Interactions between Antitumoral Models of Ruthenium and DNA Purines in a Confined Environment (Nanostructured Silica Matrices)

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Although new cancer treatment strategies have been evolving towards specific pathways, notably those involved in cell signalling, the majority of cytotoxic metal complexes available and under research have as target the DNA, given its importance in replication process and cell viability. In order to achieve a clear understanding of the role of metal complexes on these processes, a wide range of studies centred on the interactions of the coordination complexes with DNA and its constituents and derivatives, as well as with other biological targets have been conducted. Some interaction mechanisms have been proposed based on theoretical approaches and experimental studies in homogeneous medium (aqueous or gaseous phase), but no so far in a confined environment. The binding of nucleic acid bases to the metal atoms of coordination complexes seems to be determinant on the antitumoral activity of those compounds.[1]

Among coordination compounds, the ruthenium complexes have been target of great attention as antitumoral agents, given their lower toxicity and higher specificity comparatively to platinium-based complexes. A few are presently standing clinical trials (phase II), namely NAMI-A (imidazolium [trans-tetrachloro(1H-imidazole)(S-dimethylsulfoxide)ruthenate(III)]) and KP1019 (indazolium [trans-tetrachlorobis(1H-indazole)ruthenate(III)]).

In the present work, some Ru(II) and Ru(III) complexes ($RuNO(NO_3)_3$ and the ammine complexes $Ru(NH_3)_6Cl_3$, $Ru(NH_3)_6Cl_2$ and Ru-red) were coencapsulated with DNA purines (adenine (Ade) and guanine (Gua)) within nanostructured silica matrices prepared by a two-step sol-gel process. These Ru complexes were used as models and pro-drugs of antitumoral agents and their interactions with the DNA purines were investigated by infrared and UV-Visible spectroscopies.

This research shows that Ade interacts with the complexes, or with their decomposition products, only by hydrogen bonds (Figure 1). However, these interactions are strong enough to inhibit or delay the decomposition of the ammine complexes. Adenine showed also high affinity to the silica network, which increases with the amount of silanol groups on the matrix.

Guanine behaves differently with each complex: it interacts strongly with $RuNO(NO_3)_3$, since direct covalent bonding of the metal to the N7 or N9 of Gua was detected (Figure 2) [2]; on the other hand, the interactions with ammine complexes are much weaker given that only hydrogen bonds were confirmed. Guanine seems to have preferential interactions with the silanol or siloxy groups of the matrix, certainly by the carbonyl group, allowing the complexes to undergo further oxidation reactions.[3]

It was also proved that the nanostructure of the silica matrix plays an important role on the interactions established between the purines and the Ru complexes, namely the pore structure (shape and dimensions) and the amount of silanol groups, both largely affected by the nature of the dopants.

References:

[1] M. J. Clarke, *Coord. Chem. Rev.*, **232** (2002) 69-93.
[2] L. M. F. Lopes, A. R. Garcia, A. Fidalgo, L. M. Ilharco, *Langmuir*, **25** (2009), 10237-10242.
[3] L. M. F. Lopes, A. R. Garcia, P. Brogueira, L. M. Ilharco, *J. Phys. Chem. B*, (accepted).

Figures:

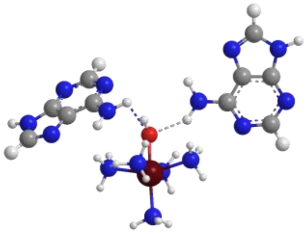

Figure 1: Schematic representation of possible hydrogen bonds between Ade and the intermediate $[Ru(NH_3)_5OH]^{2+}$

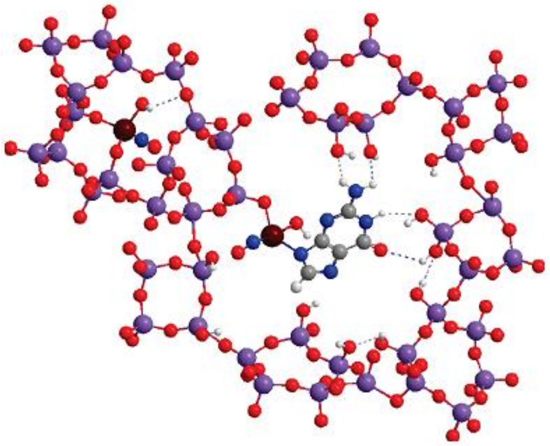

Figure 2: Proposed interactions between Gua and Ru(III) nitrosyl nitrate ($RuNO(NO_3)_3$) within the silica matrix.