Journal of Inorganic Biochemistry 143 (2015) 56–63

Contents lists available at ScienceDirect

Journal of Inorganic Biochemistry

journal homepage: www.elsevier.com/locate/jinorgbio

Effect of ancillary ligands on the interaction of ruthenium(II) complexes with the triplex RNA poly(U)·poly(A)*poly(U)

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ARTICLE INFO

Article history:
Received 5 September 2014
Received in revised form 3 December 2014
Accepted 3 December 2014
Available online 11 December 2014

Keywords:
Ru(II) complexes
Triplex RNA
Interaction
Stabilization

ABSTRACT

Two new Ru(II) complexes with 1,8-naphthalimide group, $[Ru(phen)_2(pnip)]^{2+}$ (Ru**1**; phen = 1,10-phenanthroline, pnip = 2-[*N*-(*p*-phenyl)-1,8-napthalimide]imidazo[4′,5′-*f*][1,10]phenanthroline) and $[Ru(bpy)_2(pnip)]^{2+}$ (Ru**2**; bpy = 2,2′-bipyridine), have been synthesized and characterized. The interactions of Ru**1** and Ru**2** with the triplex RNA poly(U)•poly(A)*poly(U) (where • denotes the Watson–Crick base pairing and * denotes the Hoogsteen base pairing) were studied by various biophysical. Electronic spectra established that the binding affinity for Ru**1** was greater than that for Ru**2**. Fluorescence and viscosity studies gave convincing evidence for a true intercalative binding of both complexes with the RNA triplex. UV melting studies confirmed that the two complexes could stabilize the triplex, whereas the effects of the two complexes on the stability of the Hoogsteen base-paired strand ploy(U) and the Watson–Crick base-paired duplex poly(U)•poly(A) of the triplex were different. In the case of Ru**1**, the increase of the thermal stability of the Hoogsteen base-paired strand was stronger than that of the Watson–Crick base-paired duplex. However, an opposite effect was observed in the case of Ru**2**. Circular dichroic studies suggested that the RNA triplex undergoes a conformational transition in the presence of Ru**1**, whereas the helicity of the RNA triplex still remains A-type in the presence of Ru**2**. The main results obtained here further advance our knowledge on the interaction of RNA triple-stranded structures with metal complexes, particularly ruthenium(II) complexes.

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1. Introduction

Nucleic acid triple-stranded structures, also called triplexes, are complexes of three oligonucleotide strands made from either RNA or DNA [1–3]. Over the last decades, there is renewed interest in investigating triplex nucleic acids because triplexes may be implicated in a range of cellular functions, such as transcriptional regulation, post-transcriptional RNA processing and modification of chromatin [4,5]. However, due to the Hoogsteen base pairing, the stability of triplexes is much lower than that of the corresponding duplex, which hinders the practical applications of triplexes [6,7]. In this regard, small molecules able to recognize, bind and stabilize the specific sequences of the triple helical nucleic acid structures are of very importance.

In recent years, many natural and synthetic compounds able to enhance the stability of triplexes have been reported [8–10]. In contrast to DNA triplexes, investigations of small molecules effect on the stabilization of RNA triplexes at present are mainly limited to organic compounds [11–13] and, to a far lesser extent, on metal complexes [14–16]. Previous reports indicate that the stabilization of RNA triplexes can be achieved by the action of intercalators [17,18], in particular when covalently linked to the third strand [19]. However, intercalators not covalently linked can either stabilize or destabilize RNA triplexes [20,21]. For example, the melting experiments reveal that proflavine (PR) and its platinum(II)-proflavine complex PtPR [14] (Fig. 1) and ethidium [22] tend to destabilize the triplex, whereas berberine analogs [12] are able to strongly stabilize the Hoogsteen base-paired third strand of the triplex by intercalation. Interestingly, some alkaloids stabilize the Hoogsteen base-paired third strand of the triplex almost without affecting the stability of the duplex, such as berberine, palmatine and coralyne [17]. These studies reveal that the binding processes and modes effect on the stability of RNA triplexes are more complicated than previously thought. Recently, we reported the recognition of triplex RNA structures by Ru(II) complex, $[Ru(phen)_2(mdpz)]^{2+}$ [15]. The results indicate that this intercalator can enhance the stability of the triplex RNA poly(U)•poly(A)*poly(U) and act as a first emission 'light switch' for this triplex.

