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Polyelectrolyte effects in G-quadruplexes

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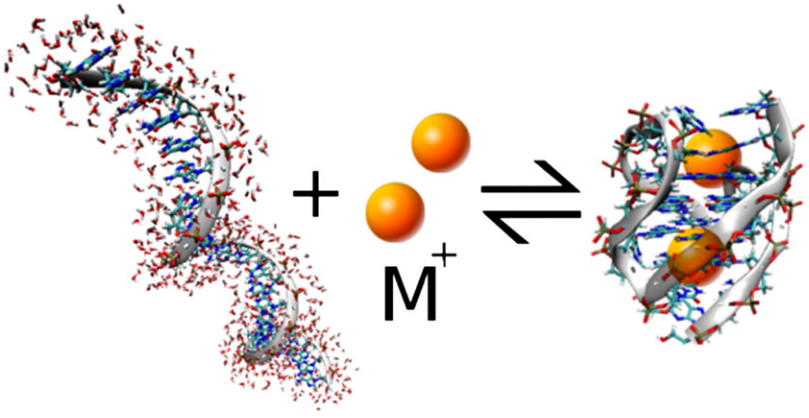
HIGHLIGHTS

- We studied the counterion condensation effect on the stability of two G-quadruplexes.
- The stabilities were measured in the presence of stabilizing and nonstabilizing ions.
- Counterion condensation plays a minor role in G-quadruplex stability.
- The main contribution to stability comes from the binding of ions in central cavity.

GRAPHICAL ABSTRACT



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ABSTRACT

The role of counterion condensation as a dominant force governing the stability of DNA duplexes and triplexes is well established. In contrast, the effect of counterion condensation on the stability of G-quadrupex conformations is poorly understood. Unlike other ordered nucleic acid structures, G-quadruplexes exhibit a specific binding of counterions (typically, Na^+ or K^+) which are buried inside the central cavity and coordinated to the O6 carbonyls of the guanines forming the G-quartets. While it has been known that the G-quadruplex-to-coil transition temperature, T_M, increases with an increase in the concentration of the stabilizing ion, the contributions of the specific (coordination in the central cavity) and nonspecific (condensation) ion binding have not been resolved. In this work, we separate the two contributions by studying the change in T_M of preformed G-quadruplexes following the addition of nonstabilizing ions Li^+, Cs^+, and TMA^+ (tetramethylammonium). In our studies, we used two G-quadruplexes formed by the human telomeric sequences which are distinct with respect to the folding topology and the identity and the number of sequestered stabilizing ions. Our data suggest that the predominant ionic contribution to G-quadruplex stability comes from the specifically bound Na^+ or K^+ ions and not from counterion condensation. We offer molecular rationalizations to the observed insensitivity of G-quadruplex stability to counterion condensation and emphasize the need to expand such studies to assess the generality of our findings.

1. Introduction

Although the genomic DNA overwhelmingly exists in the B-double helical conformation, many genomic sequences may give rise to stable non-B-DNA conformations. For example, guanine-rich single-stranded

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stretches are susceptible to spontaneous dissociation from their complementary strands and folding into various G-quadruplex structures in which guanine bases associate with each other in G-quartets, stable hydrogen-bonded arrangements [1–3]. The biomedical relevance of G-quadruplexes stems from the fact that the consensus G-quadruplex sequence motifs are found in critical loci of the genome, including telomeres, centromeres, immunoglobulin switch regions, mutation-prone hot spots, and promoter regions of many oncogenes [2,4–8]. Telomeric sequences have become an important target for anti-cancer drug development, since drug-induced G-quadruplex structures are incompatible with telomerase function and induce rapid senescence in cancer cells [9]. Search for G-quadruplex-stabilizing molecules has quickly emerged as part of novel anti-cancer strategies [6,8]. The ultimate success of such strategies depends, in part, on our ability to understand thermodynamic forces stabilizing G-quadruplex conformations relative to their respective double- and single-stranded conformations and modulation of these forces by environmental conditions and the presence of G-quadruplex-stabilizing agents (drugs).

Owing to their polyelectrolyte nature, DNA and RNA are surrounded by a cloud of mobile counterions which exert a powerful influence on the stability of nucleic acid structures [10–15]. Counterion condensation in the vicinity of DNA and the concomitant entropic penalty introduces a thermodynamic leverage that can produce shift in an equilibrium of virtually any helix-to-coil and ligand binding reaction simply by a change in salt [15]. Helical forms of DNA, due to their higher axial charge density, $\xi = e^2/(\varepsilon k_B Tb)$ (where e is the electron charge, ε is the dielectric constant of the solvent, k_B is the Boltzmann constant, T is the thermodynamic temperature, and b is the average axial distance between the polyelectrolyte charges), condense more counterions per phosphate relative to the single-stranded conformation [10,14–17]. Consequently, helix-to-coil transitions of nucleic acids are accompanied by a release of counterions to the bulk, while an increase in salt results in an increase in the thermal and thermodynamic stability of the helical forms due to a diminution of the mixing entropy penalty [10,13–16]. At low ionic strength, the number of associated counterions per phosphate is given by $\theta = 1 - \xi^{-1}$. For example, the values of θ for a double-stranded B-DNA and a single-stranded DNA are 0.76 and 0.44, respectively [10]. Thus, the helix-to-coil transition of a B-DNA is accompanied by a release of 0.32 monovalent cations to the bulk.

