A–D Circular Dichroism spectra of poly(dG-m^{5}dC) · poly(dG-m^{5}dC) incubated with NaCl at (**A**) 0.50 M, (**B**) 0.65 M, (**C**) 0.75 M and (**D**) 0.95 M for different periods of time. Controls are indicated by (—). The CD spectra shown in the figure were averaged from three independent experiments

scriptional activity of the gene (Razin and Riggs 1980). To induce the B- to Z-DNA transition we have used mono-, di-, and trivalent salts. It is known that the concentration of $MgCl_2$ necessary to trigger the B-Z transition of poly(dG-m^{5}dC) · poly(dG-m^{5}dC) is about three orders of magnitude smaller than the concentration of NaCl required, and is close to that present inside the cell in metabolic conditions (Behe and Felsenfeld 1981).

Materials and methods

DNA solutions

Poly(dG-m^{5}dC) · poly(dG-m^{5}dC) and poly(dG-dC) · poly(dG-dC) were purchased from Pharmacia. A stock solution of polynucleotides of 0.7 mg/ml was prepared in TE buffer (Tris-HCl pH 8.0, 0.1 mM EDTA) containing 50 mM NaCl. The densitometric analysis of both polymers after agarose gel electrophoresis revealed that 95% of the polynucleotide molecules migrated at a DNA band with an average length of 2,900 and 1,800 base pairs, respectively. The stock solutions of the polynucleotides were kept at –20 °C until use.

CD spectroscopy. CD spectra were recorded on a JASCO J-600 spectropolarimeter interfaced to an Armstrad 386 computer. The measurements were performed at 37 °C using 1-cm path length cells. Each spectrum represents the mean of three scans. Aliquots containing 20 µg/ml of poly(dG-m^{5}dC) · poly(dG-m^{5}dC) or poly(dG-dC) · poly(dG-dC) were prepared from the stock solution. CD spectra were run from 220 to 320 nm at a speed of 50 nm/min. Scans were recorded at 0.4 nm intervals. Evaporation was minimized by covering the sample with a plastic cover.

Kinetic studies. The measurements of the B-Z transition were carried out after addition to the polynucleotide solution of the amount of a concentrated salt (5 M NaCl, 3.5 M $MgCl_2$, 10 M $NaClO_4$ and 0.1 mM $Co(NH_3)_6Cl_3$ needed to reach the desired concentration. After mixing by shaking, the CD spectra of the polynucleotide was determined at several time intervals. The time dependent change of the CD was recorded at 250 nm and 290 nm.

