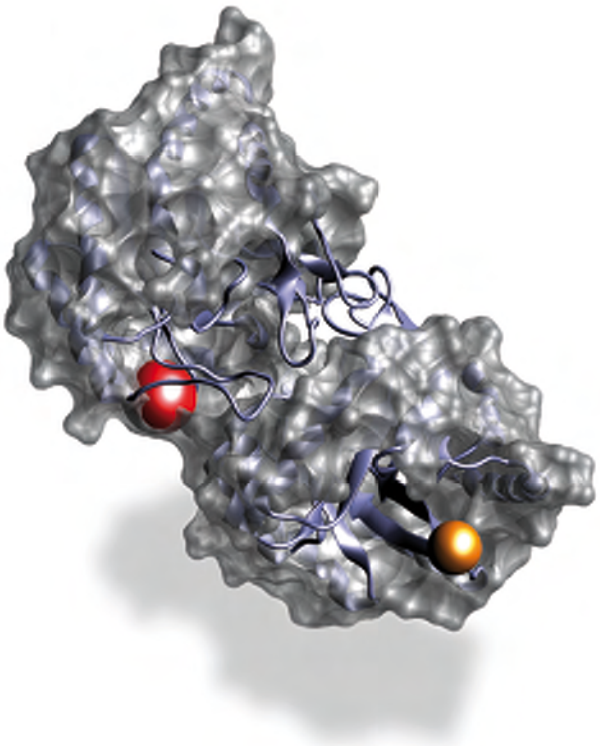

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DIVISIONE DI CHIMICA INORGANICA

SCUOLA NAZIONALE DI CHIMICA BIOINORGANICA

14 – 16 Settembre, 2008
Via Mezzocannone,16 – Napoli

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Transition metal complexes as DNA-intercalators

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My research project focuses on the interaction of transition metal complexes with native or synthetic polynucleotides. Among the various topics concerning the DNA-binding field, the intercalation process has incremented his importance in the last years due to the potential applications of DNA-intercalators as diagnostic probes, anticancer or therapeutics agents and in genomic research.[1]
In particular, in our laboratory we have studied complexes of metals belonging to the first transition row, such as Fe, Co, Ni, Cu and Zn,[2,3] taking into account that these metals offer the possibility of a facile interchange of ligands as well as unique photophysical and electrochemical properties.[1]
Particular attention has been devoted to ligands such as heterocyclic compounds[2] and Schiff bases[3,4] for their potentially remarkable biological activity.
For example, recently two new Fe^{III} complexes of the dppz ligand, i.e. $[Fe(dppz)]Cl_3$ and $[Fe(dppz)_2]Cl_3$, were synthesized and characterized with the aim to find DNA intercalator iron-dppz complexes with non-chelating ancillary ligands. The interaction of the Fe^{III}dppz hydrolyzed aquo complex, presumably $[Fe(dppz)(OH)_2(H_2O)_2]^+$, with native calf thymus DNA has been monitored as a function of the metal complex-DNA molar ratio, by variable temperature UV absorption spectrophotometry, circular dichroism (see Figure 1) and fluorescence spectroscopy. These techniques allowed us to conclude that the metal complex binds to DNA mainly through intercalation, although other binding modes, in particular the electrostatic interaction of the complex with the DNA surface, seem to be also present and visible at molar ratios higher than 2 metal complex molecules per 3 DNA base pairs.[2]

