Journal of Organometallic Chemistry 787 (2015) 44–50

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

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

Delivery of porphin to cancer cells by organometallic Rh(III) and Ir(III) metalla-cages

Gajendra Gupta [a], Emmanuel Denoyelle-Di-Muro [a], Jean-Pierre Mbakidi [b], Stéphanie Leroy-Lhez [b], Vincent Sol [b], Bruno Therrien [a, *]

[a] Institute of Chemistry, University of Neuchatel, Avenue de Bellevaux 51, CH-2000, Neuchatel, Switzerland
[b] Laboratoire de Chimie des Substances Naturelles, Université de Limoges, 123 Avenue Albert Thomas, 87060, Limoges, France

ARTICLE INFO

Article history:
Received 10 February 2015
Received in revised form
18 March 2015
Accepted 30 March 2015
Available online 20 April 2015

Keywords:
Half-sandwich complexes
Photodynamic therapy
Drug delivery
Porphin
Bioorganometallic

ABSTRACT

Two pentamethylcyclopentadienyl (Cp*) rhodium(III) and iridium(III) metalla-prisms of the general formula $[(Cp^*M)_6(tpt)_2(dhnq)_3]^{6+}$ (tpt = 2,4,6-tri-(pyridin-4-yl)-1,3,5-triazine, dhnq = 5,8-dihydroxy-1,4-naphthoquinonato; M = Rh, $[\mathbf{1}]^{6+}$; M = Ir, $[\mathbf{2}]^{6+}$) have been synthesized by mixing in methanol the neutral dinuclear complexes $(Cp^*M)_2(dhnq)Cl_2$ (M = Rh, Ir), $AgCF_3SO_3$ and tpt. In a similar fashion, the addition of porphin during the formation of $[\mathbf{1}]^{6+}$ and $[\mathbf{2}]^{6+}$ leads to the carceplex systems [porphin⊂**1**]$^{6+}$ and [porphin⊂**2**]$^{6+}$. All complexes were isolated as their triflate salts and characterized by different analytical techniques including for the carceplex [porphin⊂**1**][CF_3SO_3]$_6$ by a single-crystal X-ray structure analysis. The hosts were evaluated as drug delivery vectors on the HT-29 cancer cell line, and after internalization, porphin was photo-activated to generate phototoxicity. Interestingly, the IC_{50} values of the empty and filled metalla-cages are around 1 μM, while upon irradiation (20 J/cm^2) only lower nanomolar concentrations of the [porphin⊂**cage**][CF_3SO_3]$_6$ systems are necessary to inhibit cell growth by 50%, showing an excellent ratio between cytotoxicity and phototoxicity.

Introduction

In recent years, the number of biological studies involving arene ruthenium metalla-assemblies is booming [1]. So far, trinuclear [2], tetranuclear [3], hexanuclear [4], octanuclear [5] and dodecanuclear [6] metalla-assemblies incorporating arene ruthenium(II) complexes have been synthesized and often they have been tested as anticancer agents. In general, these cationic complexes have showed an *in vitro* anticancer activity in the lower micromolar range. Interestingly, some of the hexanuclear and octanuclear arene ruthenium metalla-assemblies possess a hydrophobic cavity which can be filled with a guest molecule [7], and consequently, these cationic water soluble metalla-hosts have been used as drug delivery vectors [8]. Despite the huge popularity of arene ruthenium metalla-assemblies, the biological side of their pentamethylcyclopentadienyl (Cp*) rhodium(III) and iridium(III) analogues remains unexplored. In fact, several Cp*Rh and Cp*Ir metalla-assemblies can be found in the literature [9], however, only a handful of these metalla-assemblies has been biologically evaluated. Among them, the embelin-derived tetranuclear [10] and hexanuclear complexes [11], and the 5,8-dihydroxy-1,4-naphthoquinonato tetranuclear metalla-cycles with bipyridyl linkers [12]. On the other hand, mononuclear and dinuclear Cp*Rh and Cp*Ir complexes have showed great promises as anticancer agents [13], with even in some cases possessing an excellent selectivity for cancerous over noncancerous cell lines [10].