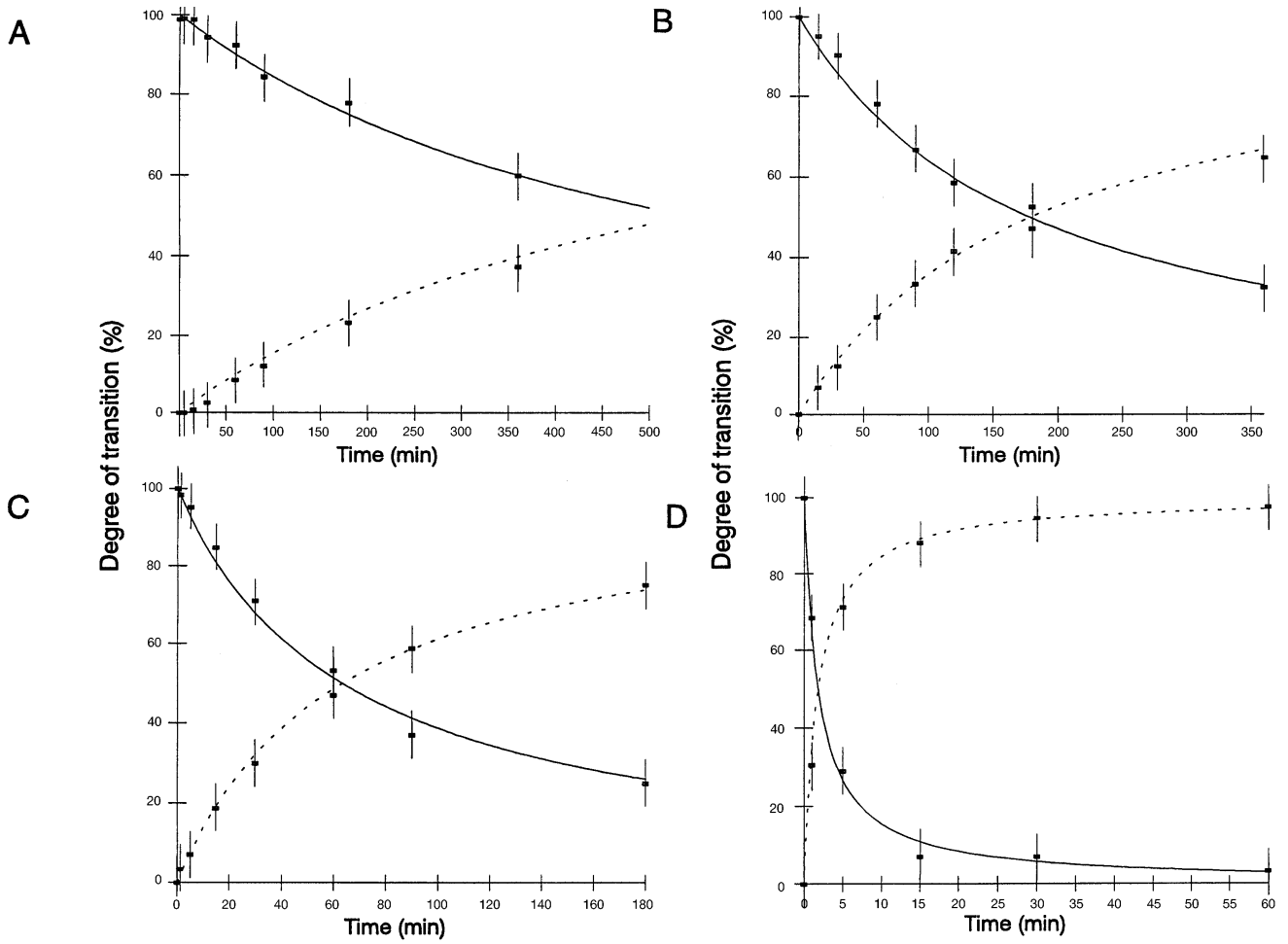

Fig. 2 A–D Degree of B-Z transition obtained for poly(dG-m^{5}dC) · poly(dG-m^{5}dC) for different periods of incubation and NaCl concentrations. (**A**) 0.65 M, (**B**) 0.70 M, (**C**) 0.75 M and (**D**) 0.95 M. *Points* represent the experimental values extracted from CD spectra at 250 and 290 nm. The *continuous* (—) and *dashed* (- - -) *lines* show the data at 290 and 250 nm. Obtained from Eq. (3)

Results

Since it is known that the midpoint of the B-DNA to Z-DNA transition is obtained when the ellipticities at 250 and 290 nm reach the same value (Chen et al. 1983), we have analyzed the influence of the incubation time on the B-Z transition process induced in synthetic methylated and non-methylated polynucleotides at several salt concentrations by the determination of the change in molecular ellipticity. Figure 1 (A–D) shows the incubation time dependent changes detected in the CD spectrum of poly(dG-m^{5}dC) · poly(dG-m^{5}dC) after incubation with different NaCl concentrations. After 72 hours of incubation in the presence of 0.50 M NaCl (Fig. 1 A) the CD spectrum of the polynucleotide remains unchanged relative to that of the canonical B-form of control DNA.

However, as monitored by CD the poly(dG-m^{5}dC) · poly(dG-m^{5}dC) incubated with 0.65 M NaCl undergoes the B-Z transition with time (Fig. 1 B) although at this salt concentration the midpoint of the B-Z transition is not reached even after 72 hours of incubation. We observed that at concentrations of NaCl above 0.65 M the CD spectrum of the polynucleotide changes gradually from the B-form towards the Z-form until all the DNA adopts the Z-DNA conformation. Thus, Fig. 1 (C and D) reveals that the poly(dG-m^{5}dC) · poly(dG-m^{5}dC) takes the Z form at NaCl concentrations higher than 0.65 M and that the time needed to have all the polynucleotide in the Z form varies with the NaCl concentration. The existence of an isoelliptic point in the CD spectra suggests that a two-state transition model is an appropriate description of the conformational change that occur in the poly(dG-m^{5}dC) · poly(dG-m^{5}dC).