It is well established that Ru(II) polypyridyl complexes, due to a combination of easily constructed rigid chiral structures spanning all three spatial dimensions and a rich photophysical repertoire, prominent DNA binding properties and promising biological activity, have attracted considerable attentions in recent years [23–25]. However, the interactions of Ru(II) polypyridyl complexes between RNA triplexes

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http://dx.doi.org/10.1016/j.jinorgbio.2014.12.007
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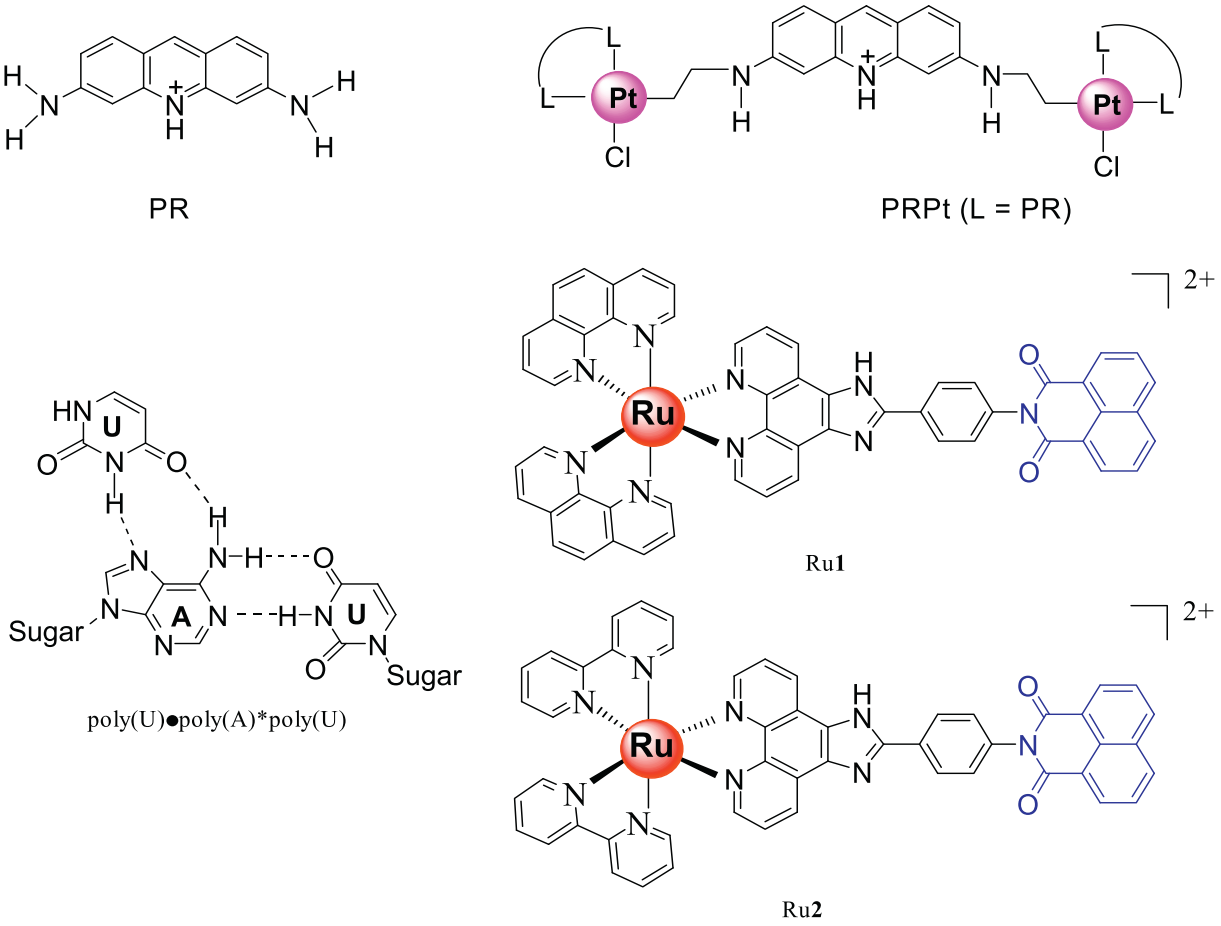

Fig. 1. Chemical structures of PR, PtPR, Ru**1**, Ru**2** and the base pairing scheme in poly(U)•poly(A)*poly(U) (symbols • and * represent Watson–Crick and Hoogsteen base pairing).

have attracted a spot of front attention [14,15]. To more clearly evaluate and understand the factors effect on the stability of RNA triplexes, further studies using Ru(II) polypyridyl complexes with different shapes and electronic properties are quite significant and necessary.