The conventional way of experimental determination of the number of cations, $\Delta n = \theta_h - \theta_c$, released to the bulk upon a helix-to-coil transition of a DNA relies on measuring the salt dependence of the transition temperature, T_M:

$$\Delta n_{M+} = \left(\Delta H_M / RT_M^{\,2}\right)\left(\partial T_M / \partial \ln\left[M^+\right]\right) \quad (1)$$

where $[M^+]$ is the molar concentration of the counterion [11,16,18,19].

In contrast to all other ordered nucleic acid structures, G-quadruplexes, in addition to non-specific binding (condensation), exhibit a specific binding of counterions (typically, Na^+ or K^+) which are buried inside the central cavity and coordinated to the O6 carbonyls of the guanines forming the G-quartets [3,5,6]. Hence, application of Eq. (1) to G-quadruplex melting transitions, yields the number of cations released to the bulk from both the central cavity (bound specifically) and the cloud of counterions (bound nonspecifically). The problem of discrimination between the two cation populations remains unsolved which prevents one from elucidating the role of the polyelectrolyte effect in stabilization of G-quadruplex structures [3]. In one study, it has been concluded that the specific cation binding plays a more prominent role in stabilizing a G-quadruplex than counterion condensation [20]. This conclusion is in agreement with our results presented below. However, it has been reached based on comparative G-quadruplex stability studies in binary solvents containing water and a variety of cosolvents. In particular, it has been assumed that the influence of a particular cosolvent on G-quadruplex stability is predominantly determined by the dielectric constant of the medium. However, such an oversimplification may not be warranted given the complexity of the effect of cosolvents on the stability of biopolymers [21–23].

In this work, we evaluate the influence of the polyelectrolyte effect on G-quadruplex stability by separating the effect of the stabilizing cations in the central cavity from the effect of the cations condensed in the vicinity of the DNA. More specifically, after saturating a G-quadruplex by the stabilizing cation (Na^+ or K^+), a further increase in the solution ionic strength is accomplished by the addition of either the stabilizing or a non-stabilizing cation [Li^+, Cs^+, TMA^+ (tetramethylammonium)]. The latter cannot penetrate the central cavity being either too large or too small and, therefore, influence the G-quadruplex stability only via the effect of counterion condensation. We study the differential effect of salt on the G-quadruplex-to-single strand transition temperature, T_M, when the ionic strength is modulated by the stabilizing or non-stabilizing cations. To increase the generality of our work and the ensuing conclusions, we have chosen two G-quadruplexes varying in topology and the identity and number of the sequestered stabilizing cation (Na^+ and K^+). Our results suggest that, in contrast to the duplex and T-rich triplex conformations, the polyelectrolyte effect plays a small to negligible role in maintaining G-quadruplex stability. The observed salt-dependent increase in G-quadruplex stability predominantly reflects the specific binding of the Na^+ or K^+ cations.

2. Materials and methods

2.1. Materials

The oligodeoxyribonucleotides, $d[A(G_3T_2A)_3G_3]$ (Tel22) and $d[A_3(G_3T_2A)_3G_3A_2]$ (Tel26), containing four repeats of the human telomeric DNA sequence were synthesized and cartridge purified by ACGT, Inc. (Toronto, ON, Canada). Potassium chloride, sodium chloride, cesium chloride, lithium chloride, tetramethylammonium chloride, and phosphoric acid were purchased from Sigma-Aldrich Canada (Oakville, ON, Canada). EDTA (free acid) was purchased from Fisher Biotech (Fair Lawn, NJ, USA). These reagents were of the highest grade commercially available and used without further purification. All solutions were prepared using doubly distilled water.

Prior to all experiments, the Tel22 oligonucleotide was dissolved in and exhaustively dialyzed against a pH 7.0 buffer consisting of 10 mM sodium phosphate, 0.1 mM EDTA, and 20 mM NaCl. The Tel26 oligonucleotide was dissolved in and dialyzed against a pH 7.0 buffer consisting of 10 mM potassium phosphate, 0.1 mM EDTA, and 20 mM KCl. In these conditions, both Tel22 and Tel26 are fully folded in their respective G-quadruplex conformations [24,25]. Dialysis was carried out in 1000 Da molecular weight cut-off Tube-O-Dialyzers from G Biosciences (St. Louis, MO, USA). For UV melting and CD experiments, the ionic strengths of the DNA solutions were adjusted to the desired level by addition of aliquots of NaCl, KCl, LiCl, CsCl, or TMACl on top of the existing 20 mM of NaCl (Tel22) or KCl (Tel26).

The CD and UV melting experiments were performed at the following ionic conditions. For the experiments involving Tel22, the ionic conditions were 20, 50, 100, 200, 400, and 800 mM NaCl or 20 mM NaCl plus 30, 80, 180, 380, and 780 mM LiCl, CsCl, or TMACl. For the experiments involving Tel26, the measurements were performed at 20, 50, 100, 200, 400, and 800 mM KCl or 20 mM KCl plus 30, 80, 180, 380, and 780 mM LiCl, CsCl, or TMACl.

The concentrations of the oligonucleotides were determined from the UV light absorbance at 260 nm measured at 25 °C with a Cary 300 Bio spectrophotometer (Varian Canada, Inc., Mississauga, Ontario, Canada) using molar extinction coefficients of 228,500 and 278,200 $M^{-1}\,cm^{-1}$ for the unfolded conformation of Tel22 and Tel26, respectively. These extinction coefficients were calculated using an additive nearest neighbor procedure as described by Dr. Richard Owczarzy (http://www.owczarzy.net/extinct.htm). For our CD measurements and temperature-dependent

UV light absorption measurements, the DNA concentrations were ~30 and ~3 μM, respectively.

