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2'-Deoxyribo-oligonucleotides duplexes and G-quadruplexes structures and thermal stability in 1-butyl-1-methylpiperidinium and 1-octyl-3-methylimidazolium bromide ionic liquid solutions

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Abstract

Conformation and thermal stability of duplexes made of various ratio of purine and pyrimidine, but also of two G-quadruplexes, were evaluated in two different ionic liquids, aliphatic 1-butyl-1-methylpiperidinium bromide and 1-octyl-3-methylimidazolium bromide with an aromatic moiety, by means of UV-spectroscopy and circular dichroism. It appeared that no conformational change occurred within all structures studied whatever the medium was, only thermal stabilities were affected.

Keywords : Nucleic acids, duplex, quadruplex, ionic liquid, circular dichroism, UV, thermal denaturation.

Introduction

DNA-based artificial enzymes have been described where nucleic acids played the pivotal role of the chiral microenvironment for the catalysis of enantioselective chemical reactions such as Michael addition, Friedel-Crafts alkylation and others.¹ The main drawback of this technology is that whereas nucleic acids are soluble and structured in aqueous media, the substrates are organic compounds that generally exhibit a poor water solubility. On the other hand, efforts have been made to render nucleic acids more soluble in organic solvents by covalent grafting of polyethylene glycol unit,² and their behaviour have been evaluated in non-aqueous medium such as deep eutectic solvent,³ molecular crowding agents⁴ or hydrated ionic liquids.⁵ It appeared that the well known DNA double helical structuration and stability were highly dependent of the nature and the level of hydration of the organic solvent or ionic liquids with the observation of B- to A- or Z-form transition, reverse Watson-Crick base pairing rule, change in persistence length.^{6,7,8} Moreover, DNA G-quadruplex structures that are very good candidate as chirality transfer surrogate exhibit similar stability than duplexes in these media but also failed to fold in deep eutectic solvent in the absence of metallic ion.⁹

Water-soluble ionic liquids are efficient hydrotropes that can be used to increase the water solubility of non- or poorly water-soluble organic molecules. Mixtures of ionic liquids and water have therefore been used as extractive solvents for a variety of natural compounds¹⁰ or as reaction medium.¹¹ Aqueous solution of ionic liquids may therefore be able to dissolve small hydrophobic organic molecules while preserving the solubility of nucleic acids.

As part of an on-going program devoted to the development of catalytic chemically modified oligonucleotides,¹² and in order to have a rational knowledge of the structure of the catalytic system,¹³ we explored the behaviour of small synthetic DNA fragments that can be structured into duplex (12 to 16 base-pairs) or G-quadruplex (15 or 22 bases) dissolved in aqueous solutions of two ionic liquids. We investigated the thermal stability of these nucleic acids structures by means of UV-spectroscopy and their shape by means of circular dichroism in these ionic liquids in comparison with aqueous phosphate buffer.

Results and discussion

With the aim of exploring the potential influence of the solvent depending on the oligonucleotides base composition, we chose three different duplexes: one composed with only AT base pairs (D_{AT}), one with GC base pairs (D_{GC}), one with a one to one mixture of AT and GC base pairs (D_{Mix} , Figure 1). The thrombin-binding aptamer (**TBA**) and the human telomeric G-quadruplex (**Tel₂₂**) are two well studied G-quadruplexes forming sequences, that have been also selected for this study. The former is known to form a two G-tetrad stacked on each other resulting in a G-quadruplex with an antiparallel structure whereas the latter exhibits a three G-tetrad stacked in a G-quadruplex structure more sensitive to the surrounding composition.¹⁴