Figure 2 (points) represents the changes in ellipticity at 250 and 290 nm of the CD spectrum of the poly(dG-m^{5}dC) · poly(dG-m^{5}dC) as a function of the incubation time at several NaCl concentrations. As indicated above we observe that the midpoint of the B-Z transition is not reached even after 72 hours of incubation at 0.65 M NaCl (Fig. 2 A) but that at NaCl concentrations above 0.65 M, the poly(dG-m^{5}dC) · poly(dG-m^{5}dC) does reach the midpoint of the B to Z transition. In fact, the ellipticities at 250 and 290 nm have the same value after a period of time which varies with the salt concentration (Fig. 2, B–D).

Because it is known that the B to Z transition of a polynucleotide is an equilibrium between two species (Pohl and

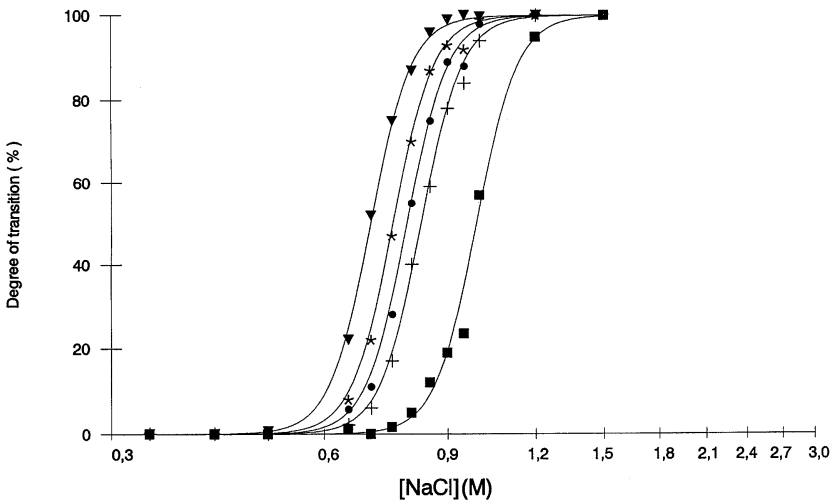

Fig. 3 Variation of K for the B-Z transition of poly (dG-m^{5}dC) · poly(dG-m^{5}dC) incubated with different NaCl concentrations at several incubation times. *Points* show experimental data obtained from CD spectra at salt concentrations of 0.30, 0.40, 0.50, 0.65, 0.70, 0.75, 0.80, 0.95, 1.00, 1.20 and 1.50 M NaCl. The *lines* are the result of fitting CD data to Eq. (1). The incubation times were 1 min (■), 15 min (+), 30 min (●), 60 min (∗) and 180 min (▼). The standard error of the estimate was <120 s for NaCl

Jovin 1972), we have adjusted the CD data to a logistic function previously used by Chen et al. (1983) to quantify the degree of cooperativity of the B-Z process of poly(dG-m^{5}dC) · poly(dG-m^{5}dC):

$$\theta = \theta_\infty + \frac{\theta_0 - \theta_\infty}{1 + \left(\frac{x}{K}\right)^n} \quad (1)$$

where θ is the spectroscopic response, x is the concentration of added salt, θ_0 is the response when $x = 0$, θ_∞ is the response when $x = \infty$, K is the concentration of x at the midpoint of the transition and n is the degree of cooperativity of the B-Z transition process which determines the slope of the curve. For this purpose, the CD data at 250 and 290 nm of Fig. 2 were expressed as percentage of the change of ellipticity after they were averaged.

Figure 3 (points) shows the degree of the B-Z transition reached at various NaCl concentrations after several incubation times. The lines represent the best fit of the experimental data to Eq. (1) for different K values. It can be observed that the K values vary with the incubation time. Thus, in order to fit the CD data to Eq. (1) the equilibrium equation has to be transformed into a kinetic equation by substitution of the equilibrium constant K by a time-dependent function.

