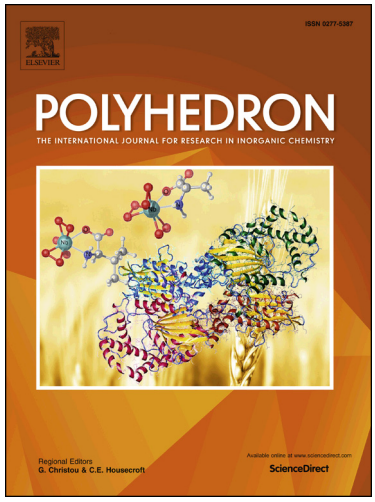

Kinetic and mechanistic study of substitution on a cytotoxic Pt^{II} complex with biologically relevant thiols and a density functional study

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Kinetic and mechanistic study of substitution on a cytotoxic Pt^{II} complex with biologically relevant thiols and a density functional study

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Abstract

A systematic investigation of the interactions of platinum antitumor complexes with sulfur-containing biomolecules is of paramount importance to gain an insight into platinum metabolism. To this effect, the rate of substitution of aqua ligands by biologically relevant nucleophiles, L-cysteine (L-cys) and N-acetyl-L-cysteine (NALC), for the complex $[Pt(AMBIM)(H_2O)_2]^{2+}$ (where AMBIM = 2-aminomethylbenzimidazole) was investigated under pseudo-first-order conditions as a function of concentration and temperature by UV/Visible spectrophotometry. The reaction proceeded in two consecutive steps; the first being a ligand-assisted anation followed by a chelation step. The activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) for both steps have been evaluated using the Eyring equation, which suggest an associative mode of activation for both the displacement processes. The kinetic study was substantiated by spectroscopic results and density functional theory (DFT) calculations, such as NBO analyses. Time dependent DFT (TD-DFT) was also performed to comprehend the nature of the electronic transitions in the product complexes. Global reactivity parameters were incorporated to unravel the reactivity of the Pt-S adducts towards potential targets, such as nucleobases.

Keywords: Kinetics and mechanism • Activation parameters • NBO Analysis • TD-DFT

1. Introduction

Platinum complexes have been in the forefront of anticancer chemotherapy since the validation of the cytotoxic effect of *cis*platin in 1978 [1]. The great success story of platinum-based cytostatics is, however, tainted by certain major shortcomings which curb their usages, such as severe dose-limiting side effects, intrinsic or/and acquired resistance [2,3] and the uncomfortable and cost-intensive way of