XXI Brazilian Meeting on Inorganic Chemistry
X Brazilian Meeting on Rare Earths
III Workshop on Theoretical Bioinorganic Chemistry
Belo Horizonte, September 12 - 15th 2024

Interactions of Pt(II) ions with fludarabine and albumin

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Thematic Area: Biological Inorganic Chemistry

Keywords: platinum, purine analogue, anticancer agents

Cancer is among the leading causes of death in the world. One of the forms of treatment is the use of chemotherapeutic agents, which despite demonstrating effectiveness, have their limitations due to acquired cellular resistance and unwanted side effects. For this reason, there is a need to synthesize new, more active and less toxic drugs. Purine analogues are the second most frequently used cytotoxic agents in the treatment of certain hematologic malignancies. Aiming to ally the anticancer properties of platinum compounds to those of purine analogues, in this work, the interactions of fludarabine (flu), with Pt(II) ions, in aqueous solution, were studied by ^{1}H NMR spectroscopy. Two-dimensional COSY NMR helped to assign the signals. ^{1}H NMR spectra were performed in D_2O at pD 6.0 containing flu ($1x10^{-3}$ mol/L) in the absence and presence of increasing concentrations of Pt(II) (from $2x10^{-4}$ to $1x10^{-2}$ mol/L). The main changes caused by the addition of Pt(II) ions were the disappearance of the peak at δ 8.31, attributed to H8 of the nitrogenous base of free fludarabine, and the appearance of a new peak at δ 8.78, indicating the complexation of platinum to the nitrogen N7. The intensity of the doublet centered at δ 6.31, attributed to H1' of the sugar, decreased with the increase in platinum concentration, until its disappearance and the appearance of a new doublet at δ 6.37, which suggests the occurrence of a conformational change in the molecule [1, 2, 3]. Both fludarabine and its Pt(II) complex were highly cytotoxic in a chronic leukemia cell line. When planning a new medicine, an initial step involves studying interactions with plasma proteins, such as albumin. The interactions between the Pt(II) complex with flu and BSA were studied by spectrofluorimetry. In solution, BSA exhibits a strong fluorescent signal, due to the presence of two tryptophan residues, Trp134 and Trp212, with maximum emission at 340 nm, when excited at 280 nm. The interaction of the protein with complexes can cause the extinction of this band [4,5,6]. It should be noted that the studied compounds are not fluorescent in the same region as BSA. The fluorescence data were analyzed with the help of the Stern-Volmer equation, and the Ksv and kq values obtained for the Pt(II) complex were 2.87×10^{4} L mol^{-1} and 2.87×10^{12} L mol^{-1} s^{-1}, respectively, and 2.13×103 L mol^{-1} and 2.13×10^{11} L mol^{-1} s^{-1} for free fludarabine. As the calculated kq values were greater than 2.0×10^{10} L mol^{-1} s^{-1}, it is likely that the quenching of BSA fluorescence by the compounds occurs through a static quenching mechanism. For the binding constant, Kb, the values obtained were 1.20×10^{4} and 8.57×10^{2} L mol^{-1} for the Pt(II) complex and free fludarabine respectively, which shows that the complexation with platinum increases by 14 times the affinity for BSA. For both, the number of binding sites is approximately 1, thus showing that only one molecule of the compound is inserted into the protein frameworks.

Acknowledgments: FAPEMIG, CNPq, INCT-Catálise

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