Modification of the logistic function. Introducing the incubation time as a variable. Statistical analysis of the bivariate population (t_m, K)

From previous data it is, thus, reasonable to assume that $K = f(t, n)$. In that context we may write the following expression:

$$K^n = \frac{K_s^n}{t} \quad (2)$$

Where K_s is a constant characteristic of the salt used and is defined as the salt concentration needed to reach the B-Z transition-midpoint in the time unit. Substituting Eq. (2) in Eq. (1), the following expression is obtained that expresses the variation of the spectroscopic response θ versus the salt concentration x at any incubation time t:

$$\theta = \theta_\infty + \frac{\theta_0 - \theta_\infty}{1 + t\left(\frac{x}{K_s}\right)^n} \quad (3)$$

This allows the derivation of the following equation:

$$t = \left(\frac{K_s}{x}\right)^n \quad (4)$$

and then:

$$\text{Log}\,(t) = n \cdot \text{Log}\,(K_s) - n \cdot \text{Log}\,(x) \quad (5)$$

It is clear from Eq. (5) that for the process under study a plot of Log (t) against Log (x) will be linear with slope, n, and intercept (at Log (t) = 0) equal to K_s. This allows one to calculate the K_s value. Such an equation fits adequately (lines) with the experimental data (points) observed for the variation of the ellipticity values shown in Figs. 2 and 4 (see inserts). It is clear from Eq. (3) that when the incubation time is equal to the B-Z midpoint transition time ($t = t_m$) then the change in ellipticity is 50%. Thus, the linearity of the plots in Fig. 4 (inserts) and the fits to the data of Fig. 2 may be taken to validate the assumptions in the derivation. We calculated the line of regression of t_m on K for NaCl in order to verify the validity of Eq. (2). The study reveals that the best fit of the function is a potential one (see Eq. (2)) which allows us to obtain the averaged parameters of the curve for the salt. Thus, for NaCl the cooperativity index is $n \approx 14.86 \pm 0.22$ for $K_s \approx 1.30 \pm 0.14$ M · s$^{1/n}$, the salt concentration needed to reach the B-Z transition midpoint per time unit. The coefficient of determination has a value of $r^2 \approx 0.998$. The standard error of the estimate for the B-Z transition-midpoint at the salt concentrations studied was <120 s for NaCl.

To validate the kinetic equation and extend it to other salt conditions we further examined the effects of other monovalent ($NaClO_4$), divalent ($MgCl_2$) and trivalent salts ($Co(NH_3)_6Cl_3$) on the B- to Z-DNA transition of methylated and non-methylated polynucleotides. The data from