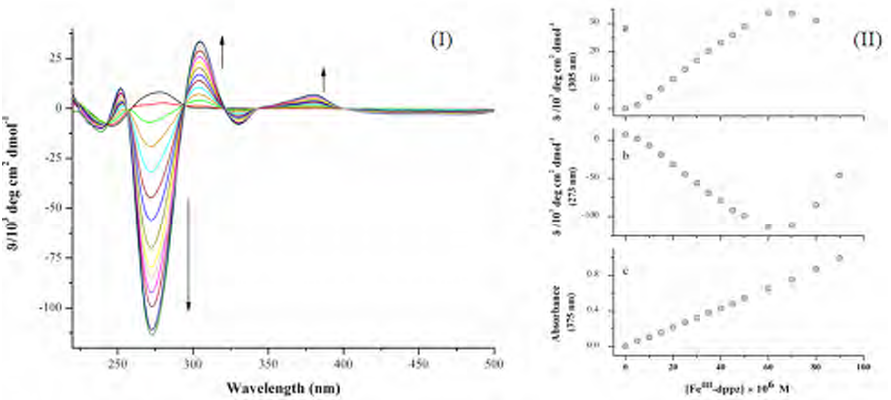

Figure 1 - (I) Circular dichroism spectra of CT-DNA in the presence of increasing amounts of Fe^{III}-dppz in 1.0 mM Tris–HCl. $[DNA_{phosphate}] = 100$ μM, $[Fe^{III}\text{-dppz}] = 0.00$ (—), 4.98 (—), 10.0 (—), 15.0 (—), 20.0 (—), 25.0 (—), 30.0 (—), 35.0 (—), 40.0 (—), 45.0 (—), 50.0 (—), 60.0 (—), 70.0 (—), 80.0 (—) μM; (II) Molar ellipticity at 305 nm (a), at 273 nm (b) and UV-vis absorption at 375 nm (c) of Fe^{III}dppz-DNA aqueous solutions in the presence of increasing amounts of Fe^{III}dppz.

Another aspect recently investigated concerns the confinement effect of reverse micellar systems on the interaction of DNA with an intercalator. In details, confinement effects of native calf thymus DNA interacting with the complex Cu(II)-5-triethyl ammonium methyl salicylidene orto-phenylendiiminate (CuL^{2+}) perchlorate in tetraethylene glycol monododecyl ether ($C_{12}E_4$) liquid crystals have been

investigated by UV absorption spectrophotometry, circular dichroism (CD) and small angle X-ray scattering (SAXS).[4] The results obtained indicate the occurrence of dramatic structural changes of both the DNA and the CuL^{2+}-DNA system, when going from aqueous solution to $C_{12}E_4$ liquid crystals, due to confinement constrains imposed by the closed structure of $C_{12}E_4$ reverse micelles. In particular, the confinement causes the formation of a more compact and thermoresistent DNA structure, accompanied by a transition from right- to left-handed form. Moreover, a tight CuL^{2+}-DNA binding has been revealed by the appearance of a broad induced CD band in the range 350–450 nm.[4]

At present, we are carrying out the synthesis and characterization of a Cu^{II} complex (**1**) of 3,5-bis(2'-pyridil)-1,2,4-oxadiazole (Figure 2b). The study of its interaction with native DNA is being performed by using the same spectroscopic techniques described above. Preliminary UV-vis absorption data (see Figure 2a) show that hypochromism and bathochromic shift occur on the band of the metal complex, centred at about 340 nm, as a result of DNA addition.

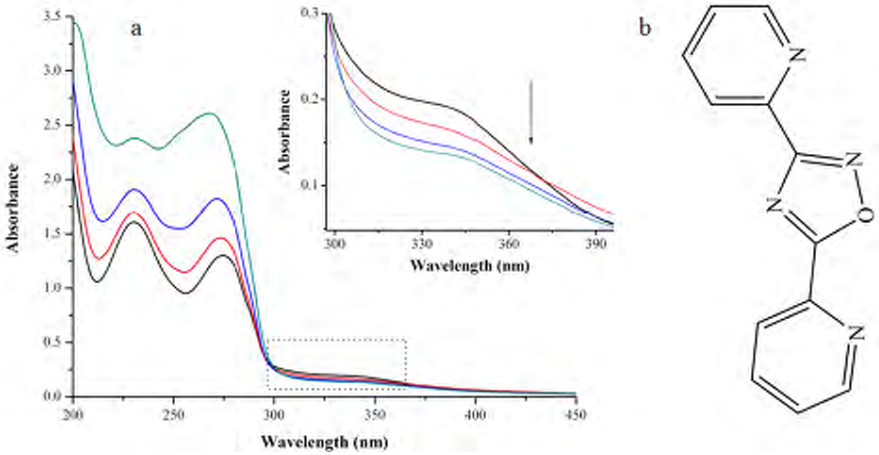

Figure 2 - a) UV-vis absorption spectra of complex 1 in the presence of increasing amounts of CT-DNA in Tris-HCl 1.0 mM. [Complex 1] = 50 μM, $[DNA_{phosphate}]/[Complex\ 1]$ = 0.0 (—), 0.5 (—), 2.0 (—), 4.0 (—) μM; b) structure of the 3,5-bis(2'-pyridil)-1,2,4-oxadiazole ligand.

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2. Terenzi, A.; Barone, G.; Silvestri, A.; Giuliani, A.M.; Ruggirello, A.; Turco Liveri, V. submitted.
3. Silvestri, A.; Barone, G.; Ruisi, G.; Anselmo, D.; Riela, S.; Turco Liveri, V. *J. Inorg. Biochem.* **2007**, *101*, 841-848.
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