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Novel metal-coordinated 1,10-phenanthroline ligands functionalized with a lactam or imide

Hao Yao [a], Lilu Zhang [b], Yanqiu Peng [a], Patrick J. Carroll [c], Lei Gong [a,*], Eric Meggers [a,b,*]

[a] Key Laboratory for Chemical Biology of Fujian Province and Department of Chemical Biology, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, People's Republic of China
[b] Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Straße, 35043 Marburg, Germany
[c] University of Pennsylvania, Department of Chemistry, 231 S. 34th Street, Philadelphia, PA 19104, USA

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ABSTRACT

Metal-coordinated "γ-lactam-capped" and "imide-capped" 1,10-phenanthroline ligands are reported. Whereas the imide-functionalized ligand 1,10-phenanthroline-5,6-carboximide could not be obtained as a free ligand, probably due to its extremely low solubility, we developed a protocol to first introduce the more soluble 1,10-phenanthrolino[5,6-c]pyrrole in the ligand sphere of cyclometalated iridium(III) complexes, followed by the oxidation of the pyrrole moiety to a maleimide utilizing a peroxybenzoic acid. The hydrogen bond donor–acceptor properties of the new ligands should make them suitable building blocks for the design of metal-based protein binders. Furthermore, we unexpectedly found that bis-cyclometalated iridium(III) complexes coordinated to 1,10-phenanthroline-5,6-carboximide display luminescence properties that are dependent on the protonation state of the maleimide NH group. It can be envisioned to exploit this behavior for the real-time monitoring of hydrogen bonding interactions in biological systems.

1. Introduction

The last several years have witnessed an increasing interest towards the utilization of metal complexes as inert templates for the design of protein binders (e.g. enzyme inhibitors) for applications in drug design and as molecular probes in chemical biology [1,2]. For example, Spencer and coworkers developed ferrocene-based inhibitors for protein kinases [3] and histone deacetylases [4]. Poulsen and co-workers demonstrated the usefulness of metallocenes for the inhibition of carbonic anhydrases [5], whereas Alberto and coworkers reported technetium(I) and rhenium(I) half-sandwich complexes as selective inhibitors of human carbonic anhydrase IX [6]. Jaouen's group recently disclosed organometallic derivatives of non-steroidal antiandrogen drugs [7], Metzler-Nolte reported arene-$Cr(CO)_3$ and ferrocene analogues of the antibiotic platensimycin which are designed to bind to the bacterial enzyme FabF [8], Ang and coworkers designed selective ruthenium half-sandwich inhibitors of protein tyrosine phosphatase 1B [9], and Pastorin, Ang, and coworkers reported organoruthenium antagonists of the human A_3 adenosine receptor [10]. Recently, Oliveira, Correira, and coworkers found a rhenium(I) complex as a low micromolar inhibitor of inducible nitric oxide synthase [11], whereas Che and coworker reported stable gold(III) porphyrin complexes which target the Wnt/β-catenin signaling pathway potentially through histone deacetylase inhibition, and an unusual ruthenium-oxo oxalate cluster as highly potent, single digit nanomolar HIV-1 reverse transcriptase inhibitor [12,13]. Finally, in a series of interesting studies [14], Ma and coworkers designed kinetically inert cyclometalated octahedral iridium(III) complexes as inhibitors of the tumor necrosis factor-α [15] and kinetically inert cyclometalated rhodium(III) complexes as inhibitors of Janus kinase 2 [16], the NEDD8-activating enzyme [17], and potential modulators of the mTOR-FKBP12 [18] interaction.

Our laboratory contributed to this area of research by demonstrating that substitutionally inert ruthenium(II) [19], osmium(II) [20], rhodium(III) [21], and iridium(III) [19,22] complexes can serve as highly selective and potent ATP-competitive inhibitors for protein kinases. Our previous design was predominantly based on a staurosporine-inspired metallo-pyridocarbazole scaffold (Fig. 1), in which a maleimide moiety forms one or two key hydrogen bonds with the hinge region of the ATP binding site, the

* Corresponding authors. Address: Key Laboratory for Chemical Biology of Fujian Province and Department of Chemical Biology, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, People's Republic of China. Tel.: +86 5922188086.
E-mail addresses: gongl@xmu.edu.cn (L. Gong), meggers@chemie.uni-marburg.de (E. Meggers).

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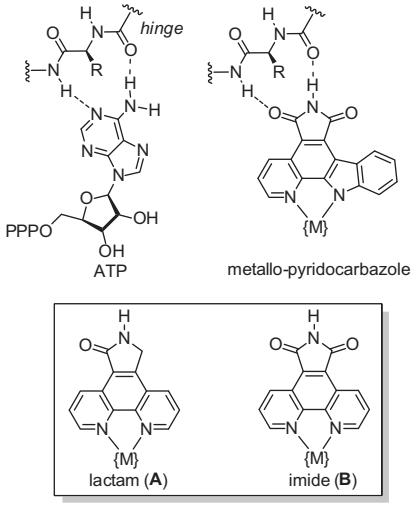
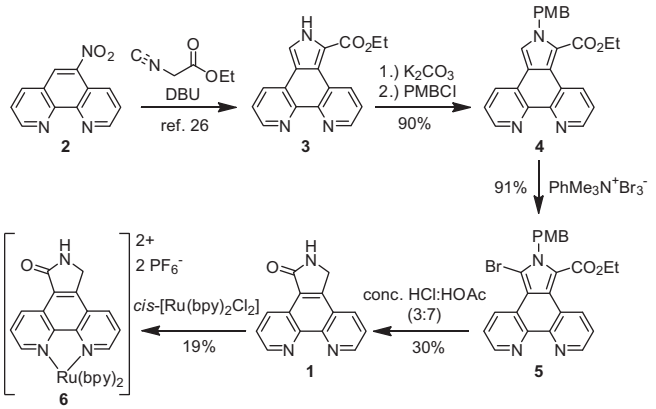


Fig. 1. Previous and new design (**A** and **B**) for metal complexes with hydrogen-bond donor–acceptor properties. Shown are the typical ATP-mimicking interactions of the previously developed metallo-pyridocarbazole scaffold with the hinge region of the ATP-binding site of protein kinases.