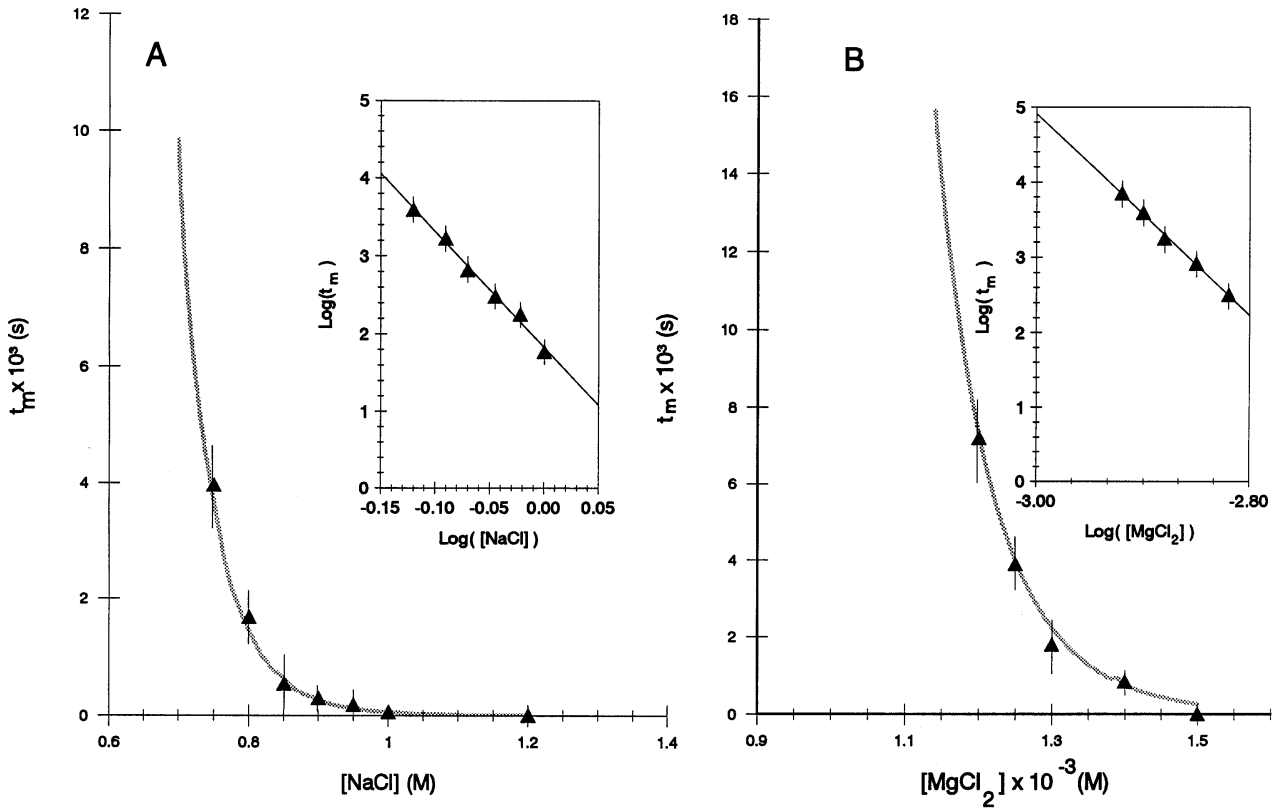

Fig. 4A, B Plots of the B-Z transition midpoint (t_m) versus NaCl (**A**) and $MgCl_2$ (**B**) concentrations. Experimental data are represented by (▲). The *lines* represent t_m data obtained from Eq. (2). The *upper-right frames* show a logarithmic plot of t_m versus NaCl and $MgCl_2$ concentrations, respectively

Table 1 K_s values for different salts given as concentration of cation needed to reach the midpoint of the B-Z transition in the time unit

	Poly(dG-dC) · poly(dG-dC)	Poly(dG-m^{5}dC) · poly(dG-m^{5}dC)
NaCl	3.51±0.35	1.30±0.14
$NaClO_4$	2.71±0.24	1.28±0.15
$MgCl_2$	1.43±0.124.40	$2.17\times10^{-3}\pm0.16\times10^{-3}$
$Co(NH_3)_6Cl_3$	$4.40\times10^{-5}\pm0.43\times10^{-5}$	$8.80\times10^{-6}\pm0.64\times10^{-6}$

K_s values are given as M · $s^{1/n}$

CD show that the alternating polymer poly(dG-m^{5}dC) · poly(dG-m^{5}dC) undergoes the transition from the B to the Z form at salt concentrations much lower than those required to induce the transition in poly(dG-dC) · poly(dG-dC), as described by Behe and Felsenfeld (1981). The kinetics of the B-Z DNA transition for both polymers as detected in the CD spectra after incubation with $MgCl_2$ and $Co(NH_3)_6Cl_3$ are similar to those observed after incubation with NaCl but at salt concentrations three-, and six order of magnitude lower, respectively. In the case of the monovalent salt, $NaClO_4$, the concentration was similar to that used for NaCl. The K_s values for NaCl, $NaClO_4$, $MgCl_2$ and $Co(NH_3)_6Cl_3$ with poly(dG-m^{5}dC) · poly(dG-m^{5}dC) and poly(dG-dC) · poly(dG-dC) are given in Table 1. Thus, we believe, that the kinetic expression (Eq. (3)) may be useful to quantify the amount of Z-DNA induced at any given time under various salt conditions at a constant temperature.

Relationship between the B to Z transition kinetics induced by two different salts

The results shown in Figs. 1–4 indicate that at a given concentration of NaCl above the threshold, x_1, the midpoint of the transition in the polynucleotide will be reached at an incubation time t_{m1}. Likewise, the B-Z transition midpoint of the polynucleotide after incubation with a different concentration of $MgCl_2$, x_2, will be reached at an incubation time, t_{m2}. Substituting x_1 and t_{m1} in Eq. (4) we obtain a kinetic expression for the B-Z transition induced by NaCl. A similar expression for the $MgCl_2$-induced B-Z transition can be obtained by substitution of x_2 and t_{m2}. Equating these expressions for the same value of ellipticity and when the rest of the parameters are known gives the following relationship:

$$\frac{x_2}{x_1} = \frac{K_{s2}}{K_{s1}} \left(\frac{t_{m1}}{t_{m2}} \right)^{\frac{1}{n}} \tag{6}$$

we note that we have considered the same cooperativity index for the B-Z transition of both salts (NaCl or $MgCl_2$) as has been previously reported by Pohl and Jovin (1972) and Kagawa et al. (1993). Thus, once the kinetics of the

B-Z DNA transition induced by a given salt are known it would be possible to determine the kinetics of the B-Z DNA transition induced by another salt when K_{s_2} is known.