2.2. Circular dichroism spectroscopy

The CD spectra of Tel22 and Tel26 were recorded in a 1 mm path-length cuvette at 25 °C using an Aviv model 62 DS spectropolarimeter (Aviv Associates, Lakewood, NJ). CD spectroscopy was used to probe the conformations adopted by the oligonucleotides at the various ionic conditions employed in the present study.

2.3. UV melting experiments

UV light absorption at 295 nm was measured as a function of temperature in DNA samples contained in a 1 cm path-length cuvette. These measurements were performed by a Cary 300 Bio spectrophotometer (Varian Canada, Inc., Mississauga, Ontario, Canada). The temperature was changed at a rate of 1 °C per minute. The G-quadruplex-to-coil transition temperatures, T_M, and van't Hoff enthalpies, ΔH_{vH}, were evaluated from our experimental UV melting profiles using standard procedures [26,27].

It should be noted that temperature scanning experiments performed on Tel22 in NaCl solutions at a rate of 0.2 °C per minute did not reveal any change in the shape of the melting profiles. By extension, we assume that the scanning rate of 1 °C per minute is optimal for all DNA melting experiments reported here.

3. Results

3.1. CD spectra

In the presence of Na^+ ions, the Tel22 human telomeric sequence, $d[A(G_3T_2A)_3G_3]$, forms an antiparallel structure with three Na^+ ions coordinated within the central cavity [28]. To monitor the G-quadruplex formation in the presence of NaCl and its maintenance throughout our experimental protocols (in the presence of LiCl, CsCl, and TMACl), we measured the CD spectrum of the DNA at each salt. Fig. 1 presents the CD spectra of Tel22 in the presence of 20 mM NaCl and various concentrations of LiCl (panel A), CsCl (panel B), and TMACl (panel C). Previous investigations have shown that the CD spectrum of antiparallel telomeric G-quadruplexes display a negative peak at 260 nm and a positive peak at 295 nm [3]. The CD spectra of Tel22 in Fig. 1a, b, and c with the characteristic bands at 260 and 295 nm are consistent with the formation of an antiparallel G-quadruplex structure.

In the presence of K^+ ions, the Tel26 sequence $d[A_3G_3(T_2AG_3)_3A_2]$ overwhelmingly exists as a hybrid-type (hybrid-1) intramolecular G-quadruplex consisting of three G-tetrads linked with mixed parallel/antiparallel G-strands [29–31]. The structure has a sequential double-chain-reversal side loop and two lateral loops each consisting of three nucleotides (-TTA-) thereby making the third G-strand antiparallel. In contrast to Tel22 with three sequestered Na^+ ions, the Tel26 G-quadruplex coordinates only two K^+ ions within its central cavity. The CD signature of the hybrid-1 conformation of Tel26 is a double-headed positive domain with maxima at 260 and 295 nm and a negative domain with a minimum at 240 nm [29]. The CD spectra of Tel26 in the presence of 20 mM KCl and various concentrations of LiCl (Fig. 2a), CsCl (Fig. 2b), and TMACl (Fig. 2c) display the characteristic bands at 240, 260, and 295 nm. Thus, the CD spectra of Tel26 are consistent with the CD spectrum reported for the hybrid-1 conformation of Tel26 [25,29].

3.2. Melting profiles

Fig. 3 shows representative UV melting profiles measured at 295 nm for Tel22 in 100 mM NaCl and Tel26 in 100 mM KCl. These and similar profiles determined at other salt conditions all exhibit a sigmoidal