Nevertheless, to obtain temporal and spatial-controlled activation of a drug for an optimal selectivity, and accordingly to alleviate side effects associated to non-specific accumulations, the use of an external stimulus to activate a drug to treat cancers is quite attractive [14]. Among these stimuli, light is commonly employed to activate biologically relevant compounds [15]. The utilization of light for therapeutic purposes is nowadays called photodynamic therapy (PDT), but the concept of using light to cure diseases has been exploited under different terminologies for centuries [16]. Recently, we have inserted a photosensitizer in the hydrophobic cavity of arene ruthenium metalla-assemblies [17]: The metalla-assembly was protecting, transporting and shielding the

* Corresponding author. Tel.: +41 0 32 718 2499.
E-mail address: bruno.therrien@unine.ch (B. Therrien).

http://dx.doi.org/10.1016/j.jorganchem.2015.03.035
0022-328X/

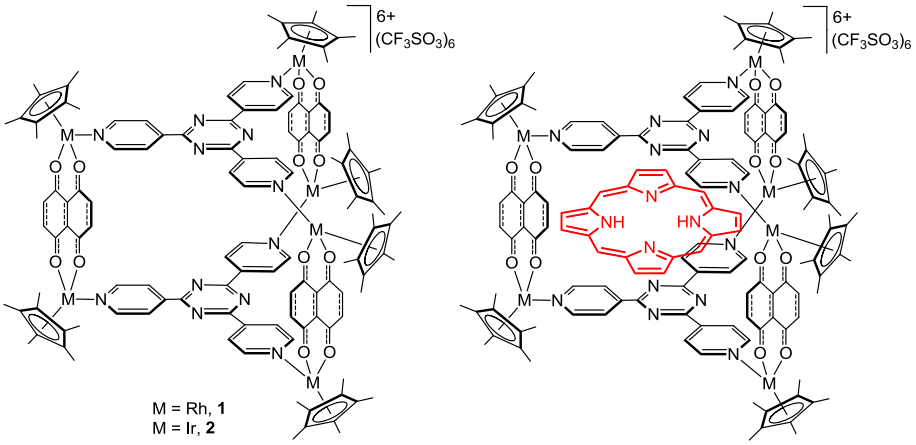

Fig. 1. Molecular structures of $[\mathbf{1}]^{6+}$, $[\mathbf{2}]^{6+}$, [porphin⊂$\mathbf{1}$]$^{6+}$ and [porphin⊂$\mathbf{2}$]$^{6+}$.

photosensitizer until it was delivered to its target. Then following the uptake of the host-guest system by cells, the photosensitizer was released and photo-activated, providing a new strategy to deliver hydrophobic photosensitizers to cancer cells [18].

Herein we report the synthesis and characterization of the 5,8-dihydroxy-1,4-naphthoquinonato (dhnq) Cp*Rh and Cp*Ir metalla-prisms of the general formula $[(Cp^*M)_6(tpt)_2(dhnq)_3]^{6+}$ (tpt = 2,4,6-tri-(pyridin-4-yl)-1,3,5-triazine), and the corresponding complexes in which porphin sits inside the cavity. The anti-proliferative activity of the complexes and their photodynamic activity were evaluated on the human colon cancer cell line HT-29.