Discussion

Although the salt-induced B- to Z-DNA transition process in polynucleotides has been studied by several authors their contributions to the kinetic aspects of the B-Z transition process have been qualitative rather than quantitative (Chaires 1983; Feuerstein et al. 1985; Jiménez-García and Portugal 1992; Takeuchi et al. 1994). In order to obtain a more detailed picture of the kinetics of the salt-induced B- to Z-transition of polynucleotides with potential to form Z-DNA we report in the present paper a kinetics function (Eq. (3)) which describes that process. This kinetic function was obtained by introducing time in the equilibrium logistic function and, consequently, substituting the equilibrium constant, K, by another constant, K_s, characteristic of the salt used. Thus, the constant K_s was defined as the amount of salt needed to reach the B-Z transition midpoint in the time unit. Most likely, covalent modifications of the polymer (Moller et al. 1981, 1984; Uesugi et al. 1982; Sage and Leng 1981; Santella and Grunberger 1983; Malfoy et al. 1981; Ushay et al. 1982), ionic changes in solution (Behe and Felsenfeld 1981, Pohl 1983; van de Sande and Jovin 1982), solvent modifications by alcohols and small molecule effectors (Watson and Crick 1953; Pohl 1976; Zacharias et al. 1983; Feigon et al. 1983; Zimmer et al. 1982) must also affect K_s in the kinetic function since they are known to affect K in the two-state equilibrium logistic function.

It is interesting to point out that the sigmoid shape for the curves obtained by substituting the CD data in Eq. (3) (see Fig. 3, lines) is indicative of a strong cooperative process for the B- to Z-DNA transition of the (dG-dC) · (dG-dC) polynucleotides in agreement with the cooperativity index that we have calculated from Eq. (3) for all the salts tested. Moreover, we have also found good fits when testing Eq. (3) with the values obtained from the data reported by other authors using (dG-dC) · (dG-dC) polynucleotides, under different experimental conditions (Pohl and Jovin 1972; Behe and Felsenfeld 1981; McIntosh et al. 1983). Thus, Eq. (3) may be a valid tool for quantifying the kinetics of the B to Z transition in polynucleotides.

It has been reported that at a constant temperature the B to Z transition of a (dG-dC) · (dG-dC) polynucleotide of a given chain length is affected by Na^+ and Mg^{2+} cations and that the cooperativity index, n, is a parameter independent of the type and valency of the salt (Pohl and Jovin 1972; Kagawa et al. 1993). We believe that the kinetic equation reported in this paper gives a clear account of the results shown by these authors since when the incubation time with the salt is kept constant, the slope of the curves obtained by plotting the salt concentration versus the percentage of relative ellipticity does not change with the type of salt used for both polynucleotides. In other words, the cooperativity index, n, is a parameter independent of the type of salt used. Another fundamental outcome of the kinetic equation is that it allows one to analyze the cooperativity of the process for different periods of incubation with the salt. As noted, the slopes of the curves and, thus, the cooperativity index of the B-Z transition do not vary with the incubation time.

It was interesting to observe in Fig. 1 that, at a constant temperature, there is a threshold concentration of salt at which the B-Z transition of the polynucleotide is induced with time. In fact, for example, 37 °C and salt concentrations ≤0.5 M NaCl or ≤0.9 mM $MgCl_2$ are not enough to induce the transition of the methylated polynucleotide. In contrast, when the salt concentration is ≥0.65 M NaCl (≥1.1 mM $MgCl_2$) the B-Z transition of the polynucleotide was triggered in a time dependent manner. In view of this fact, we think that it is crucial to take into account the effect of the salt present in the buffer solution when designing experiments directed to study the influence of chemical and physical factors in the B- to Z-DNA transition (i.e., drugs, proteins, supercoiling, etc.). We think that Eq. (3) acquires additional relevance because it allows one to quantify the effect of the salt present in the buffer solution at a given time.

In summary, from a two-state equilibrium function and by introducing time as a variable we have obtained a new kinetic function (Eq. (3)) which allows one (i) to quantify the effect of different salts on the B-Z transition of synthetic polynucleotides, and (ii) to calculate the threshold salt concentration able to induce the B-Z transition at a given incubation time. We think that this new kinetic function may be a very useful tool for quantifying Z-DNA formation at different times of incubation with salts.

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