The importance of metal geometry in the recognition of G-quadruplex-DNA by metal-terpyridine complexes†

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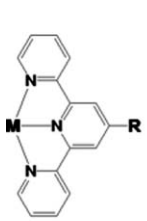
A family of terpyridine metallo-organic complexes has been designed and its recognition properties of G-quadruplex-DNA investigated. The series combines easy synthetic access and good affinity–selectivity ratio for quadruplex-DNA. Our study also highlights that the geometry of the metal center strongly governs the ability of the compounds to discriminate quadruplex from duplex-DNA.

G-quadruplex-DNA is a highly dynamic and polymorphic DNA-structure, making it a particular challenge to target in rational drug design.[1,2] Nevertheless, since its targeting *via* specific ligands is emerging as a novel anti-cancer strategy,[3] the past few years have seen considerable scientific efforts for designing and synthesizing novel and efficient G-quadruplex ligands.[1,3] Actually, an impressive number of compounds with various architectures have been developed, some of them being challenging in terms of synthesis. This is especially exemplified by telomestatin,[4] a potent G-quadruplex ligand that is accessible *via* a low-yielding multistep process[5] which dramatically restrains future pharmaceutical developments. Therefore, a current trend resides either in designing ligands that are structurally simpler[6] or in simplifying synthetic access to interesting ligands.[7]

In this line, a promising recent approach is based on the use of metallo-organic complexes. Actually, recent results reporting on the high performances of Ni(II)-salphen[8] and Mn(III) cationic porphyrins[9] gave much impetus to this approach.[10] It is worth pointing out that the use of metal complexes for G-quadruplex-DNA recognition is still under-developed in contrast to their considerable use as duplex-DNA binders.[11] In metallo-organic chemistry, the main synthetic challenge often resides in the synthesis of the ligand that surrounds the metal, but more rarely in the association of the metal with its ligand. Thus, by a careful choice of commercially available or readily accessible complexing agents, it should be possible to considerably simplify access to G-quadruplex ligands. Finally, other clear advantages of metallo-organic complexes are their defined and controllable geometry that, along with their usual crystalline nature, offers an ideal platform for sharp drug design and rationalization of structural interactions.

In this context, we designed a series of metal–terpyridine complexes, which show a good affinity and high selectivity for quadruplex-DNA. Herein, we would like to report on the synthesis and on G-quadruplex interaction properties of this series.

Terpyridine (2,2′:6′,2″ terpyridine, **tpy**) and tolyl-terpyridine (4′-(4-methylphenyl)-2,2′:6′,2″-terpyridine, **ttpy**) are tridentate nitrogen-containing ligands, widely used in coordination chemistry since they offer a planar, convergent and well-defined triple chelation.[12] For many years, a considerable number of terpyridine derivative complexes with various transition metals have been synthesized and are well-characterized in the literature.[13] They are simply obtained by mixing the ligand and the appropriate metal salt. Following this simple route, we prepared an array of complexes using four transition metals *i.e.* Cu(II), Pt(II), Zn(II) and Ru(III) and three terpyridine derivatives: **tpy**, **ttpy** and **ctpy** (Fig 1). **ctpy** is a cationic derivative obtained *via* successive bromination and amination of **ttpy** (see ESI†); this ligand was synthesized in an attempt to increase the water solubility and to afford supplementary electrostatic interactions with the DNA target, as already observed for polyammonium substituted G-quadruplex binders.[14]



R = / M =	—H	—CH$_3$	—HN—(CH$_2$)$_3$—N
no metal	tpy	ttpy	ctpy
$Cu(NO_3)_2$	Cu-tpy	Cu-ttpy	Cu-ctpy
$Pt(Cl)^+$	Pt-tpy	Pt-ttpy	Pt-ctpy
$Zn(Cl)_2$	-	Zn-ttpy	-
$Ru(Cl)_3$	-	Ru-ttpy	-

Fig. 1 Structure of terpyridines **tpy**, **ttpy** and **ctpy** and of their related metallo-organic complexes with Cu(II), Pt(II), Zn(II) and Ru(III). Full structures are given in the ESI†; Cl^- is the counter-ion for Pt-complexes.