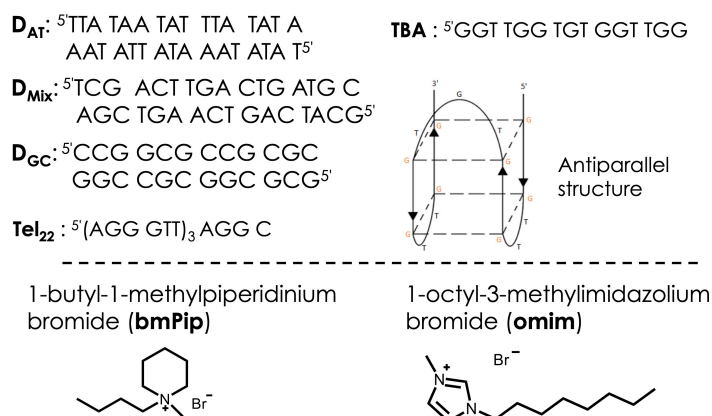


Figure 1. Up: duplex DNA and G-quad forming sequences. Down: structures of ionic liquids in this study.

As common and commercially available ionic liquids for solvating of organic compounds, we selected the aliphatic 1-butyl-1-methylpiperidinium bromide (denoted as **bmPip** for clarity) and 1-octyl-3-methylimidazolium bromide (**omim**) with an aromatic moiety (Figure 1). **Omim** water solutions have been used with success as extractive solvents for a variety of natural organic compounds such as alkaloids,¹⁵ flavonoids,¹⁶ terpenoids^{17,18} and other natural compounds.^{17,19}

To the best of our knowledge, aqueous solution of aliphatic **bmPip** have never been used as extractive solvents although the structurally related 1-butyl-1-methylpyrrolidinium bromide was proved to be an efficient additive to water for the extraction of mono- and diiodotyrosine from brown algae *Laminaria*.²⁰

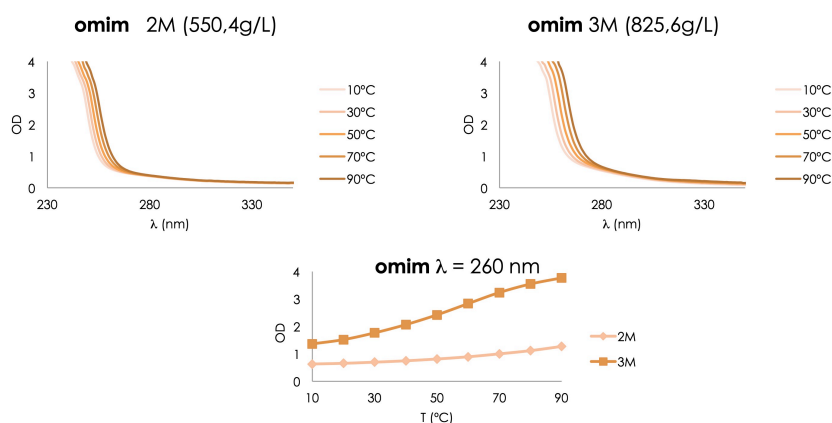


Figure 2. UV spectra of 1-octyl-3-methylimidazolium bromide (**omim**) at 2 and 3M in water in function of temperature.

These common ionic liquids are susceptible to solvate most of the organic compounds either alone or in combination, due to their structures. However if **bmPip** is UV-transparent at 260 and 295 nm, the wavelengths of interest to determine the nucleic acids structures melting temperatures, **omim** exhibits an aromatic moiety with a significant absorbance at 260 nm that can interfere with the measurements. Indeed, at high concentration of 2M (550.4 g/L) and above 50°C, the absorbance at 260 nm gets closed to 1 and largely goes beyond this value for the 3M (825.6 g/L) concentration of

omim (Figure 2). Therefore, the oligonucleotides behaviour can be evaluated accurately only up to 1M **omim** (225.2 g/L) solution.

UV spectra of all duplexes and G-quadruplexes were recorded in phosphate buffer at various salt concentrations as reference, and then in **bmPip** and **omim** aqueous solutions at concentration ranging from 0.1 to 2M. In Figure 3 are reported comparative and representative spectra of duplexes **D_{AT}**, **D_{Mix}** and **D_{GC}** at 1M concentration of each studied media.

