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01–30 November 2023 | Online

The X-ray structure of the primary adduct formed upon reaction between dirhodium tetraacetate and B-DNA double helical dodecamer

Chaired by Dr. Alfredo Berzal-Herranz and Prof. Dr. Maria Emília Sousa

pharmaceuticals MDPI

Gabriella Tito[1]*, Romualdo Troisi[1], Giarita Ferraro[1], Andrea Geri[2], Lara Massai[2], Luigi Messori[2], Filomena Sica[1] and Antonello Merlino[1].

1 Department of Chemical Sciences, University of Naples Federico II, Complesso Universitario di Monte Sant'Angelo, Via Cintia, I-80126, Napoli, Italy; antonello.merlino@unina

2 Department of Chemistry "U. Schiff", University of Florence, via della Lastruccia 3, 50019 Sesto Fiorentino, Italy

*Correspondence: A.M., antonello.merlino@unina.it;

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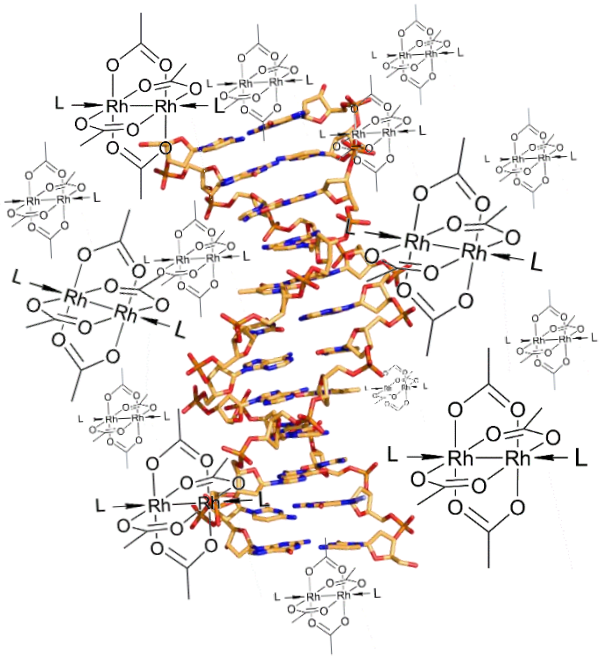
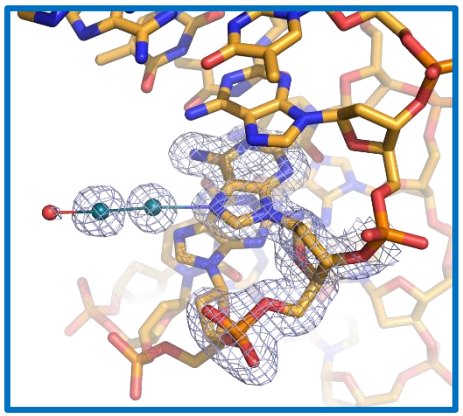
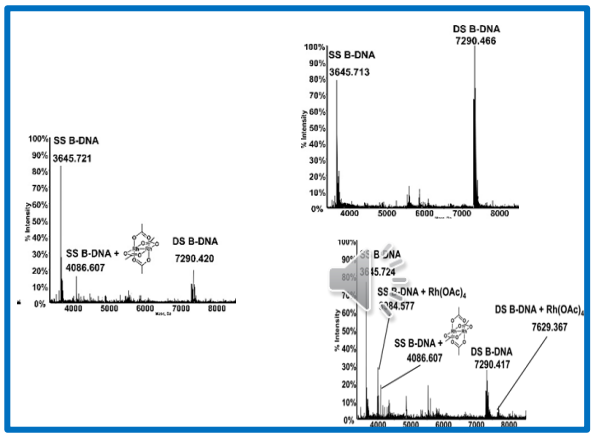
X-ray crystallography