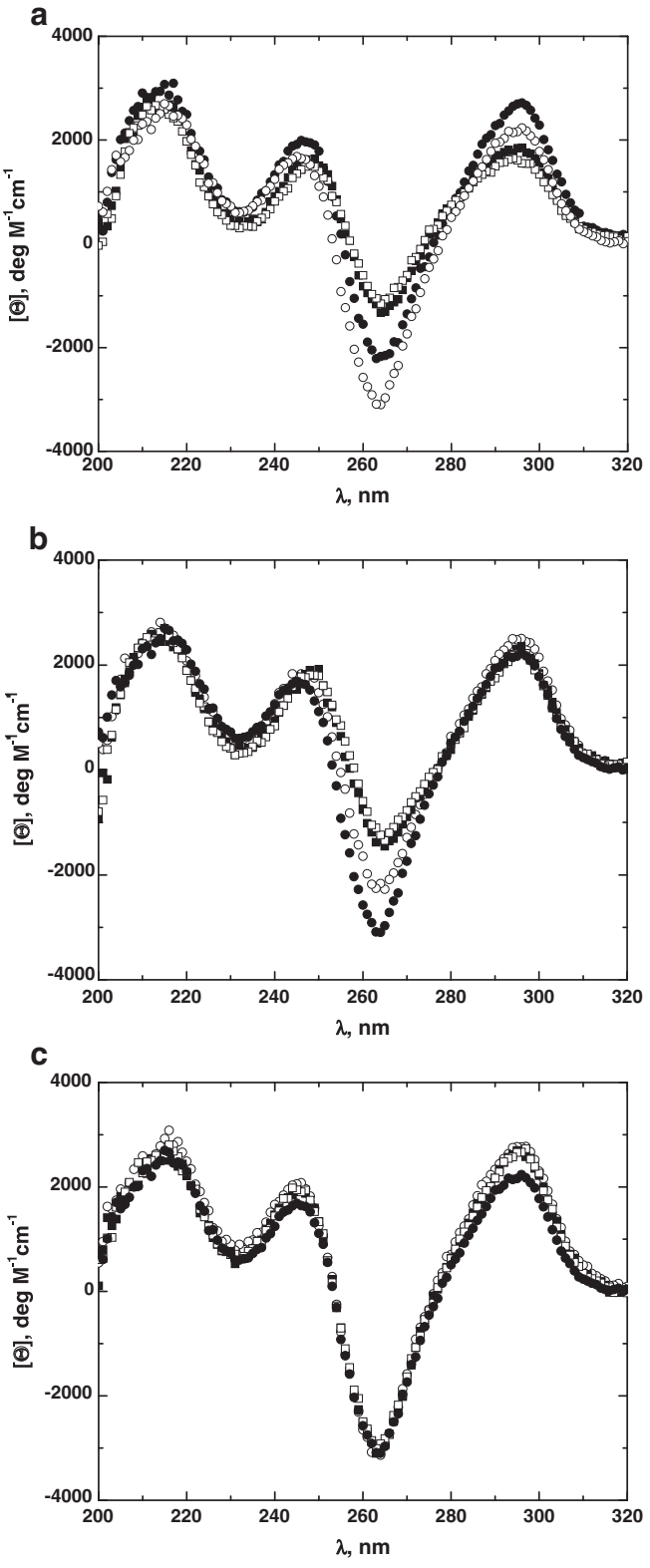

Fig. 1. CD spectra of Tel22 in the presence of 20 mM NaCl and 0 (●), 180 (○), 380 (■), and 780 (□) mM LiCl (panel A), CsCl (panel B), and TMACl (panel C).

shape. The UV melting profiles were approximated by the analytical relationship for the two-state transition:

$$\alpha = \left[1-\exp\left(\Delta H_{vH}\left(T^{-1}-T_M{}^{-1}\right)/R\right)\right]^{-1} \quad (2)$$

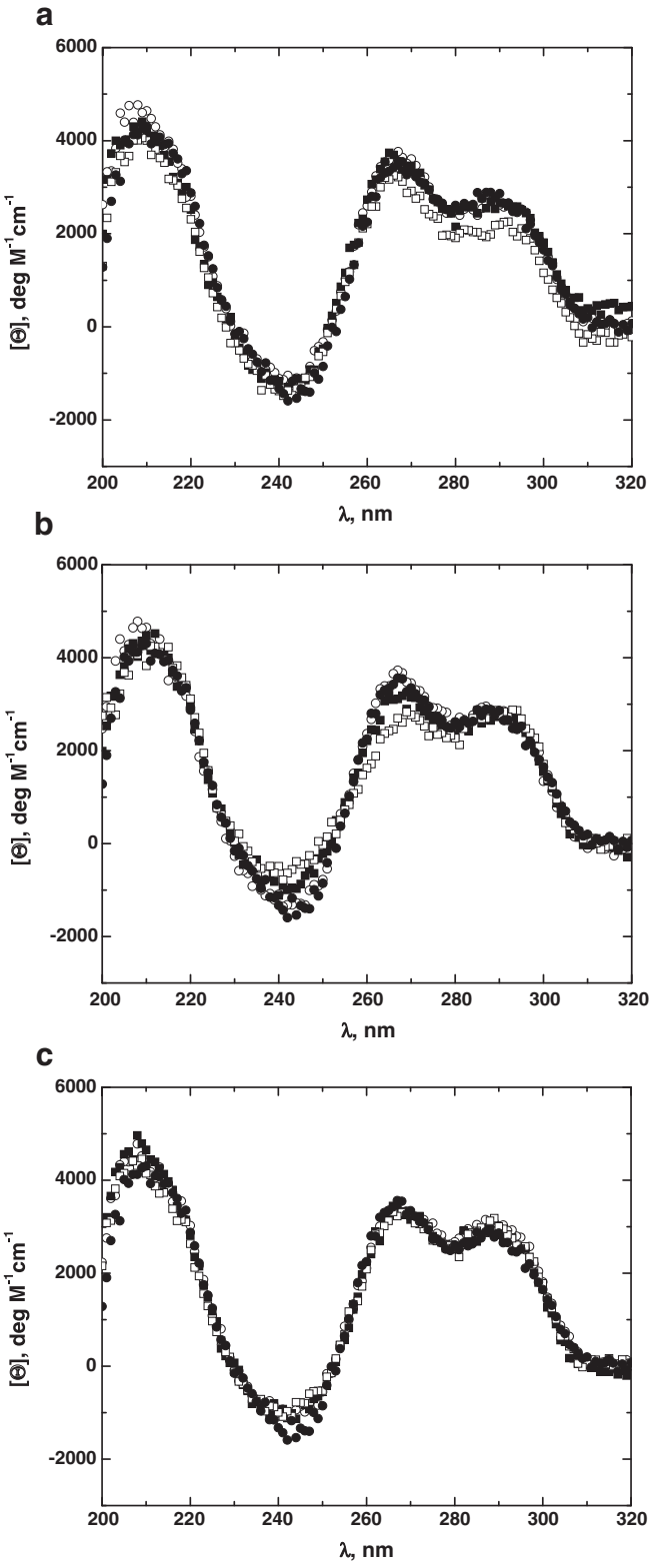

Fig. 2. CD spectra of Tel26 in the presence of 20 mM KCl and 0 (●), 180 (○), 380 (■), and 780 (□) mM LiCl (panel A), CsCl (panel B), and TMACl (panel C).

