Inorganic Chemistry Communications 36 (2013) 130–132

Contents lists available at ScienceDirect

Inorganic Chemistry Communications

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

Synthesis of enantiomers of mononuclear Ru(II) complexes with 10,13-diaryl substituted dppz ligands

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ARTICLE INFO

Article history:
Received 21 June 2013
Accepted 22 August 2013
Available online 4 September 2013

Keywords:
Ruthenium complexes
dppz
Enantiomer
10,13-Diaryl

ABSTRACT

An array of enantiomerically pure mononuclcear $[Ru(bpy)_2(dppz)]^{2+}$ derivatives with 10,13-diaryl substituted dppz ligand has been synthesized and characterized (bpy = bipyridine, dppz = pyrido-[3,2-a:2′,3′-c]phenazine). These new complexes exhibit substantially similar absorption spectra, resembling the parent complex $[Ru(bpy)_2(dppz)]^{2+}$, and the enantiomerically pure analogues show the similar CD spectra in buffer solution despite the structural difference.

Transition metal complexes that possess selective DNA binding properties are an attractive and substantial significant subject by virtue of their potential use as DNA conformational probes, potential drug leads for chemotherapy, and cellular imaging agents [1–3]. Particularly, Ru(II) polypyridyl complexes have been intensively synthesized and studied due to their tuneable photophysical and photochemical properties by changing the ligands [4,5]. Moreover, complexes (such as $[Ru(bpy)_2(dppz)]^{2+}$ and its derivatives) that function as excellent DNA "light switch" i.e., exhibiting nonluminescent in aqueous solution but intensely luminescent upon binding with DNA [6,7], hold special potential as DNA-drug or biological imaging agents. Strong DNA affinity and slow dissociation kinetics are considered to be especially important for antitumor application [8], which is proved by the cytotoxic natural product nogalamycin. The majority of synthetic intercalators reported in the literature have dissociation rate constants in the order of 10^{1}–10^{-1} s^{-1} [9–11]. While an earlier reported semi-rigid dimer $[\mu\text{-bidppz(phen)}_4Ru_2]^{4+}$ (bidppz = dipyrido-[3,2-a:2′,3′-c]phenazinyl), in which a single bond connects the two dppz moieties, exhibits even slower dissociation with rate constants in the range of 10^{-3}–10^{-4} s^{-1}, which is similar to that observed for nogalamycin [8,12]. In support of this finding, an array of binuclear ruthenium complexes with varying auxiliary and bridging ligands has been synthesized to elucidate how complex structure affects the dissociation kinetics from DNA [13–15]. Although kinetically slow and highly selective for long AT stretches, the binuclear complex $[\mu\text{-bidppz(phen)}_4Ru_2]^{4+}$ and its congeners have the drawback of being highly charged molecules with high molecular weights, which are disadvantageous properties for potential drugs. It thus appears motivated to also study smaller systems to find the minimal requirements for selective intercalation. As starting minimal systems, we earlier synthesized several mononuclear ruthenium with different quaternary ammonium substituents in the 11-position of the dppz ligand and found dissociation rate to be reduced compared to the mononuclear unsubstituted complex, even though faster than $[\mu\text{-bidppz(phen)}_4Ru_2]^{4+}$ [16]. Just as described above, the DNA threading intercalators about ruthenium complex previously reported were only the complexes containing a dppz ligand with substituents in the 11-position. How about substitution in the 10-position? We hypothesize that introduction of large substituents perpendicular to the dppz long axis could impair intercalation of the dppz ligand due to steric interactions with the DNA backbone. Inspired by this idea, we have recently synthesized two new 10,13-diaryl substituted dipyridophenazine ruthenium complexes and found that small changes in the structure of the substituents has an extremely intense influence on DNA binding properties [17]. The di(2-thienyl) substituted complex displays slow dissociation kinetics characteristic for threading intercalation, while its diphenyl substituted analogue seems to bind DNA by partial intercalation of one phenyl substituent resulting in faster dissociation. With the view of developing this area even further, we have set out to generate novel 10, 13-position substituted dppz ligands that could make us understand deeply how structures affect binding properties of ruthenium complexes. Herein, in this work three new mononuclear $[Ru(bpy)_2(dppz)]^{2+}$ derivatives with 10,13-diaryl substituted dppz ligands and their corresponding enantiomers have been synthesized (Ru-T, Ru-BT and Ru-BF, Scheme 1). To assess the effect of auxillary ligand on binding property of complex, the complex $[(bpy)_2Ru(dppz)]^{2+}$ derivative with 10,13-di(2-thienyl) substituted dppz ligand (Ru-T) was prepared in comparison to previously reported $[(phen)_2Ru(dppz)]^{2+}$ analogue. To investigate how the threading intercalation kinetics may depend on the size

