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Therapeutic potential of electrochemically active nitrosyl ruthenium complexes as nitric oxide deliver agents. Kinetic and biological assays

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Introduction

The nitric oxide has brought attention to its physical-chemistry properties, as well as its action in biological systems. The electronic distribution of the NO molecule shows that it's paramagnetic and allows the coordination with a metallic center, resulting in a metal complex, which properties depends on the co-ligands bonded to the metal ion. This kind of compound works as an efficient NO carrier. This offers potential for NO precursors be used as a tool for understanding biological functions and also in clinical therapy. Among them coordination compounds involving nitric oxide derivatives bonded to ruthenium have been postulated as possible metal-based drug. A promise class is *cis*-$[Ru(L)(bpy)_2(NO)](PF_6)_3$, where L = pyridine type ligands, that have been described as stable specie and capable to release NO under reduction process.[1] Based on this, the aim of this work is to study the kinetic parameters in several temperatures related to the nitric oxide (NO) release. Biological studies were also carried out with those complexes in liposomes, as drug delivery system.

Results and Discussion

The nitric oxide (NO) release kinetics of a new promising anticancer agent – donor of NO, namely, water-soluble nitrosyl bipyridine ruthenium complex, $[Ru(NO)(bpy)_2L]^{3+}$ (L = pyridine, 4-picoline, 4-acetyltpyridine) **(1)**, has been studied by chemical, electrochemical and spectroscopic methods in aqueous solution. Rate constant in aqueous solution solution has been measured (Table 1, Figure 1).

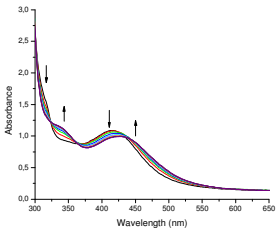

Figure 1. Figure 1: UV-visible variation for $[Ru(NO)(bpy)_2(L)]^{2+}$ in aqueous solution.

The temperature dependence of nitric oxide release rate constant of complex **(1)** has been determined (Table 1). High enough rates of the nitric oxide release of these complexes at high negative entropy of activation can be explained by the low value of activation energy. This results demonstrate that the reaction can happen spontaneously, according to the Gibbs energy obtained, -70,4 kcal/mol when L = pyridine and -69,4 kcal/mol when L = 4-picoline.

Table 1. Kinetics results for *cis*-$[Ru(py)(bpy)_2(NO)](PF_6)_3$.

T (°C)	K_{obs} ($x10^{-2}s^{-1}$)	$\Delta H^{\neq}$(kcal/mol)	$\Delta S^{\neq}$(J/K)
25	1.48 ± 0,0005	9,9	-33,626
30	1.84±0,0008	10,0	-33,363
35	2.68±0,0011	10,1	-33,009
40	2.48±0,0031	10,3	-33,092

Table 2. Kinetics results for cis-$[Ru(py)(bpy)_2(NO)](PF_6)_3$.

T(°C)	K_{obs} ($x10^{-2}s^{-1}$)	$\Delta H^{\neq}$(kcal/mol)	$\Delta S^{\neq}$(J/K)
25	1.53	9,9	-33,534
30	1.93±0,0004	10,0	-33,323
35	2.56±0,0001	10,1	-33,047
40	2.56±0,0008	10,3	-33,062

The kinetic process could be described as in Scheme 1:

$$\{Ru\text{-}NO\}^{3+} + O_2^{-} \longrightarrow \{Ru\text{-}NO\}^{2+} \xrightarrow{H_2O} \{Ru\text{-}H_2O\}^{2+} + NO$$

Scheme 1: General reaction mechanism for $[Ru(NO)(bpy)_2L]^{3+}$ type complex.

The liposome preparation results in 121 nm empty liposome, according to the Malvern Zetasizer measurement. Studies on the encapsulated complex by the liposome are been developed.

Conclusion

In summary, the results of this study provide a quantitative measure of the effects of temperature upon $\{Ru\text{-}NO\}^{3+}$ reduction in the presence of superoxide. The reactions are quite slow in aqueous solution. The activation parameters are consistent with the view that the reactivities of these metal centers with NO are dominated by the labilities of the ligand being replaced and suggest that the ligand substitution occurs by an associative interchange mechanism.

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