The ability of the terpyridines and terpyridine complexes to bind G-quadruplex DNA was then evaluated *via* two biophysical assays, *i.e.* the recently reported G4-FID assay[15] and the well-established FRET-melting assay.[16] The principle of the G4-FID assay relies on the ability of a given ligand to displace the fluorescent probe thiazole orange (TO) from a quadruplex-architecture (22AG, an oligonucleotide that mimics the human telomeric repeats d[$AG_3(T_2AG_3)_3$]). This method allows the semi-quantitative analysis of ligand affinity,[15] which is expressed as the

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concentration required to displace 50% of the TO from 22AG ($^{G4}DC_{50}$). The FRET-melting assay is based on the monitoring of the stability imparted by a ligand to a fluorescently labeled quadruplex-structure (F21T, *FAM*-$G_3(T_2AG_3)_3$-*Tamra*). This stabilization, measured *via* a *fluorescence resonance energy transfer* (FRET) effect between the two fluorescent partners, is expressed as an increase in melting temperature of F21T ($\Delta T_{1/2}$) induced by the presence of the ligand.

We have firstly performed G4-FID and FRET-melting assays with the free terpyridines **tpy**, **ttpy** and **ctpy**. As depicted in Fig. 2A (white motifs), none of the three terpyridines was able to reach the 50% threshold of displacement of the fluorescent probe in the concentration range examined and were thus characterized by $^{G4}DC_{50} > 2.5$ μM. The weak quadruplex affinity of the free terpyridines was subsequently confirmed by FRET-melting assay, as the three compounds exhibit $\Delta T_{1/2}$ lower than 8 °C (Fig. 3 and Table 1). These results are nevertheless of poor significance *per se* since **tpy** and **ttpy** show a poor solubility in water. However, they can be used as references for evaluating the effect of the metal on quadruplex recognition. The expected positive impact related to the introduction of a metallic cation is based on the following assumptions: (*i*) the metallic cation may act as a "pseudo-potassium ion" lying above the central ion channel of the quadruplex,[1,2,14a] and (*ii*) the positioning of the aromatic surface around the metal could stabilize the quadruplex-structure by stacking on the external G-quartet.[8] Results from G4-FID (Fig. 2A) and FRET-melting measurements (Fig. 3) are summarized in Table 1. Cu and Pt-complexes (blue and red motifs respectively) are much more potent G-quadruplex binders than the corresponding free terpyridines (with $^{G4}DC_{50} < 0.30$ μM), with the notable exception of **tpy**-complexes ($^{G4}DC_{50} > 2.5$ and $= 1.46$ μM for **Cu-tpy** and **Pt-tpy** respectively, Fig. 2A). This trend is further confirmed by FRET-melting assay since stabilizations comprised between 10 and 16 °C are observed for complexes **Cu-ttpy**, **Cu-ctpy**, **Pt-ttpy** and **Pt-ctpy** (Fig. 3 and Table 1), while a stabilization of only ~1 °C was obtained with **Cu-tpy** and **Pt-tpy**. Altogether, these results underscore the importance of the aromatic ligand and imply that extended terpyridines **ttpy** and **ctpy** are more favorable to target quadruplex-DNA than **tpy**, even when coordinated to a metal moiety.