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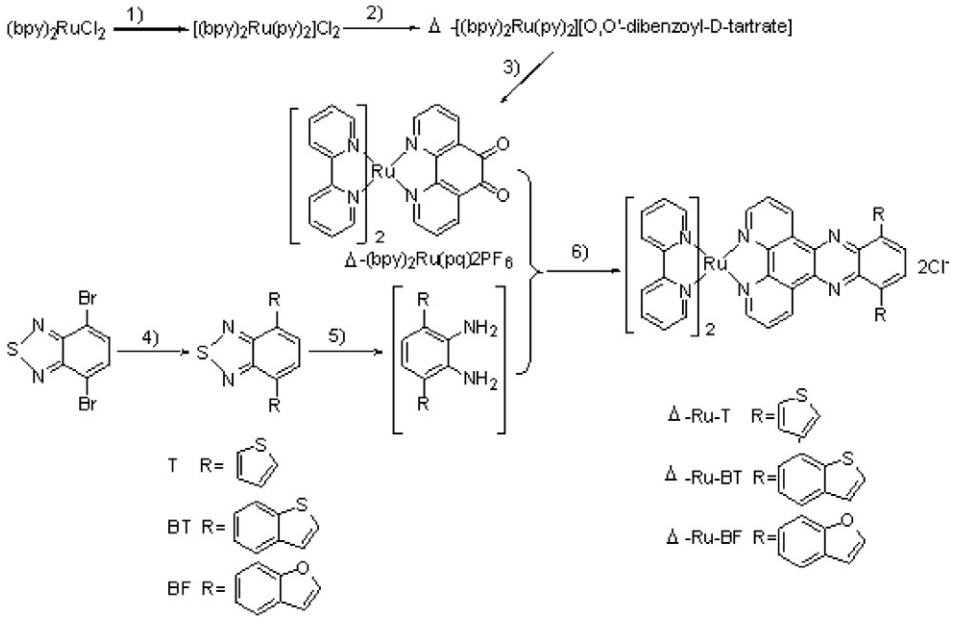
1387-7003/$ – see front matter.
http://dx.doi.org/10.1016/j.inoche.2013.08.016



Scheme 1. The synthetic routes of Δ-enantiomers of three new $[(bpy)_2Ru(dppz)]^{2+}$ derivatives. Reaction conditions: 1) pyridine, MeOH, H_2O, reflux; 2) disodium (+)-O,O′-dibenzoyl-D-tartrate; 3) (i) 1,10-phenanthroline-5,6-dione, ethylene glycol:H_2O (9:1), 120 °C, (ii) H_2O, NH_4PF_6; 4) boric acid analogues, $Pd(PPh_3)_4$, K_2CO_3, dioxane/H_2O (4/1), reflux; 5) $NaBH_4$, $CoCl_2$, EtOH, reflux; 6) CH_3CN, HOAc, reflux. Bpy = 2,2′-bipyridine, dppz = pyrido-[3,2-a:2′,3′-c]phenazine, Ph = phenyl.

of the substituent on the dppz ligand, we designed Ru-BT, which has 2-benzo[b]thienyl substituents in 10, 13-position respectively on the dppz ligand, and compared to Ru-T. The complex Ru-BF, which correspondingly has 2-benzo[b]furanyl substituents on the dppz ligand, was synthesized to explore the influence of van der Waals radius of hetero atom on the aryl-substituent or the electron distribution on the binding properties of ruthenium complexes in contrast with Ru-BT.