ESI mass spectrometry





Abstract: Since the clinical success of cisplatin, there is a growing demand for cytotoxic metal complexes able to overcome the limitations associated with cisplatin therapy. It has been extensively demonstrated that its cytotoxic activity is due to interaction with DNA. In fact, cisplatin interferes with DNA replication and transcription processes, kinking the DNA duplex by covalently binding two adjacent guanines in the major groove. Unfortunately, the use of cisplatin is associated with undesirable side effects. Therefore, a second generation of Pt-based complexes (oxaliplatin, carboplatin), and a series of non-Pt-based complexes, with different mechanisms of action, have been developed. In this frame, dirhodium tetracarboxylates, especially dirhodium tetraacetate [$Rh_2(\mu\text{-}O_2CCH_3)_4$], attracted great interest. The paddlewheel dirhodium tetraacetate complex has been considered a potential anticancer compound since it exhibits an appreciable carcinostatic activity. Information on the interaction of this metallodrug with DNA are limited. To obtain insights on its mechanism of action, X-ray crystallography and mass spectrometry have been carried out. The X-ray structure of the dirhodium/DNA adduct reveals a bimetallic center bound to an adenine via axial coordination. This result is significant since dirhodium mode of binding to DNA is different from that of cisplatin, which binds guanines. This view is supported by ESI MS experiments, pointing out that, at short incubation times, adducts are formed between the DNA and [$Rh_2(\mu\text{-}O_2CCH_3)_4$] in agreement with crystallographic results. Furthermore, for longer incubation times, the dirhodium tetraacetate converts into a mono-rhodium tetraacetate fragment as the consequence of progressive cleavage of the Rh-Rh bond.

Keywords: antitumor complexes, DNA-binding, dirhodium compounds

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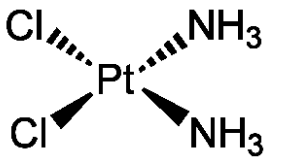
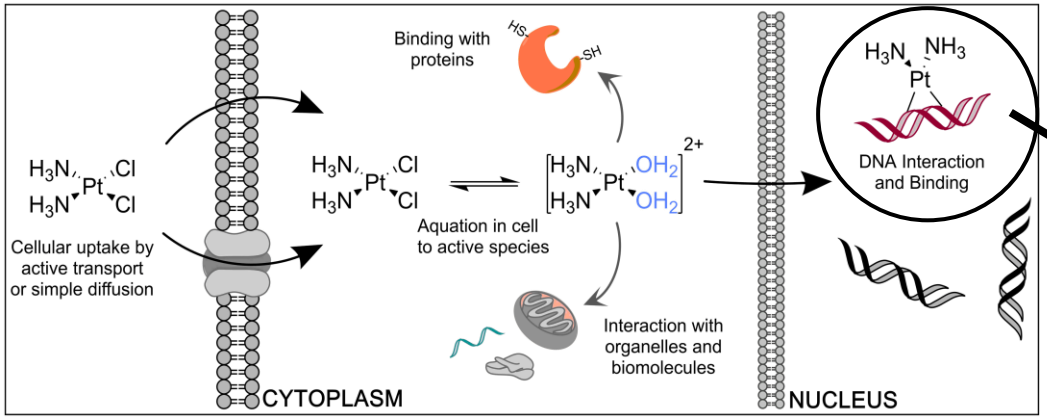
Metal complexes in medicine

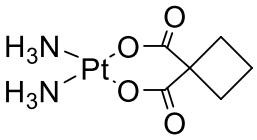


1960 Barnett Rosenberg
Cisplatin

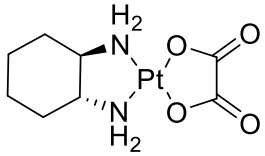


Cell death following DNA damage

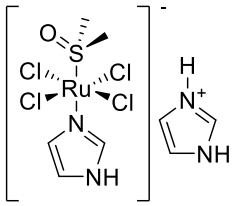
Searching new metal-based drugs…



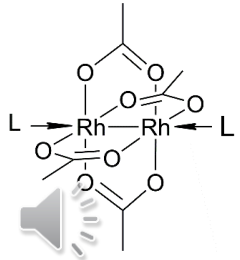
carboplatin



oxaliplatin



NAMI-A



dirhodium tetraacetate

N. Z. Fantoni, T. Brown, A. Kellett, *Chem.Bio.Chem.*, 22 (**2021**) 2184–2205, S. Dasari and P. B. Tchounwou, *European Journal of Pharmacology*, 740 (**2014**) 364–378.