Results and discussion

The reaction of the dinuclear pentamethylcyclopentadienyl complexes $(Cp^*M)_2(dhnq)Cl_2$ (M = Rh, Ir) with $AgCF_3SO_3$ followed by the addition of tpt (2,4,6-tri-(pyridine-4-yl)-1,3,5-triazine) affords the cationic hexanuclear metalla-prisms of the general formula $[(Cp^*M)_6(tpt)_2(dhnq)_3]^{6+}$ (dhnq = 5,8-dihydroxy-1,4-naphthoquinonato; M = Rh, $[\mathbf{1}]^{6+}$; M = Ir, $[\mathbf{2}]^{6+}$), see Fig. 1. However, the synthesis of the carceplexes [porphin⊂$\mathbf{1}$]$^{6+}$ and [porphin⊂$\mathbf{2}$]$^{6+}$ is achieved by the addition of porphin during the formation of the metalla-prisms $[\mathbf{1}]^{6+}$ and $[\mathbf{2}]^{6+}$. The empty and filled metalla-prims are equally obtained in moderate yields as their triflate salts, suggesting no template effect from porphin. The metalla-prisms and the host-guest systems were fully characterized by infrared and NMR spectroscopies, ESI mass spectrometry and for [porphin⊂$\mathbf{1}$][CF_3SO_3]$_6$ by a single-crystal X-ray structure analysis. All complexes are non-hygroscopic and soluble in common polar solvents and insoluble in non-polar solvents. In addition, all the metalla-prisms are moderately soluble in water.

The formation of these complexes was easily monitored by ^{1}H NMR spectroscopy (Fig. 2). The complexes $[\mathbf{1}]^{6+}$ and $[\mathbf{2}]^{6+}$ show well-defined structures with relatively simple sets of signals in their ^{1}H NMR spectra, displaying the expected resonances for the metalla-prisms. Yet, in the host-guest systems [porphin⊂$\mathbf{1}$]$^{6+}$ and

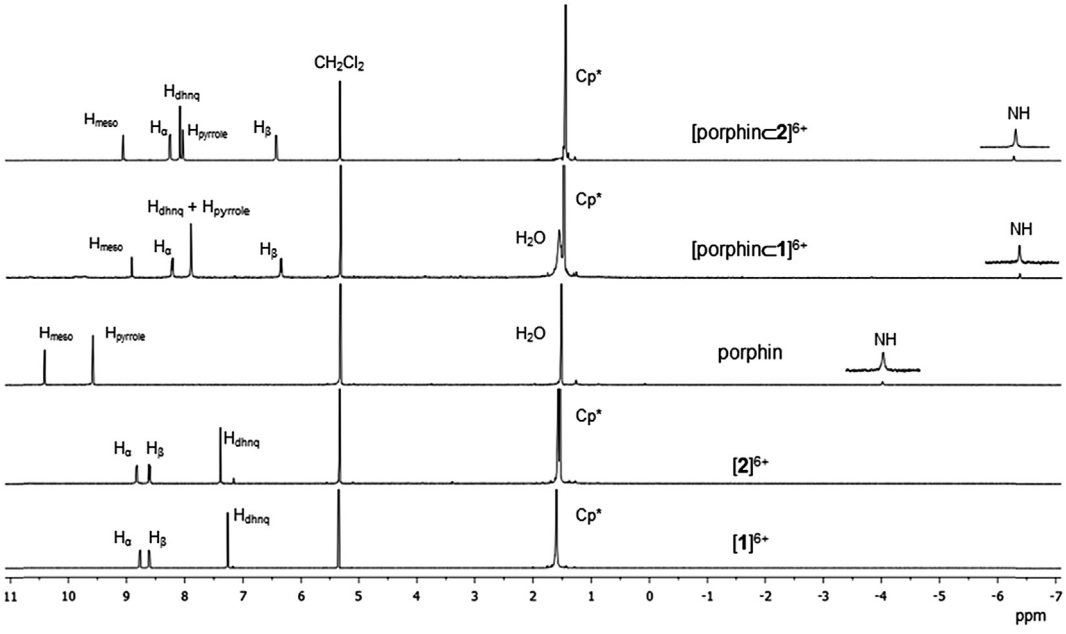

Fig. 2. ^{1}H NMR spectra (21 °C, CD_2Cl_2) of $[\mathbf{1}]^{6+}$, $[\mathbf{2}]^{6+}$, porphin, [porphin⊂$\mathbf{1}$]$^{6+}$ and [porphin⊂$\mathbf{2}$]$^{6+}$.