The aliphatic ionic liquid **bmPip** did not significantly change the values of the UV maximum of absorption of all duplexes with only 1nm < DI_{max} < 2nm when compared with those determined in 1M NaCl phosphate aqueous buffer. On the other hand, the aromatic ionic liquid **omim** induced a red shift of these maxima by 4 nm for **D_{AT}**, 11 nm for **D_{Mix}** and 19 nm for **D_{GC}**. These observations suggest that interactions of **omim** with duplex slightly modify the base environment by affecting orientation of the hydrogen bonds and/or base stacking and that these interactions are maximized with the GC rich duplex, in which the hydrogen bonding is more effective than in the others, whereas **bmPip** does not interfere significantly.

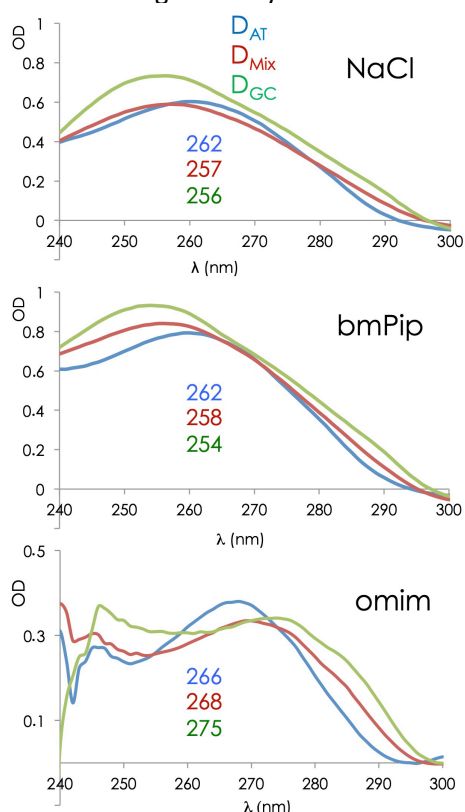


Figure 3. UV spectra of **D_{AT}**, **D_{Mix}** and **D_{GC}** duplexes in phosphate buffer 0.1 M, pH7, **NaCl** 1M, or **bmPip**, **omim** 1M in water at 20°C.

Similarly, we investigated the conformation of the duplexes by means of circular dichroism in order to have insight on the influence of the ionic liquid solvent on the helix structure. Representative CD spectra of duplexes **D_{AT}**, **D_{Mix}** and **D_{GC}** are given in Figure 4, where are compared their behaviour in 1M NaCl, **bmPip** and **omim**.

D_{AT} and **D_{Mix}** provided similar spectra whatever the solvent was. This was indicating that the ionic liquids did not modified the helix structures that are in between the A- and B-form for **D_{AT}** with a maximum of the positive Cotton's band around 275 nm, and in a more pronounced B-form for **D_{Mix}** in which the positive Cotton's band maximum is around 282 nm. The **D_{GC}** duplex was a little bit more sensitive to the variation of the solvent composition. In 1M NaCl, both A- and B-form are coexisting within the helix with a major shoulder around 270 nm representative of the former and to a lower extend there is an another maximum at 290 nm indicative of the B-form. In **bmPip**, it can be assumed that the A- and B-form are in equal proportion whereas in **omim** the B-form becomes majority. It can

be proposed that in the latter case the ionic liquid participated to an extended dehydrated form of the duplex.²¹

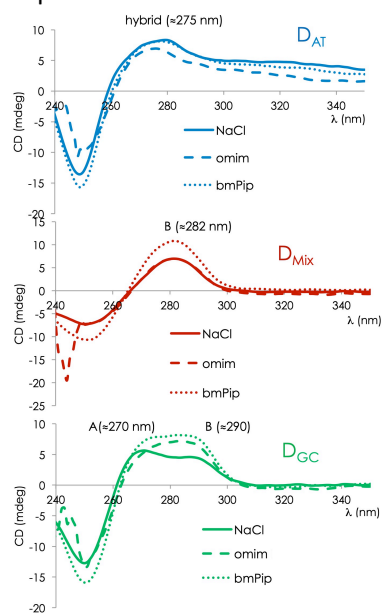


Figure 4. Circular dichroism spectra of D_{AT} , D_{Mix} and D_{GC} duplexes in phosphate buffer 0.1 M, pH7, NaCl 1M, omim 1M in water, or bmPip 1M in water at 20°C.