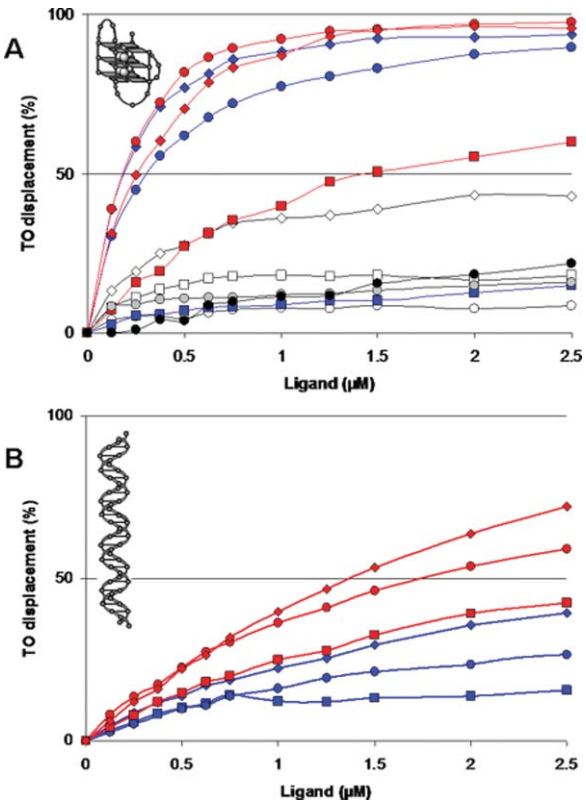

Fig. 2 G4-FID results for compounds **tpy** (□), **ttpy** (○), **ctpy** (◇), **Cu-tpy** (■), **Cu-ttpy** (●), **Cu-ctpy** (♦), **Pt-tpy** (■), **Pt-ttpy** (●), **Pt-ctpy** (♦), **Zn-ttpy** (●) and **Ru-ttpy** (●), for experiment carried out with quadruplex-DNA (22AG (0.25 μM), **A**) or duplex-DNA (ds26 (0.25 μM), **B**), with TO (0.50 and 0.75 μM for **A** and **B** respectively) in 10 mM sodium cacodylate buffer (pH 7.2) with 100 mM KCl.

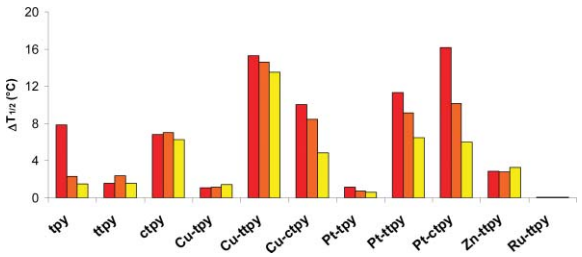

Fig. 3 FRET-melting results for terpyridines **tpy**, **ttpy** and **ctpy**, and for their related metallo-organic complexes with Cu(II), Pt(II), Zn(II) and Ru(III), at 1 μM concentration, carried out with F21T (0.2 μM) without (red bars) or with 3 μM (orange bars) or 10 μM (yellow bars) of ds26, in 10 mM lithium cacodylate (pH 7.2) with 100 mM NaCl.

In contrast, **Zn-ttpy** and **Ru-ttpy** (grey and black motifs respectively, Fig. 2A) were found to be poor TO displacers ($^{G4}DC_{50} > 2.5$ μM, Table 1) and poor quadruplex stabilizers ($\Delta T_{1/2} < 4$ °C, Fig. 3 and Table 1). The striking difference between the binding ability of Zn and Ru-complexes as compared to Pt and Cu-complexes indicate that the nature of the metal is a strong determinant for target recognition. Logically, this difference may originate in the different geometries of the complexes: actually square planar (Pt(II))[17] and square pyramidal (Cu(II))[18] complexes feature one flat face whereas metals that adopt trigonal bipyramidal (Zn(II))[19] and octahedral (Ru(III))[20] geometries lead to the steric hindrance of both faces of the complex as schematized in Fig. 4. Therefore π–π interactions with the external G-quartets should be favored in the former cases whereas they might be impeded in the latter cases.

Finally, the quadruplex *vs.* duplex-DNA selectivity of the complexes was investigated since this is a critical issue for the design of specific G-quadruplex ligands. To this end, comparative G4-FID and competitive FRET-melting assays were performed.[15,16] As previously described, the former relies on the displacement of TO from a 17bp duplex-DNA matrix (see ESI†) while the latter is based on ligand-induced stabilization of the quadruplex-DNA F21T in the presence of various amounts of a 26bp duplex-DNA competitor (ds26, see ESI†). In order to work under identical conditions (especially in terms of electrostatic interactions), G4-FID was carried out herein with ds26 as a duplex-DNA matrix (see ESI†). Comparative G4-FID was then performed with the more promising Cu and Pt-derivatives. As depicted in Fig. 2B,

Table 1 Comparative G4-FID and competitive FRET-melting assay results for terpyridines **tpy**, **ttpy** and **ctpy**, and their related metallo-organic complexes

