MECHANISTIC STUDIES ON THE INTERACTION OF THE ANTILEUKEMIC ALKALOID CORALYNE WITH POLYNUCLEOTIDES

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Coralyne is a fluorescent synthetic alkaloid, analogous of the natural alkaloid berberine, that has been found to exhibit antileukemic activity. This activity, together with the low toxicity, is the basis of the high interest aroused by this molecule in recent years. Coralyne strongly binds to polynucleotides of both DNA and RNA type, showing high affinity also for poly(dA)-2poly(dT) triple helices and for poly(A) single strands. The binding follows an intercalative mode but, for high dye concentrations, molecular aggregation, induced by the DNA template, is also found to occur. Despite the high number of studies performed on this molecule, an in depth understanding of the binding mechanism is lacking, this being principally due to the fact that experiments are difficult to carry out due to the high tendency of coralyne to self-aggregation. Fluorescent measurements constitute an important tool to overcome such a problem, grace to the very low dye concentration that can be used with this technique. We have performed a kinetic analysis (T-jump technique) of coralyne self-aggregation, in water (0.1M NaCl, pH = 7) and in the presence of increasing amount of ethanol (0-20%). Then, spectrofluorometric, spectrophotometric, viscometric and circular dichroism titrations were performed on Coralyne/polynucleotide systems, where as polynucleotides calf-thymus DNA, poly(dA-dT)-poly(dA-dT), poly(dG-dC)-poly(dG-dC), poly(A), poly(A)-poly(U), poly(A)-2poly(U) were employed. The experiments concerned with polynucleotide binding were also carried out both in water and water-ethanol mixtures. The results obtained indicate that coralyne self-aggregation is indeed strong, ethanol affecting both the forward and backward aggregation rates, but scarcely modifying the aggregation constant. Concerning polynucleotides, it was found that binding to DNAs differs from that to RNAs, as shown by the sharply different viscosimetric and dichroic behaviours. Among DNA sequences, A-T base pairing was found to be preferred, whereas concerning RNA, higher affinity for the triple helix respect to the double was found to occur. Further details of this analysis will be presented.