The UV-spectra of the G-quadruplexes **Tel22** and **TBA** did not exhibit any change whatever the solvent was (Figure 5).

It is noteworthy that the G-quadruplex conformation has no influence on the maxima of UV-absorption (259 and 258 nm for **TBA** and **Tel22**, respectively) even if it is well known that **Tel22** conformation is sensitive to the cation nature and therefore could modify bases interactions.⁹

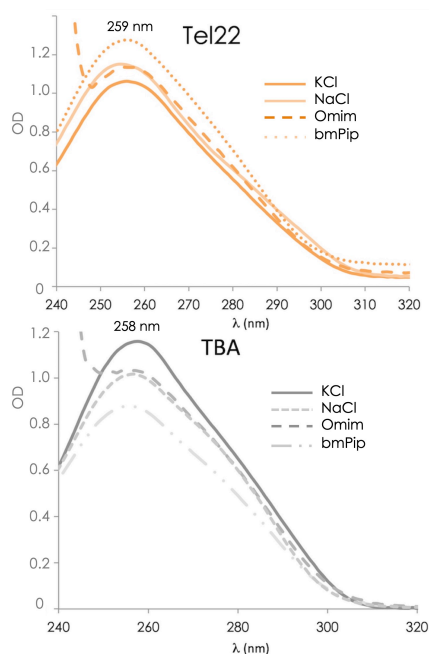


Figure 5. UV spectra of **TBA** and **Tel22** G-quadruplexes in phosphate buffer 0.1 M, pH7, NaCl 1M, phosphate buffer 0.1 M, pH7, KCl 1M or omim 1M in water, or bmPip 1M in water at 20°C.

Recording circular dichroism spectra can better outline the possible conformational change in function of the cation nature, which can turn antiparallel structures to hybrid ones for example.

Indeed, whereas **TBA** was insensitive to the cation nature and kept an antiparallel structure either in potassium or sodium rich buffer with a negative Cotton effect band around 269 nm and a positive one close to 295 nm (Figure 6), **Tel22** showed, as already reported⁹, a shift from an antiparallel conformation in sodium rich buffer to a hybrid structure in potassium rich buffer, depicted by the loss of the negative band at 270 nm and the appearance of a positive shoulder around 255 nm.

Neither **omim** nor **bmPip** induced a conformational modification of the antiparallel structure of **TBA** with a similarity of the CD spectra in these ionic liquids with those recorded in sodium or potassium buffers. The antiparallel conformation is well characterized by two positive bands around 250 and 295 nm and a negative one around 265 nm. On the other hand, the more sensitive **Tel22** exhibited CD spectra closed to an antiparallel structure either in **omim** than in **bmPip**. However, the shape of the spectrum is not as characteristic as the one in sodium buffer with two clean positive bands at 290 and 255 nm whereas either in **omim** or in **bmPip** the negative band around 265 nm almost disappeared.

These techniques allowed having qualitative information's about the influence of the selected ionic liquids on duplex and G-quadruplex nucleic acid structures. More quantitative insight on the temperature range useful to keep the proper folding of the nucleic acid was provided by thermal denaturation studies.

