Reactivity Studies on Iron(III) Complexes for the Development of Bioreductive Prodrugs

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Introduction

Common therapies against cancer – chemo and radiotherapy – find resistance in the treatment of solid tumors.[1] Poor vascularization is common in tumor and frequently leads to a low concentration of oxygen (hypoxia condition), which limits the success of these therapies. Nonetheless, the more reductive environment of hypoxic cells can be exploited for the development of bioreductive prodrugs. In this way, a compound might be designed to circulate intact through the body, being selectively reduced in the tumor with subsequent releasing of a cytotoxic ligand.[1,2] In this work, we present synthesis, characterization and reactivity assays of two iron(III) complexes of formula [Fe(L-R)(bhnq)]NO_3 (Fig.1) as potential bioreductive prodrugs.

Results and Discussion

A reaction between $Fe(NO_3)_3.9H_2O$, lawsone, Et_3N and the ligands L-R (R = H, CH_3), in methanol, produced complexes **1** and **2**, respectively. Anal. Calcd. for **1**, $C_{35}H_{34}FeN_5O_{12}$: C, 54.42; H, 4.44; N, 9.07 %. Found: C, 54.43; H, 4.41; N, 9.03%. Anal. Calcd. for **2,** $C_{37}H_{38}FeN_5O_{12}$: C, 55.51; H, 4.78; N, 8.75 %. Found: C, 55.94; H, 4.23; N, 6.85%.

The presence of the ligands L-R and *bhnq*$^{2-}$ coordinated to the metal center and the counter-ion NO_3^- was confirmed by the IR spectra of **1** and **2**. ESI-MS analysis of **1** and **2** reveal preeminent peaks at m/z$^+$ = 642.2 and 670.2, respectively assigned to [Fe(L-H)(bhnq)]$^+$ and [Fe(L-CH_3)(bhnq)]$^+$. The X-ray structure of **1** was described previously.[3] Cyclic voltammetry (CV) analysis showed a reversible process attributed to the couple Fe^{3+}/Fe^{2+} at $E_{1/2}$ = -0.45V *vs* Fc/Fc$^+$ for **1** and $E_{1/2}$ = -0.38V *vs* Fc/Fc$^+$ for **2**.[4] The more positive potential of **2** can be associated with the steric hindrance of the CH_3 groups that are repelled by the pyridine rings in L1-CH_3, producing a leveraging effect that pulls the nitrogen atom away from the cobalt.[5]

Reactivity assays monitored by UV-Vis spectroscopy showed that **1** and **2** are rapidly dissociated in aqueous media, without previous reduction, as illustrated in Fig. 1. Releasing of the *bhnq*$^{2-}$ ligand is detected by the appearance of a band at 480 nm (Fig. 2). No changes in the spectra were observed after the addition of ascorbic acid.

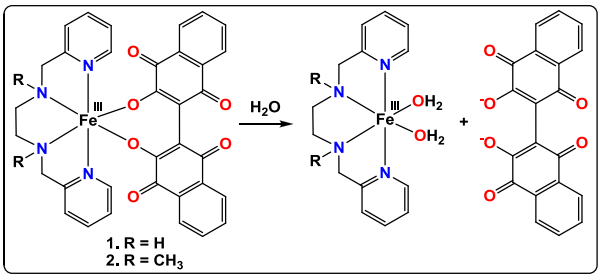

Figure 1. Dissociation scheme of **1** and **2**.

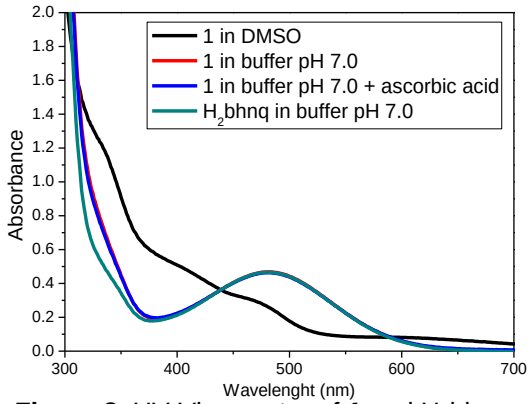

Figure 2. UV-Vis spectra of **1** and H_2bhnq.

Conclusions

Redox reversibility and reduction potentials accessible to biological reductants were observed for **1** and **2**. Reactivity assays indicated that, unlike the analogous cobalt complexes[5], iron complexes are not sufficiently stable in aqueous media to be used as bioreductive prodrugs.

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