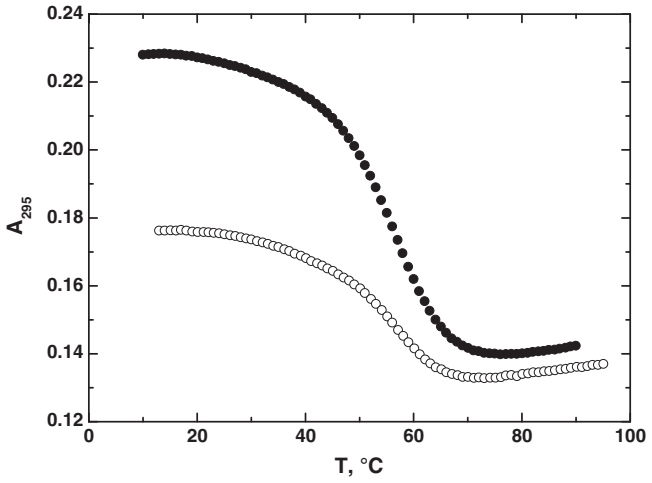

Fig. 3. UV melting profiles at 295 nm of Tel22 at 100 mM NaCl (●) and Tel26 at 100 mM KCl (○).

where ΔH_{vH} is the van't Hoff enthalpy of the transition, T_M is the transition temperature, $\alpha = [A(T) - A_N(T)] / [A_D(T) - A_N(T)]$ is the fraction of the DNA that is unfolded; A(T) is the UV light absorption at a temperature T; and $A_N(T)$ and $A_D(T)$ signify the native and denatured baselines, respectively.

Our measured UV melting profiles were used in conjunction with Eq. (2) to determine the transition temperatures, T_M, and enthalpies, ΔH_{vH}, for Tel22 and Tel26 at each experimental salt condition. Fig. 4 plots the melting temperatures, T_M, against the natural logarithm of cation concentration for Tel22 (panel A) and Tel26 (panel B).

It needs to be pointed out that G-quadruplexes, in general, may not melt in the two-state manner with no single temperature to describe the melting transition [32,33]. Therefore, the T_M, as determined from Eq. (2), should be viewed as an effective or apparent melting temperature. Nevertheless, it represents a reliable measure of the thermal stability of G-quadruplexes in comparative studies reported here.

4. Discussion

Counterions can influence the stability of a G-quadruplex in two ways by binding specifically or binding nonspecifically by condensing around the DNA polyanion. While specific binding may cause conformational transitions of G-quadruplex-forming sequences, no conformational changes are expected to accompany nonspecific ion binding. Any release of condensed counterions upon a helix-to-coil transition reflects a difference in charge density between the folded and unfolded forms. In the present study, we are interested in this type of binding (counterion condensation).

The Na^+ and K^+ ions bind specifically by penetrating the central cavity and stabilizing the G-quadruplex conformation [3]. In contrast, the Li^+, Cs^+, and TMA^+ ions do not fit inside the cavity being either too small or too large. To additionally verify that these ions do not support G-quadruplex formation, we have recorded the CD spectra of Tel22 and Tel26 in the absence of the Na^+ and K^+ ions but in the presence of Li^+, Cs^+, and TMA^+ up to 800 mM (data not shown). No G-quadruplex formation was detected.

Inspection of Figs. 1 and 2 reveals that, in the presence of Li^+, Cs^+, and TMA^+, the CD spectra of the preformed Tel22 and Tel26 G-quadruplexes undergo only quantitative, although, sizeable changes. The observed changes do not involve appearance of new CD bands or disappearance of the existing ones. Instead, the Li^+, Cs^+, and TMA^+ ions only bring about a diminution of the intensity of the existing CD bands. This observation is consistent with the picture in which the two G-quadruplexes retain their respective global conformations with no new species (including unfolded species) appearing in the presence of the three nonstabilizing cations. Thus, we conclude that the Li^+, Cs^+, and TMA^+ ions affect the thermal stability of the Tel22 and Tel26 G-quadruplexes predominantly via the effect of counterion condensation.

A note of caution is in order here. TMA^+ ions interact in a differential manner with the AT and GC base pairs in DNA duplexes [34–38]. Hence,