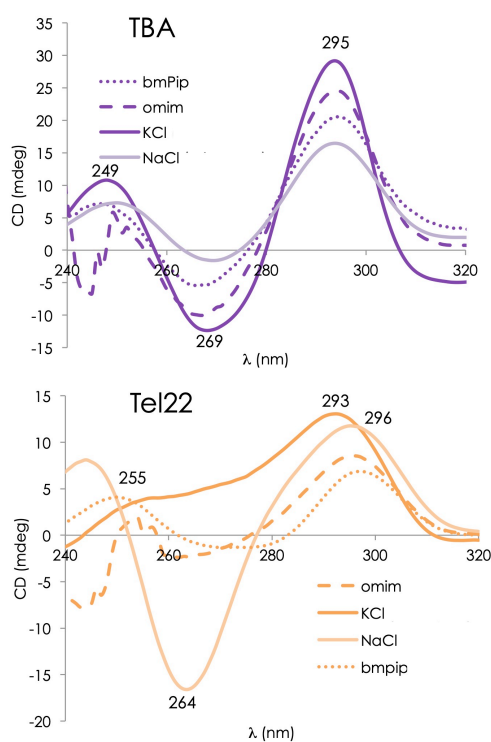


Figure 6. Circular dichroism spectra of **TBA** and **Tel22** G-quadruplexes in phosphate buffer 0.1 M, pH7, **NaCl** 1M, phosphate buffer 0.1 M, pH7, **KCl** 1M or **omim** 1M in water, or **bmPip** 1M in water at 20°C.

The melting temperatures (T_m) of duplexes D_{AT} , D_{GC} and D_{MIX} were measured by the increase of the optical absorption at 260 nm in various concentrations of **omim** and **bmPip** from 0.1 to 1M and in phosphate buffer with NaCl in the same range of concentration for comparison, results are given in Figure 7. All duplexes exhibit typical melting curves indicative of the proper formation of the double helix.

In phosphate buffer, the higher the NaCl concentration the higher the corresponding T_m of the duplex, with a more pronounced effect, as expected, for D_{AT} due to its base composition ($DT_m = +10^\circ C$) whereas D_{MIX} and D_{GC} were less affected ($DT_m = +3^\circ C$ and $+4^\circ C$, respectively).

In **omim** the duplex stability were strongly lowered but rather insensitive to the ionic liquid concentration ($DT_m = +2 \pm 1^\circ C$). With average T_m of $16 \pm 1^\circ C$ and $37 \pm 1^\circ C$, D_{AT} and D_{MIX} were roughly twice less stable in **omim** than in phosphate buffer. D_{GC} still exhibited a high T_m ($55 \pm$

2°C) but with a DT_m of $-24 \pm 3^\circ\text{C}$ compared to those measured in phosphate buffer, indicative of a large destabilisation.

The overall stability of the studied duplexes appeared to be higher in **bmPip** than in **omim** but still lower than in phosphate buffer.²² **D_{Mix}** is characterized by +11 and +8 °C increase in stability in **bmPip** compared to **omim** at 0.1 M and 1M respectively. However, the T_m values displayed by **D_{Mix}** decreased more strongly in **bmPip** by -16° C and -20 °C when compared to the T_m values recorded in phosphate buffer with NaCl at 0.1 and 1M concentration respectively. The AT base pair content seemed to have a beneficial impact on the stability of Watson and Crick base paired duplexes in **bmPip**. This observation is further corroborated by the **D_{GC}** results. .

Interestingly **D_{GC}** exhibited a particular behaviour because its stability decreased with the increase of **bmPip** concentration. The loss of 8°C from 0.1 m to 1M of **bmPip** turned this medium to be less favourable than **omim** for duplex formation at 1M. Whereas **D_{AT}** T_m values increased from 23 to 27 °C, the T_m of **D_{Mix}** was stable around 48 °C \pm 2°C. It could be proposed that AT base pair became slightly more stable than GC base pair in **bmPip** as already depicted in choline dihydrogen phosphate.^{23,24}