As shown in Scheme 1, Δ-enantiomer of each new complex was prepared by the condensation reaction of optically pure Δ-$[(bpy)_2Ru(pq)]\cdot 2PF_6$ with an excess of the appropriate 3,6-diaryl substituted benzene-1,2-diamine under boiling water in CH_3CN in the presence of a drop of acetic acid. The latter 3,6-diaryl substituted benzene-1,2-diamines were derived from reductive removal of the sulfur of 4,7-diaryl-2,1,3-benzothiadiazoles by $NaBH_4$ in ethanol with $CoCl_2$ as catalyst. It is noting that in this work 3,6-diaryl substituted benzene-1,2-diamines is utilized directly in the next reaction without further purification after evaporation of extraction solvent due to their extreme unstability in air. 4,7-Position substituted benzothiadiazole derivatives (T, BT, BF) were prepared by Suzuki-coupling reaction of 4,7-dibromo-benzothiadiazole and the corresponding aryl boronic acid analogues in the mixture of dioxane and water (4:1) in the presence of $Pd(PPh_3)_4$ and K_2CO_3. The optically pure Δ-$[(bpy)_2Ru(pq)]\cdot 2PF_6$ was achieved by the reaction of 1,10-phenanthroline-5,6-dione (pq) and Δ-$[(bpy)_2Ru(py)_2][O,O'$-dibenzoyl-D-tartrate$]\cdot 12H_2O$, followed by exchanging the tartrate counterions with PF_6^- according to the method of Ji et al. [18], and the latter complex was prepared by treating the racemic $(bpy)_2Ru(py)_2Cl_2$ with disodium (+)[O,O′-dibenzoyl-D-tartrate], followed by crystallization. The complex $(bpy)_2Ru(py)_2Cl_2$ was easily prepared by the reaction of $Ru(bpy)_2Cl_2$ and pyridine in methanol under reflux. According to a method same to the preparation of Δ-enantiomer of each new complex, Λ-enantiomer of analogues was obtained by replacing Δ-$[(bpy)_2Ru(pq)]\cdot 2PF_6$ with Λ-$[(bpy)_2Ru(pq)]\cdot 2PF_6$, and the latter complex was achieved by using dibenzoyl-L-tartrate instead of dibenzoyl-D-tartrate. Three new complexes were fully characterised by the ^1H NMR, TOF-MS and element analysis (see supporting information).

Despite the structural difference among three new complexes, the shapes of their absorption spectra in buffer solution are substantially similar (Fig. 1), where the intense band at 286 nm was characteristic of π–π* transitions of the two auxiliary bipyridines while the less intense bands at 245 nm and 450 nm were characteristic of MLCT transitions from the Ru (II) center. The transitions at 315 nm are attributed to π–π* transitions of diaryl dppz. Obviously, for three new complexes, the band at 375 nm attributed to π–π* transitions of the dppz ligand were seen to be a slight red shift in comparison to that of the parent complex $[(bpy)_2Ru(dppz)]^{2+}$, consequently overlapped with MLCT band. The similar absorption intensity at 315 nm could be found in Ru-T and Ru-BT. However, it is markedly lower both in Ru-T and Ru-BT in comparison with Ru-BF. The hypochromicity observed for the 315 nm band in Ru-T and Ru-BT is maybe due to the effect of aggregation, possibly by π-stacking of the complex in buffer solution [17].

The CD spectra of the enantiomerically pure complexes Δ-Ru-T and Λ-Ru-T exhibit the intense band at 294 nm, which is typical of π–π* exciton coupling of the two bipyridines, and the expected MLCT band at

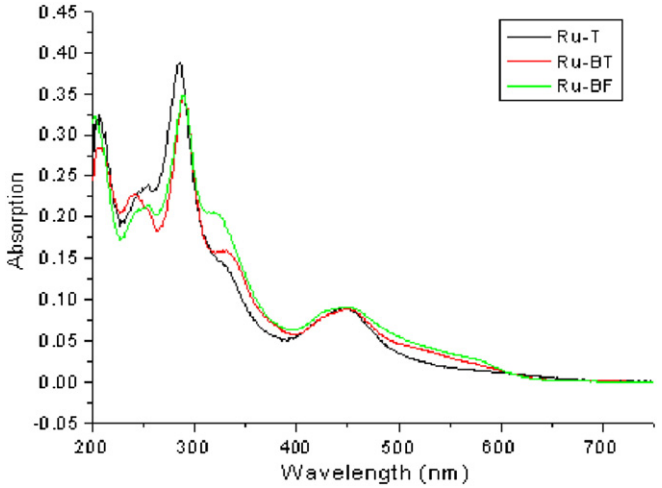


Fig. 1. UV–vis absorption spectra of three new $[(bpy)_2Ru(dppz)]^{2+}$ derivatives (38 μM) in buffer solution (150 mM NaCl, 1 mM cacodylate, pH 7.0).