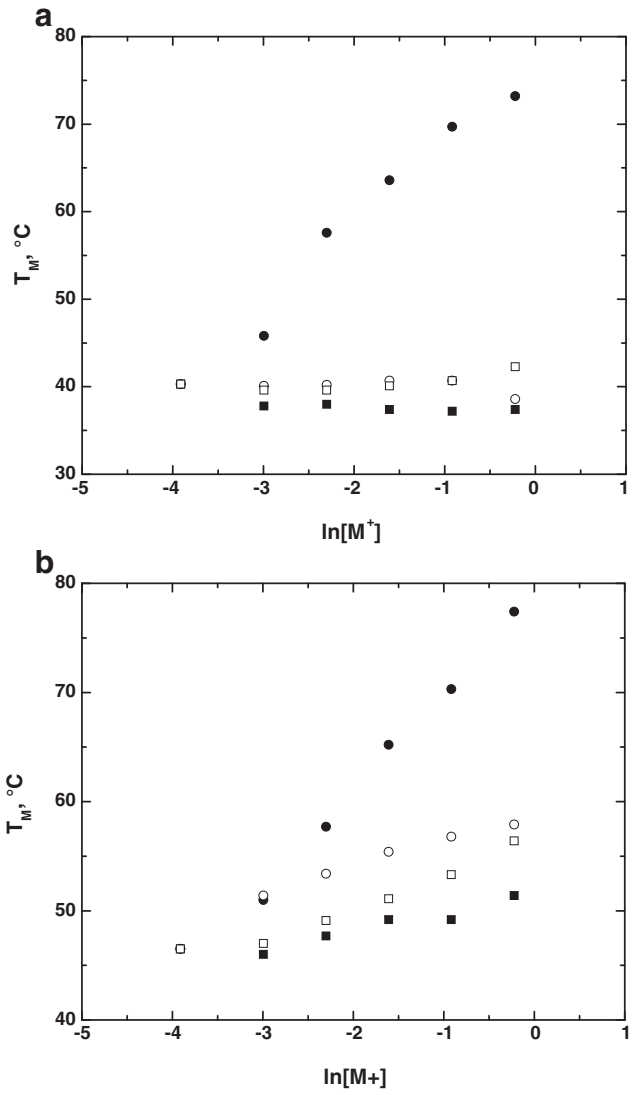

Fig. 4. (a) Dependences of the melting temperature, T_M, of Tel22 on the concentration of Na^+ (●), Li^+ (○), Cs^+ (■), and TMA^+ (□) cations; (b) dependences of the melting temperature, T_M, of Tel26 on the concentration of K^+ (●), Li^+ (○), Cs^+ (■), and TMA^+ (□) cations.

the effect of TMA^+ on G-quadruplex stability may not be limited to counterion condensation. While not ignoring this possibility, we, nevertheless, do not separate the effect TMA^+ ions from that of the Li^+ and Cs^+ ions because of the qualitative similarity of the influence of the three ions on the spectral and thermal properties of the G-quadruplexes. In fact, the CD spectral changes of Tel22 and Tel26 caused by TMA^+ are less pronounced compared to those caused by Li^+ and Cs^+ (see Figs. 1 and 2).

Inspection of Fig. 4a and b reveals that steep increases in T_M for both the Tel22 and Tel26 oligonucleotides accompany increases in the concentration of NaCl and KCl, respectively. In other words, the thermal stability of the two G-quadruplexes increases with the rise in the concentration of their respective stabilizing ions (Na^+ for Tel22 and K^+ for Tel26). We use the slope ($\partial T_M / \partial \ln[M^+]$) in conjunction with Eq. (1) to calculate the number of sodium or potassium ions, Δn_{M+}, released to the bulk upon G-quadruplex unfolding [11,18]. The numbers of counterions released to the bulk are 1.7 ± 0.5 Na^+ for Tel22 and 1.5 ± 0.2 K^+ for Tel 26. These numbers are qualitatively similar to 3 and 2, the structurally detected numbers of Na^+ and K^+ cations coordinated within the central cavities of the Tel22 and Tel26 G-quadruplexes, respectively [28,29,39].

Further inspection of Fig. 4a and b reveals that an increase in the concentration of the nonstabilizing ions Li^+, Cs^+, and TMA^+ brings about only modest (Tel26) or no (Tel22) changes in the melting temperature, T_M. Specifically, for Tel22, an increase in the concentration of these ions from 0 to 800 mM does not result in any increase in T_M. For Tel26, an increase in the concentration of the Li^+, Cs^+, and TMA^+ ions causes modest, although non-zero, changes in T_M. The strongest change is observed for Li^+ ions for which an increase in concentration from 0 to 800 mM causes T_M to increase from 46 to 58 °C. This is only a fraction of the increase in T_M from 46 to 77 °C that was detected to accompany an increase in K^+ concentration from 20 to 800 mM.

In the absence of fortuitous compensations, the observed insensitivity of the thermal stability of Tel22 with respect to the presence of the nonstabilizing ions Li^+, Cs^+, and TMA^+ is consistent with the picture in which the polyelectrolyte effects exert a negligible influence on the stability of the Tel22 G-quadruplex. By extension, this inference implies that the Tel22 oligomeric sequence condenses the same amount of counterions in its folded and unfolded states. It also suggests that the observed increase in the stability of the Tel22 G-quadruplexes upon the addition of NaCl results overwhelmingly from the specific binding of Na^+ ions in the central cavity with the former acting as a ligand. From this perspective, the observed increase in G-quadruplex stability due to Na^+ ions is similar to an enhancement of protein or DNA stability facilitated by ligand binding.

In contrast to Tel22, the thermal stability of the Tel26 G-quadruplex moderately increases with an increase in the concentration of the nonstabilizing ions Li^+, Cs^+, and TMA^+. As is seen from Fig. 4b, the increase in T_M is only 15 to 30% of that caused by the stabilizing ion K^+. Thus, although, the effect of counterion condensation in Tel26 is not zero, the predominant ionic contribution to its stability still comes from the specific K^+ binding and not from counterion condensation.

The greatly reduced effect of counterion condensation on G-quadruplex stability is related, at least, in part to the presence of coordinated cations within the central cavity with the concomitant decrease in the charge density of the DNA. This notion is supported by the fact that Tel22 with its three sequestered Na^+ ions exhibits no change in T_M with an increase in the concentration of nonstabilizing cations. On the other hand, Tel26 with only two sequestered K^+ ions and, hence, a higher charge density, exhibits a non-zero slope of the dependence of T_M on the concentration of nonstabilizing cations. This interpretation is also in line with the lack of counterion condensation contribution to the stability of C-rich triplexes which, due to the presence of protonated cytosines in the third strand, exhibit a reduced charge density [40,41]. Another contributing factor may be the globular shape of a G-quadruplex that increases the distance between the G-strands thereby diminishing the net charge density to the level characteristic of the single-stranded conformation. This conjecture is supported by the results of recent theoretical studies by Manning that revealed reduced counterion condensation around a charged spherical construct relative to a cylinder [12,13].