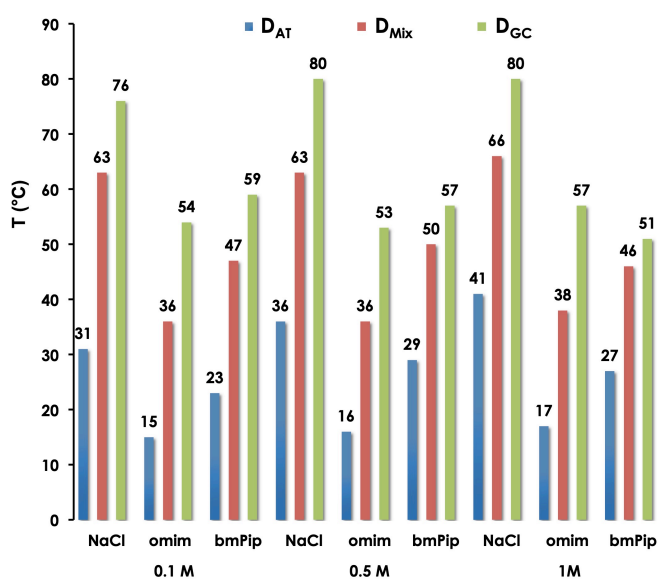


Figure 7. Thermal denaturation values (T_m) of **D_{AT}**, **D_{Mix}** and **D_{GC}** duplexes in phosphate buffer 0.1 M, pH7, with **NaCl** at 0.1, 0.5 and 1M; in **omim** 0.1, 0.5 and 1M in water or **bmPip** 0.1, 0.5 and 1M in water.

The melting temperatures of the G-quadruplexes **TBA** and **Tel22** were measured by the decrease of the optical absorption at 295 nm in various concentration of **omim** and **bmPip** from 0.1 to 1M and in phosphate buffer with **NaCl** or **KCl** (Figure 8).²⁵ It is noteworthy that **TBA** and **Tel22** displayed the expected melting curves evidencing the formation of the quadruplex structure in all studied media.

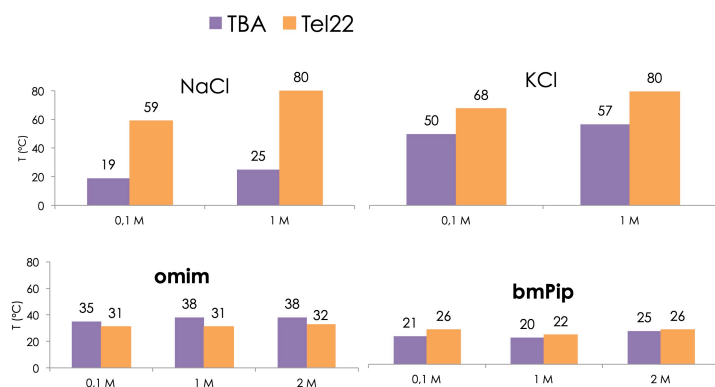


Figure 8. Thermal denaturation values (T_m) of **TBA** (orange) and **Tel₂₂** (purple) G-quadruplexes in phosphate buffer 0.1 M, pH7, with **NaCl** at 0.1 and 1M; in phosphate buffer 0.1 M, pH7, with **KCl** at 0.1 and 1M; in **omim** 0.1, 1 and 2M in water, or **bmPip** 0.1, 1 and 2M in water.

As expected, **TBA** was highly sensitive to the presence of potassium with an increase of $+31 \pm 1$ °C of T_m when compared with sodium solutions at the same concentration. The T_m of **Tel₂₂** was the same at 1M of **NaCl** or **KCl** solution (80 °C). However it was slightly higher in **KCl** 0.1 M solution than in **NaCl** 0.1 M solution ($+9$ °C). In all cases the T_m of **Tel₂₂** was always superior to the T_m of **TBA**, from $+18$ °C to $+55$ °C depending on the nature and the concentration of the cation. These results corroborate previously published data.²⁶

T_m values of **TBA** and **Tel₂₂** were recorded in **bmPip** and **omim** from concentration of 0.1 to 2M. It is remarkable that the T_m values were independent of the ionic liquid concentration. T_m were measured around 37 ± 2 °C and 31 ± 1 °C in **omim** for **TBA** and **Tel₂₂** respectively and 22 ± 2 °C and 24 ± 2 °C in **bmPip** for **TBA** and **Tel₂₂** respectively. However, the stabilities of the G-quadruplexes were considerably lowered in these solvents except when compared to that of **TBA** in **NaCl** solution.

Since **TBA** thermal stability showed **KCl** dependence,²⁷ we investigated its behaviour in **omim** or **bmPip** solution in the presence of 0.01 M **KCl** (Figure 9).