In addition, we note that 1,8-naphthalimide and its derivatives have received significant attention during the past two decades because of their excellent photophysical properties and defined structure [26–28]. Furthermore, these compounds are known to be effective binders and photoreactive reagents for DNA [29,30]. With this in mind, a novel polypyridyl ligand with 1,8-naphthalimide group and its Ru(II) complexes (Fig. 1), $[Ru(phen)_2(pnip)]^{2+}$ (Ru**1**; phen = 1,10-phenanthroline, pnip = 2-[*N*-(*p*-phenyl)-1,8-napthalimide]imidazo[4',5'-*f*][1,10]phenanthroline) and $[Ru(bpy)_2(pnip)]^{2+}$ (Ru**2**; bpy = 2,2′-bipyridine), have been synthesized and characterized. The interactions of the two Ru(II) complexes with the RNA triplex poly(U)•poly(A)*poly(U) (where • denotes the Watson–Crick base pairing and * denotes the Hoogsteen base pairing; Fig. 1) was investigated by various biophysical techniques. To the best of our knowledge, Ru**1** and Ru**2** are the first examples of Ru(II) polypyridyl complexes with 1,8-naphthalimide group as triplex RNA binders.

2. Experimental sections

2.1. Materials

1,10-Phenanthroline-5,6-dione [31], 2-(4-aminophenyl)imidazo[4,5-*f*][1,10]phenanthroline (paip) [32], *cis*-$[Ru(phen)_2Cl_2]\cdot 2H_2O$, and *cis*-$[Ru(bpy)_2Cl_2]\cdot 2H_2O$ [33] were prepared according to literature procedures. Polynucleotide samples of double-stranded poly(A)•poly(U) and single-stranded poly(U) were obtained from Sigma-Aldrich Corporation (St. Louis, MO, USA) and were used as received. The RNA triplex poly(U)·poly(A)*poly(U) was prepared as reported earlier [15]. The concentration of poly(U)·poly(A)*poly(U) was determined optically using molar absorption coefficient, ε (M^{-1} cm^{-1}) reported in the literature [34–36]. All titration experiments were conducted at 20 °C in pH 7.0 phosphate buffer (6 mmol/L Na_2HPO_4, 2 mmol/L NaH_2PO_4, 1 mmol/L Na_2EDTA, 19 mmol/L NaC1).

2.2. Physical measurement

Microanalyses (C, H and N) were carried out on a Perkin-Elmer 240Q elemental analyzer. ^1H NMR spectra were recorded on an Avance-400 spectrometer with d_6-DMSO as solvent at room temperature and TMS (tetramethylsilane) as the internal standard. Mass Spectrometer was performed on an Autoflex III™ MALDI-TOF-MS (matrix assisted laser desorption ionization time-of-flight mass spectrometry) (Bruker) using DMSO as the mobile phase. UV-visible (UV-vis) spectra were recorded on a Perkin-Elmer Lambda-25 spectrophotometer, and emission spectra were recorded on a Perkin-Elmer LS-55 luminescence spectrometer at room temperature. Circular dichroism (CD) spectra were measured on a JASCO-810 spectropolarimeter.

2.3. Synthesis of the ligand pnip

A mixture of paip (168 mg, 0.54 mmol), 1,8-naphthalic anhydride (106 mg, 0.54 mmol), and acetic acid (HAc, 15 mL) was heated at 120 °C for 5 h. The cooled solution was diluted with H_2O and neutralized with concentrated $NH_3\cdot H_2O$. The brown precipitate was collected and purified by chromatography on a neutral alumina column with ethanol-toluene (5:1, v/v) as the eluant to give the title compound as

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