The results presented in this paper suggest that, for the two G-quadruplexes differing in topology and the type of the stabilizing cations, the polyelectrolyte effects play a small to negligible role in maintaining their stability. This is in stark contrast to the thermodynamics of duplex and T-rich triplex DNA where counterion condensation provides a major contribution to thermal and thermodynamic stability [10,11,14,15,18,41]. Our data suggest that the duplex-G-quadruplex equilibrium in a system with a G-rich strand and its complementary C-rich strand will shift towards the duplex state upon an increase in the concentration of nonstabilizing counterions. This notion may be of practical importance, for example, for understanding the balance of forces governing the conformational preferences of G-rich strands in the promoter regions of oncogenes where G-quadruplex formation is preceded by duplex dissociation.

The generality of our finding is supported by the ionic, structural, and topological dissimilarities between the two G-quadruplex structures

studied in this work. However, further studies involving a larger and more diversified pool of G-quadruplexes are needed to ascertain the generality of the relative insignificance of counterion condensation in maintaining G-quadruplex stability. In particular, the influence of the G-quadruplex topology, molecularity, sequence, loop length, and composition must be studied.

5. Conclusion

G-quadruplexes are non-canonical nucleic acid constructs that exist in the genome and have been implicated in cancer research. G-quadruplexes are unusual in that, in contrast to other DNA structures, they specifically bind cations in their central cavity. There have been a long-standing question about the ionic stabilization of G-quadruplexes. It was not clear if the stabilization comes from the specific binding, nonspecifc binding (counterion condensation), or both. In this work, we resolve the specific and nonspecific contributions to the thermal stability of G-quadruplexes by separating the effect of the centrally bound ions from the effect of the cations condensed around the DNA. Our data suggest that the predominant ionic contribution to G-quadruplex stability comes from the specifically bound Na^+ or K^+ ions and not from counterion condensation around the DNA. Our results shed light on the balance of forces governing the conformational preferences of guanine-rich sequences while also being of practical importance for controlled induction of G-quadruplexes in the genome.