	Comparative G4-FID			Competitive FRET $\Delta T_{1/2}$/°C[d]		
	22AG	ds26	G4-FID	+0 μM	+3 μM	+10 μM
Ligand	$^{G4}DC_{50}$/μM	$^{ds}DC_{50}$/μM	Sel.[b]	ds26[e]	ds26[e]	ds26[e]
tpy	>2.5	*n.d.*[a]	—	7.8	2.3	1.5
ttpy	>2.5	*n.d.*	—	1.6	2.4	1.6
ctpy	>2.5	*n.d.*	—	6.8	7.0	6.3
Cu-tpy	>2.5	>2.5	—	1.1	1.1	1.4
Cu-ttpy	0.30	>2.5	22[c]	15.3	14.6	13.5
Cu-ctpy	0.19	>2.5	19[c]	10.0	8.5	4.8
Pt-tpy	1.46	>2.5	2[c]	1.1	0.7	0.6
Pt-ttpy	0.18	1.74	10	11.3	9.1	6.5
Pt-ctpy	0.25	1.37	5	16.2	10.2	6.0
Zn-ttpy	>2.5	*n.d.*	—	2.9	2.8	3.3
Ru-ttpy	>2.5	*n.d.*	—	0.1	0.1	0.1

[a] *n.d.* stands for not determined. [b] G4-FID selectivity is defined as $^{ds}DC_{50}/^{G4}DC_{50}$ ratio. [c] In the case of $^{ds}DC_{50} > 2.5$ μM, the selectivity is estimated on the basis of TO displacement (%) obtained with 2.5 μM of ligand with ds26 and the concentration required with 22AG to reach the same displacement (^{G4}C): Sel. = $2.5/^{G4}C$. [d] $\Delta T_{1/2} = [T_{1/2}(\text{F21T + ligand}) - T_{1/2}(\text{F21T})]$. [e] Expressed in strand concentration. Experimental errors are estimated at ±5% for G4-FID assay.

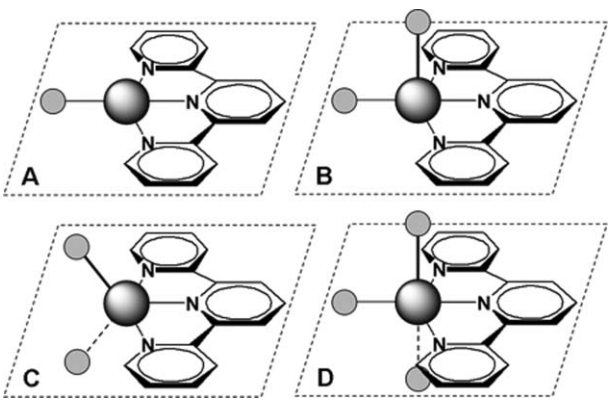

Fig. 4 Schematic representation of metallo-organic terpyridine complexes with square planar (**A**), square pyramidal (**B**), trigonal bipyramidal (**C**) and octahedral (**D**) geometry.

Pt-complexes (red motifs) appear to be better TO displacers from duplex-DNA than Cu-complexes (blue motifs). Again, this observation can be rationalized in terms of structural differences between Pt and Cu-complexes: the square planar Pt complexes exhibit two flat faces; they are consequently prone to intercalate within a duplex-DNA, as it has been extensively studied.[11] On the contrary, the square pyramidal Cu-complexes are characterized by the presence of an apical ligand (here a nitrate group) that might impede intercalation. Expectedly, in both series (Cu and Pt), the presence of an amino side-chain (**ctpy**) (diamond motifs, Fig. 2B) favors electrostatic associations with duplex-DNA, resulting in better TO displacement than **tpy** or **ttpy** complexes (square and circle motifs respectively, Fig. 2B). The ratio of $^{ds}DC_{50}$ obtained with ds26 and $^{G4}DC_{50}$ obtained with 22AG allows an evaluation of the quadruplex- over duplex-DNA selectivity (Table 1). Selectivity values of 22 and 19 were found for the two Cu-complexes **Cu-ttpy** and **Cu-ctpy**, whereas values of 10 and 5 were obtained for the Pt analogues **Pt-ttpy** and **Pt-ctpy** underlining the critical impact of both the metal geometry and the nature of the ligand surrounding the metal center. It is worth noting that similar results were obtained when comparative G4-FID was classically performed with 17bp as a duplex-DNA matrix (see ESI†). These results were subsequently confirmed by competitive FRET-melting assay. As depicted in Fig. 3, upon competition with ds26 (3 μM (15-fold excess), orange bars), the stabilization is highly maintained for **Cu-ttpy**, **Cu-cttpy** and **Pt-ttpy** (95, 84 and 80% respectively), while this effect is more modest in the case of **Pt-ctpy** (63%). At higher concentration in duplex-DNA (10 μM (50-fold excess), yellow bars), **Cu-ttpy** appears clearly the most resistant compound.