Scheme 1. Synthesis of 1,10-phenanthrolino[5,6-c]-1,5-dihydropyrrol-2-one ligand **1** and its coordination to ruthenium(II).

pyridocarbazole heterocycle occupies the hydrophobic adenine binding cleft, and the remaining metal complex fragment can interact within the ribose-triphosphate binding region [23]. Although this metallo-pyridocarbazole scaffold turned out to be highly successful, we recently became interested in designing structurally distinguished 1,10-phenanthroline-based ligands with related hydrogen-donor–acceptor properties for three reasons: first, the synthesis of the pyridocarbazole ligand is lengthy and includes one inconvenient and difficult to scale photochemical step [24]. Second, with the goal in mind to develop luminescent enzyme inhibitors that can be used for imaging purposes, we wanted to avoid indole moieties since they lead to an efficient quenching of the excited state, presumably by ligand-to-metal charge transfer. Third, the prevalence and importance of polypyridyl ligands in transition metal coordination chemistry renders the design of related hydrogen bond donor–acceptor chelators an attractive endeavor.

In this study, we now introduce simple but novel metal-coordinated "γ-lactam-capped" and "imide-capped" 1,10-phenanthroline ligands [25]. We disclose their synthesis and metal coordination, and we report the unexpected pH-dependent luminescence properties of cyclometalated iridium(III) complexes bearing 1,10-phenanthroline-5,6-carboximide.

2. Results and discussion

2.1. Synthesis and coordination of 1,10-phenanthrolino[5,6-c]-1,5-dihydropyrrol-2-one

The "γ-lactam-capped" phenanthroline ligand **1** was synthesized from readily available 5-nitrophenanthroline **2** as shown in Scheme 1. Accordingly, the reaction of **2** with α-nitriloethylacetate in presence of DBU yielded pyrrolophenanthroline **3** as described.[26] Subsequent protection with a p-methoxybenzyl group (PMB), mainly in order to improve solubility, yielded **4** in 90% yield. Regioselective bromination of the α-position of the pyrrole moiety with $PhMe_3N^+Br_3^-$ then provided the brominated product **5** in 91% yield.[27] In the key reaction of this synthesis, compound **5** was now transformed into the desired 1,10-phenanthrolino-5,6-pyrrolidinone **1** by just refluxing **5** in a mixture of HCl and acetic acid for 24 h (30%). It is noteworthy that this one-pot reaction includes four reaction steps: an acid-catalyzed ester cleavage followed by an acid-catalyzed decarboxylation, the acid catalyzed PMB-deprotection, and the hydrolysis of the bromide followed by a tautomerization to the pyrrolinone form. The reaction sequence can be scaled to yield gram quantities of **1**. However, it has to be noted that lactam **1** displays low solubility in all common solvents and is easily oxidized under air.

In order to investigate the chelation properties of the novel "lactam-capped" 1,10-phenanthroline, we introduced ligand **1** into a ruthenium complex. Accordingly, the reaction of **1** with *cis*-$[Ru(bpy)_2Cl_2]$ (bpy = 2,2′-bipyridine) yielded ruthenium complex **6** in 19% yield (Scheme 1). The low yield, at least in part, can be attributed to a limited stability of the complex towards oxidation and made it necessary to perform the silica gel chromatography under careful exclusion of air. A crystal structure of this compound is shown in Fig. 2. The bidentate coordinated ligand **1** is completely planar and the ruthenium–nitrogen bond lengths of the phenanthroline ligand **1** are 2.076 Å (Ru1–N2) and 2.060 Å (Ru1–N16), which is typical for bipyridine and phenanthroline type coordinative bonds. For comparison, the ruthenium-nitrogen bond lengths to the two 2,2′-bipyridines are between 2.059 and 2.066 Å. Thus, ligand **1** is a very strong chelating ligand which is not significantly compromised by the electron-withdrawing nature of the lactam moiety. In addition, the C7–C11 bond of the lactam moiety of coordinated **1** displays a length of 1.347 Å and has therefore almost

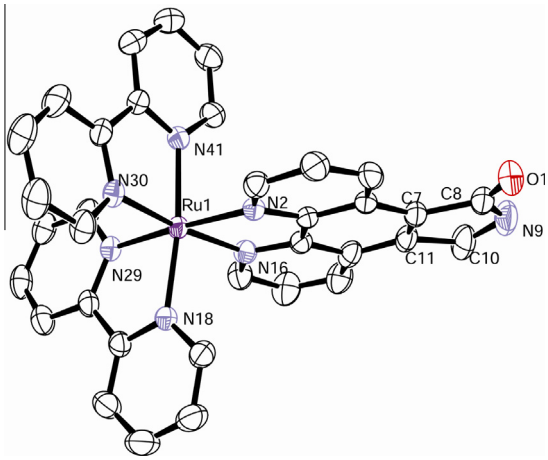


Fig. 2. Crystal structure of ruthenium(II) complex **6**. ORTEP drawing with 50% probability thermal ellipsoids. The hexafluorophosphate counterions are omitted for clarity.