Acknowledgments

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References

[1] M.A. Keniry, Quadruplex structures in nucleic acids, Biopolymers 56 (2000) 123–146.
[2] R.H. Shafer, I. Smirnov, Biological aspects of DNA/RNA quadruplexes, Biopolymers 56 (2000) 209–227.
[3] A.N. Lane, J.B. Chaires, R.D. Gray, J.O. Trent, Stability and kinetics of G-quadruplex structures, Nucleic Acids Res. 36 (2008) 5482–5515.
[4] L.H. Hurley, DNA and its associated processes as targets for cancer therapy, Nat. Rev. Cancer 2 (2002) 188–200.
[5] J.L. Huppert, Four-stranded DNA: cancer, gene regulation and drug development, Philos. Trans. R. Soc. 365 (2007) 2969–2984.
[6] J.L. Huppert, Four-stranded nucleic acids: structure, function and targeting of G-quadruplexes, Chem. Soc. Rev. 37 (2008) 1375–1384.
[7] L. Oganesian, T.M. Bryan, Physiological relevance of telomeric G-quadruplex formation: a potential drug target, Bioessays 29 (2007) 155–165.
[8] A. De Cian, L. Lacroix, C. Douarre, N. Temime-Smaali, C. Trentesaux, J.F. Riou, J.L. Mergny, Targeting telomeres and telomerase, Biochimie 90 (2008) 131–155.
[9] L.R. Kelland, European overcoming the immortality of tumour cells by telomere and telomerase based cancer therapeutics — current status and future prospects, J. Cancer Educ. 41 (2005) 971–979.
[10] G.S. Manning, Molecular theory of polyelectrolyte solutions with applications to electrostatic properties of polynucleotides, Q. Rev. Biophys. 11 (1978) 179–246.
[11] M.T. Record, C.F. Anderson, T.M. Lohman, Thermodynamic analysis of ion effects on binding and conformational equilibria of proteins and nucleic acids. Roles of ion association or release, screening, and ion effects on water activity, Q. Rev. Biophys. 11 (1978) 103–178.
[12] G.S. Manning, Electrostatic free energies of spheres, cylinders, and planes in counterion condensation theory with some applications, Macromolecules 40 (2007) 8071–8081.
[13] G.S. Manning, Counterion condensation on charged spheres, cylinders, and planes, J. Phys. Chem. B 111 (2007) 8554–8559.
[14] C.F. Anderson, M.T. Record, Polyelectrolyte theories and their applications to DNA, Annu. Rev. Phys. Chem. 33 (1982) 191–222.
[15] C.F. Anderson, M.T. Record, Salt-nucleic acid interactions, Annu. Rev. Phys. Chem. 46 (1995) 657–700.
[16] J.P. Bond, C.F. Anderson, M.T. Record, Conformational transitions of duplex and triplex nucleic acid helices. Thermodynamic analysis of effects of salt concentration on stability using preferential interaction coefficients, Biophys. J. 67 (1994) 825–836.
[17] J. Volker, H.H. Klump, G.S. Manning, K.J. Breslauer, Counterion association with native and denatured nucleic acids: an experimental approach, J. Mol. Biol. 310 (2001) 1011–1025.
[18] Y.K. Cheng, B.M. Pettitt, Stabilities of double strand and triple strand helical nucleic acids, Prog. Biophys. Mol. Biol. 58 (1992) 225–257.
[19] R. Owczarzy, I. Dunietz, M.A. Behlke, I.M. Klotz, J.A. Walder, Thermodynamic treatment of oligonucleotide duplex–simplex equilibria, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 14840–14845.
[20] I.V. Smirnov, R.H. Shafer, Electrostatics dominate quadruplex stability, Biopolymers 85 (2007) 91–101.
[21] S.N. Timasheff, Protein hydration, thermodynamic binding, and preferential hydration, Biochemistry 41 (2002) 13473–13482.
[22] J.A. Schellman, Protein stability in mixed solvents: a balance of contact interaction and excluded volume, Biophys. J. 85 (2003) 108–125.
[23] D.B. Knowles, A.S. LaCroix, N.F. Deines, I. Shkel, M.T. Record Jr., Separation of preferential interaction and excluded volume effects on DNA duplex and hairpin stability, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 12699–12704.
[24] H.Y. Fan, Y.L. Shek, A. Amiri, D.N. Dubins, H. Heerklotz, R.B. Macgregor, T.V. Chalikian, Volumetric characterization of sodium-induced G-quadruplex formation, J. Am. Chem. Soc. 133 (2011) 4518–4526.
[25] Y.L. Shek, G.D. Noudeh, M. Nazari, H. Heerklotz, R.M. Abu-Ghazalah, D.N. Dubins, T.V. Chalikian, Folding thermodynamics of the hybrid-1 type intramolecular human telomeric G-quadruplex, Biopolymers (2013)(in press).
[26] L.A. Marky, K.J. Breslauer, Calculating thermodynamic data for transitions of any molecularity from equilibrium melting curves, Biopolymers 26 (1987) 1601–1620.
[27] K.J. Breslauer, Extracting thermodynamic data from equilibrium melting curves for oligonucleotide order–disorder transitions, Methods Enzymol. 259 (1995) 221–242.
[28] Y. Wang, D.J. Patel, Solution structure of the human telomeric repeat d[$AG_3(T_2AG_3)_3$] G-tetraplex, Structure 1 (1993) 263–282.
[29] A. Ambrus, D. Chen, J.X. Dai, T. Bialis, R.A. Jones, D.Z. Yang, Human telomeric sequence forms a hybrid-type intramolecular G-quadruplex structure with mixed parallel/antiparallel strands in potassium solution, Nucleic Acids Res. 34 (2006) 2723–2735.
[30] J.X. Dai, C. Punchihewa, A. Ambrus, D. Chen, R.A. Jones, D.Z. Yang, Structure of the intramolecular human telomeric G-quadruplex in potassium solution: a novel adenine triple formation, Nucleic Acids Res. 35 (2007) 2440–2450.
[31] J.X. Dai, M. Carver, D.Z. Yang, Polymorphism of human telomeric quadruplex structures, Biochimie 90 (2008) 1172–1183.
[32] R.D. Gray, R. Buscaglia, J.B. Chaires, Populated intermediates in the thermal unfolding of the human telomeric quadruplex, J. Am. Chem. Soc. 134 (2012) 16834–16844.
[33] R. Buscaglia, R.D. Gray, J.B. Chaires, Thermodynamic characterization of human telomere quadruplex unfolding, Biopolymers 99 (2013) 1006–1018.
[34] J.T. Shapiro, B.S. Stannard, G. Felsenfeld, The binding of small cations to deoxyribonucleic acid. Nucleotide specificity, Biochemistry 8 (1969) 3233–3241.
[35] W.B. Melchior Jr., P.H. von Hippel, Alteration of the relative stability of dAdT and dGdC base pairs in DNA, Proc. Natl. Acad. Sci. U. S. A. 70 (1973) 298–302.
[36] J.J. Delrow, P.J. Heath, B.S. Fujimoto, J.M. Schurr, Effect of temperature on DNA secondary structure in the absence and presence of 0.5 M tetramethylammonium chloride, Biopolymers 45 (1998) 503–515.
[37] W.I. Wood, J. Gitschier, L.A. Lasky, R.M. Lawn, Base composition-independent hybridization in tetramethylammonium chloride: a method for oligonucleotide screening of highly complex gene libraries, Proc. Natl. Acad. Sci. U. S. A. 82 (1985) 1585–1588.
[38] K.A. Jacobs, R. Rudersdorf, S.D. Neill, J.P. Dougherty, E.L. Brown, E.F. Fritsch, The thermal stability of oligonucleotide duplexes is sequence independent in tetraalkylammonium salt solutions: application to identifying recombinant DNA clones, Nucleic Acids Res. 16 (1988) 4637–4650.
[39] R.D. Gray, J.B. Chaires, Kinetics and mechanism of K^+- and Na^+-induced folding of models of human telomeric DNA into G-quadruplex structures, Nucleic Acids Res. 36 (2008) 4191–4203.
[40] J. Volker, H.H. Klump, Electrostatic effects in DNA triple helices, Biochemistry 33 (1994) 13502–13508.
[41] G.E. Plum, D.S. Pilch, S.F. Singleton, K.J. Breslauer, Nucleic acid hybridization: triplex stability and energetics, Annu. Rev. Biophys. Biomol. Struct. 24 (1995) 319–350.