To gain preliminary insights into the putative binding mode of **Cu-ttpy** with quadruplex-DNA, given that this complex represents the best compromise in terms of quadruplex stabilization and selectivity, X-ray analysis of **Cu-ttpy** was performed.[21] As depicted in Fig. 5, the structure that has been solved ($P2_1/C$ space group‡) confirmed the pseudo-square pyramidal geometry of **Cu-ttpy**, with a deviation of 20.4° of the Cu-O(2) bond, as compared to the plan defined by the terpyridine unit. The Cu atom appears exactly in the N(1)–N(2)–N(3) plan. The apical nitrate group appears to be disordered; the occupancy factor was fixed in the ratio 50 : 50 for the N(4) atom and two oxygen atoms (O(5) and O(6)), O(4) being refined with an occupancy factor of 1. O(2)–Cu–O(5a) and O(2)–Cu–O(6b) angles have been determined as 102.3 and 76.4° respectively, which represents an average angle of 89.3°. As already reported in the case of the Cu(terpyridine)Cl_2 structure,[18] the central metal adopts an 'apically elongated' square pyramidal coordination, since apical nitrate groups appear more loosely bound to the metal, the Cu–O(5a) and Cu–O(6b) distances being greater than the Cu–O(2) one (2.15 and 2.28 *vs.* 1.99 Å respectively). Thus, the structure of **Cu-ttpy** indicates that the complex could fit nicely on quadruplex-DNA given that one of its faces is planar and thus fully accessible for π-stacking on the top

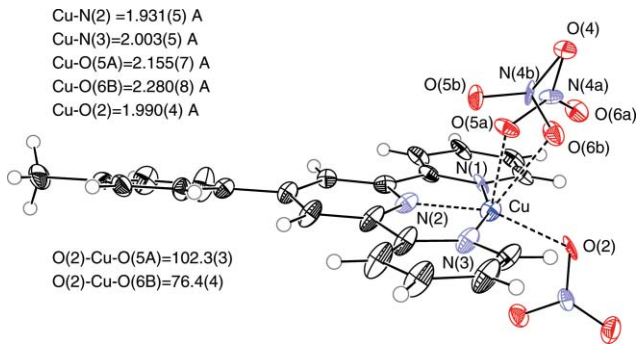

Fig. 5 Ortep view of the crystal structure of the [**Cu-ttpy**][$(NO_3)_2$] complex with ellipsoids depicted at the 50% probability level (H-atoms are shown as small spheres of arbitrary radii) that shows a disordered apical nitrate group (see text for explanation), and selected bond lengths and angles.

G-quartet. Additionally, the presence of the apical nitrate ligand on the other face should prevent intercalation within base pairs of duplex-DNA.

In conclusion, the series of terpyridine–metal complexes presented herein represent an interesting compromise between easy synthetic access and efficiency in terms of quadruplex-recognition. In particular, complex **Cu-ttpy** exhibits remarkable features: its synthesis is a one-step process from commercially available materials (tolyl-terpyridine and $Cu(NO_3)_2$), and it displays strong affinity and selectivity for quadruplex-DNA. Its pseudo-square pyramidal structure, as shown by X-ray analysis, offers unique means for rationalizing these results: (*i*) a planar aromatic face to stabilize the quadruplex-structure *via* π-stacking interactions, (*ii*) the central position of a Cu^{2+} metal to lie directly above the central ion channel of the quadruplex, (*iii*) a pyramidal shape to impede intercalation within duplex-DNA, and (*iv*) an imparted high polarization of the metal–ligand bond to favor an electrostatic interaction with negatively charged DNA. Our study also points out the critical influence of the presence of a metal, the nature of the chelating agent around the metal center and the complex geometry imparted by the metal. Further studies are currently being undertaken to benefit from the selective recognition of quadruplex-DNA by our metallo-organic complexes, in combination with their potential redox activity (Cu(II)) and covalent linking properties (Pt(II)) towards DNA.[22] Results will be reported in due time.

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