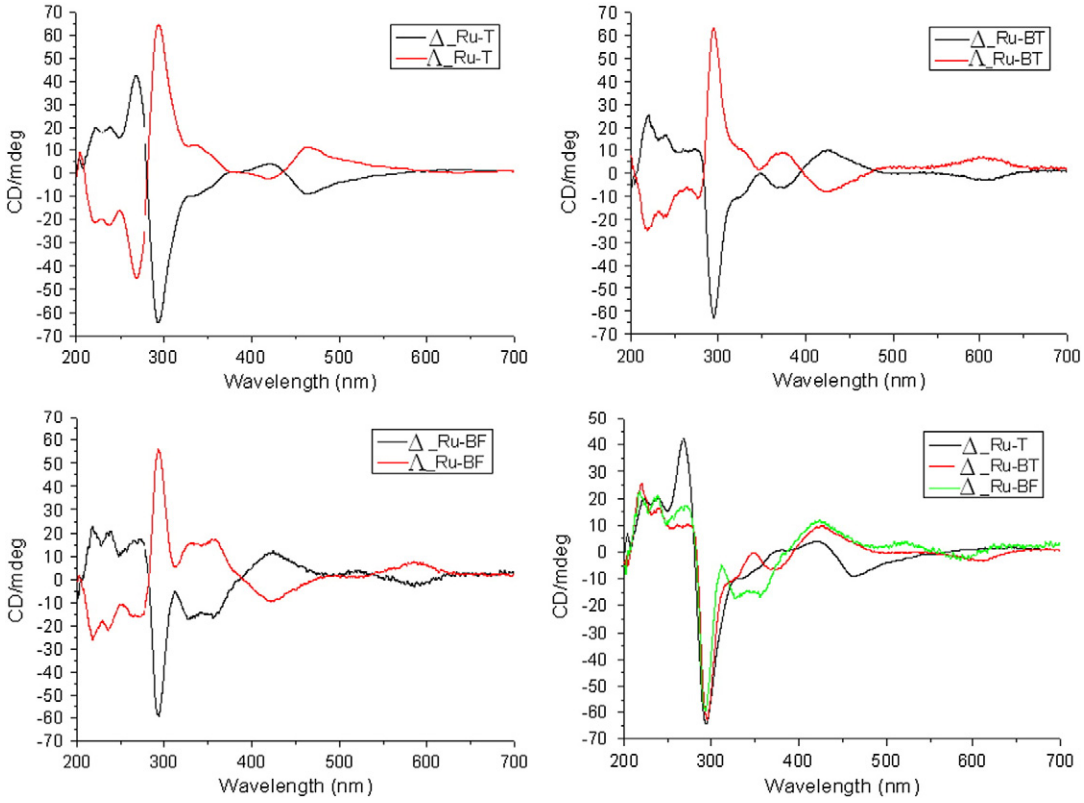


Fig. 2. CD spectra of the enantiomerically pure $[(bpy)_2Ru(dppz)]^{2+}$ derivatives (35–38 μM) in buffer solution (150 mM NaCl, 1 mM cacodylate, pH 7.0).

400–500 nm (Fig. 2). These similar absorption bands can also be observed in the other two enantiomerically pure analogues. In comparison to Ru-T, Ru-BT and Ru-BF show broader MLCT bands above 600 nm, which is in support of the observation in the MLCT band in UV–vis spectra of the analogues. The small varying intensity at 310–400 nm was also found due to the structural slight difference among three complexes.

In conclusion, the enantiomerically pure mononuclear $[(bpy)_2Ru(dppz)]^{2+}$ derivatives with 10,13-diaryl substituted dppz ligands have been synthesized and characterized. Three new complexes show the substantially similar UV–vis absorption spectra, which are characteristic for the parent complex $[(bpy)_2Ru(dppz)]^{2+}$, and the similar CD spectra could also been found for the enantiomer of analogues. Further investigations of the interaction kinetics of new complexes with DNA are in progress, which will provide a new strategy for development of DNA binding drugs with slow dissociation kinetics.

Acknowledgments

This work was financially supported by Scientific Research Common Program of Beijing Municipal Commission of Education (SQKM201210025006), Funding Project for Academic Human Resources Development in Institutions of Higher Learning under the Jurisdiction of Beijing Municipality (PHR201007114) and the Natural Science Foundation of Capital Medical University in China (2010ZR06).

Appendix A. Supplementary material

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.inoche.2013.08.016.

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