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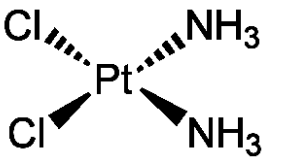

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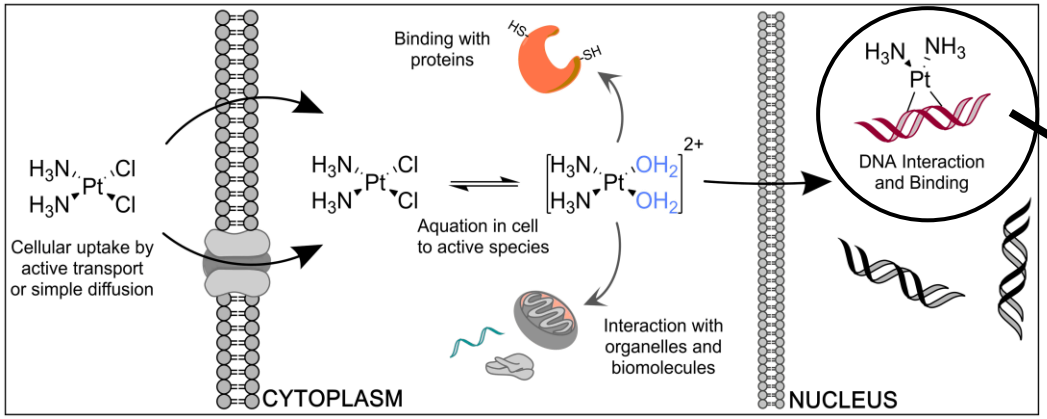

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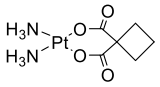

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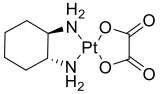
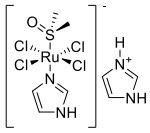


oxaliplatin



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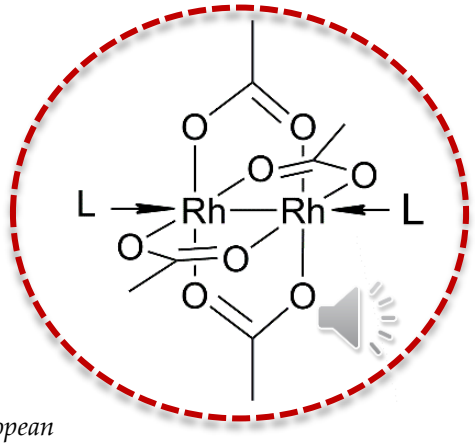

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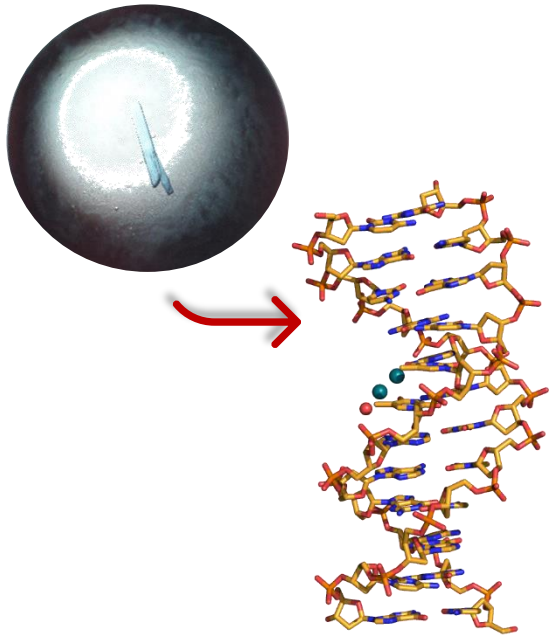
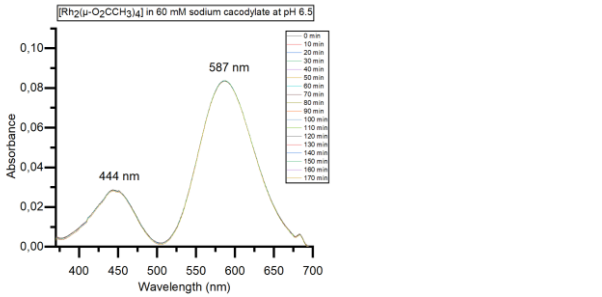
Aim of the work

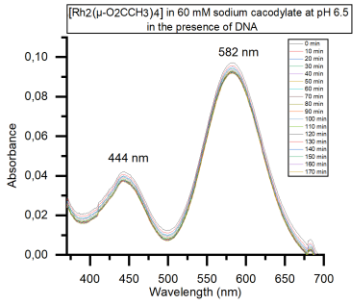
Studies of the interaction between dirhodium tetraacetate compound and a B-DNA double helical dodecamer by:

1. X-ray crystallography

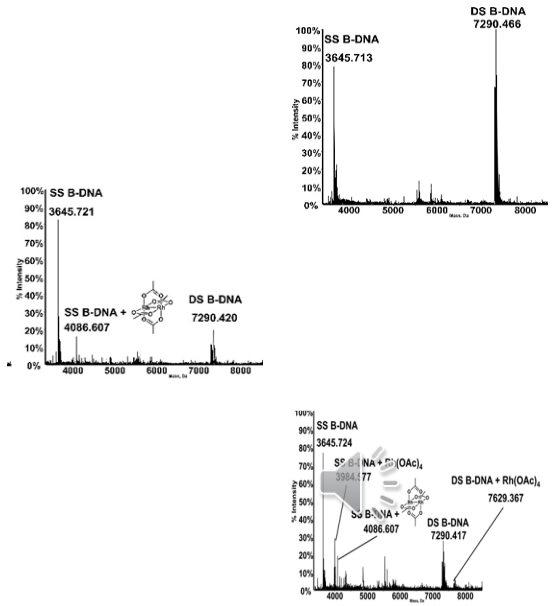


2. Spectroscopic technique



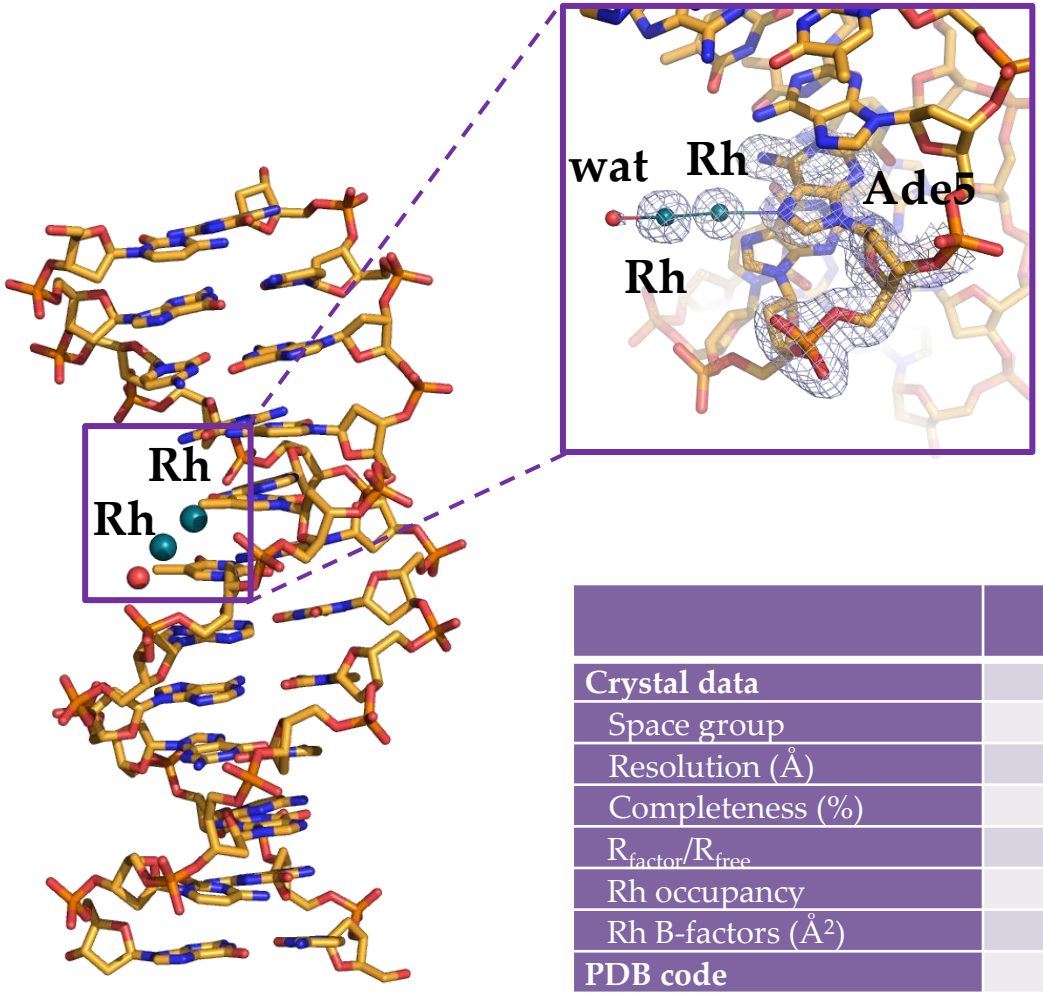


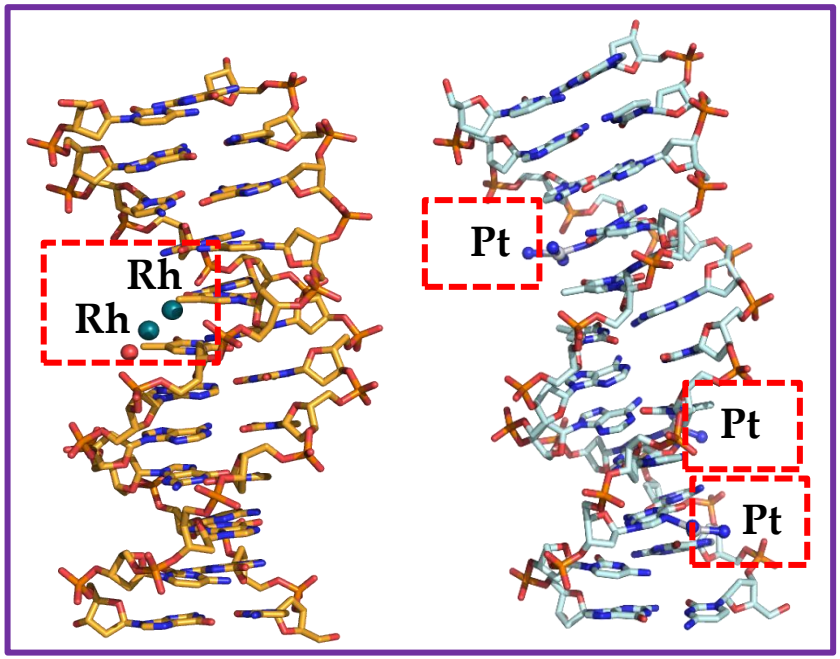
3. Mass spectrometry



Results

1. X-ray crystallography





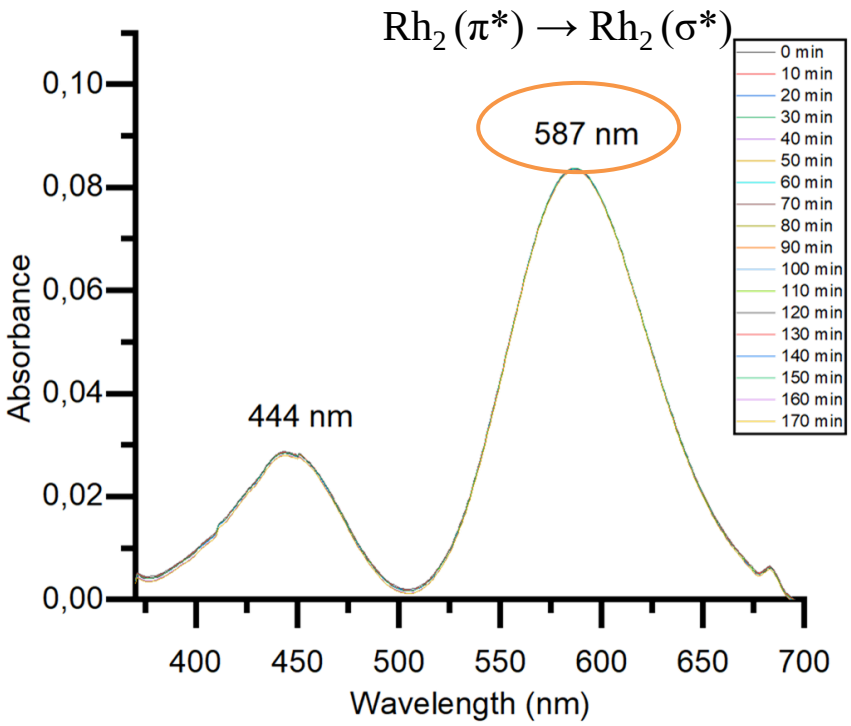
	$[Rh_2(\mu\text{-}O_2CCH_3)_4]$/DNA adduct
Crystal data	
Space group	$P2_12_12_1$
Resolution (Å)	1.24
Completeness (%)	99.9 (100.0)
R_{factor}/R_{free}	0.197/0.223
Rh occupancy	0.20/0.20
Rh B-factors (Å^2)	19.94/24.30
PDB code	8CE2

G. Tito, R. Troisi, G. Ferraro, A. Geri, L. Massai, L. Messori, F. Sica, and A. Merlino. Dalton Trans. **2023**, 52, 6992-6996.

