Mechanism of Cellular Uptake of a Ruthenium Polypyridyl Complex†

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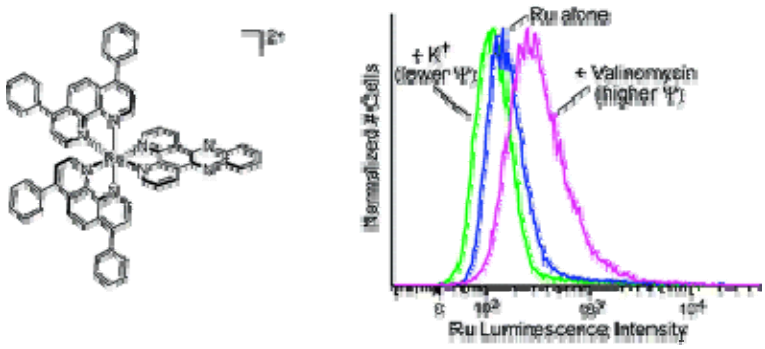
Received May 9, 2008

Revised Manuscript Received September 4, 2008



Abstract:

Transition metal complexes provide a promising avenue for the design of therapeutic and diagnostic agents, but the limited understanding of their cellular uptake is a roadblock to their effective application. Here, we examine the mechanism of cellular entry of a luminescent ruthenium(II) polypyridyl complex, $Ru(DIP)_2dppz^{2+}$ (where DIP = 4,7-diphenyl-1,10-phenanthroline and dppz = dipyridophenazine), into HeLa cells, with the extent of uptake measured by flow cytometry. No diminution of cellular uptake is observed under metabolic inhibition with deoxyglucose and oligomycin, indicating an energy-independent mode of entry. The presence of organic cation transporter inhibitors also does not significantly alter uptake. However, the cellular internalization of $Ru(DIP)_2dppz^{2+}$ is sensitive to the membrane potential. Uptake decreases when cells are depolarized with high potassium buffer and increases when cells are hyperpolarized with valinomycin. These results support passive diffusion of $Ru(DIP)_2dppz^{2+}$ into the cell.