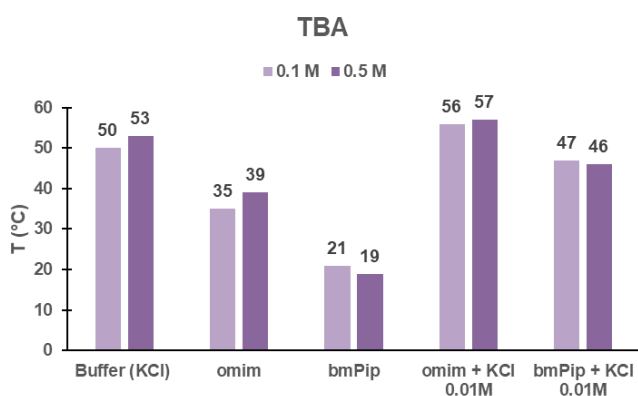


Figure 9. Thermal denaturation values (T_m) of **TBA** G-quadruplex in phosphate buffer 0.1 M, pH7, with **KCl** at 0.1 and 0.5 M; in **omim** 0.1 and 0.5 M in water, or **bmPip** 0.1 and 0.5 M in water and with 0.01 M **KCl**.

It turned out that small amount of **KCl** either in **omim** or **bmPip** solution was able to restore a high thermal stability to the G-quadruplex structure of **TBA**. In **omim**, the stability became similar to that in **KCl** containing buffer increasing by 20 °C when compared with that of **omim** alone. The effect of **KCl** was even more important in **bmPip** with a ΔT_m of 27 °C, T_m increased from 20 ± 1 °C to 47 ± 1 °C.

Materials and methods

All ODNs were purchased from Eurogentec corp and the ionic liquids from Solvionics France (**omim**) and IoLiTec (**bmPip**). Both ionic liquids were dried under high vacuum (80°C, 2h) before preparation of the ionic liquid solutions. All water used to prepare buffer or ionic liquid solutions was obtained by using a Milli-Q water system. The concentrations of ODNs were determined by ultraviolet absorbance measurements at 260 nm and at 90°C in order to get rid of any secondary structure of the strand and using the molecular extinction coefficient provided on idt.com.

UV Melting. Duplexes made of stoichiometric amount of complementary strands or G-quadruplexes forming strands were subjected to heat treatment at 90°C for 3 min in buffer or ionic liquid solutions, followed by cooling to RT at a rate of 0.5 °C min^{-1} . UV melting experiments were carried out on a Cary 300 UV/vis spectrophotometer equipped with a Peltier temperature control accessory. Absorbance changes at 260 nm or 295 nm versus temperature were collected at a heating rate of 0.5 °C min^{-1} . T_m values were taken as the

temperatures at which the formed duplex or G-quadruplex were half dissociated, determined by the sigmoidal melting curves.

Circular dichroism (CD) Measurements. Solutions were analyzed for CD using a Jasco CD J-810 spectrometer equipped with a 1-cm path length quartz cuvette and a Peltier temperature control accessory. Spectra from 220 to 320 nm were scanned at 1 nm intervals. Three scans for each sample were accumulated and averaged.

Conclusions

In this study we showed that the structural features of short oligonucleotide duplexes and G-quadruplexes were not modified when dissolved within two selected ionic liquids, **omim** or **bmPip**. Neither the double helix, nor the associated G-tetrad were affected by increasing ionic liquid concentration. However, the thermal stabilities of these nucleic acid structures decreased when the ionic liquids concentration was rising, excepted for the G-quadruplex **TBA** that can have a restored thermal stability by addition of small amount of KCl. The presented results paved the way and set the boundaries for the use of synthetic nucleic acid structures as catalysts for organic synthesis in solvents able to dissolve the reactants while keeping the knowledge of the catalyst structure.

Author Contributions

R. D. J. investigations; C.P., F.G. & B.G. supervision and reviewing; J.-M. E. conceptualization, supervision, original draft, writing & reviewing.

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Conflicts of interest

There are no conflicts to declare.

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