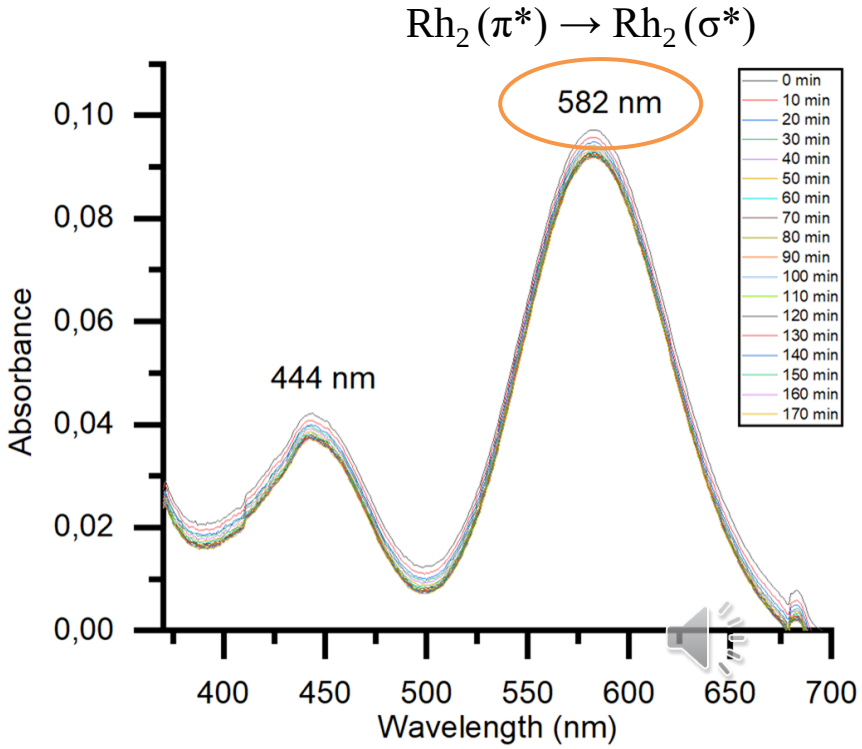
Results

2. Spectroscopic technique

[$Rh_2(\mu\text{-}O_2CCH_3)_4$] in 60 mM sodium cacodylate at pH 6.5

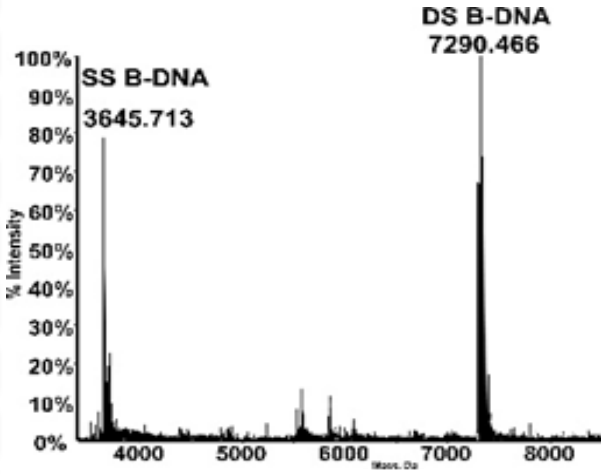


[Rh2(μ-O2CCH3)4] in 60 mM sodium cacodylate at pH 6.5 in the presence of DNA



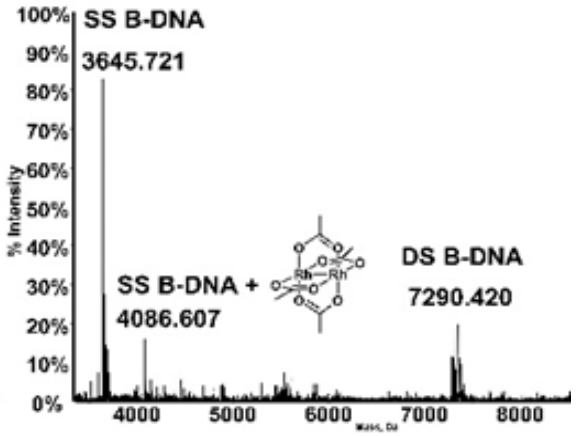
Results

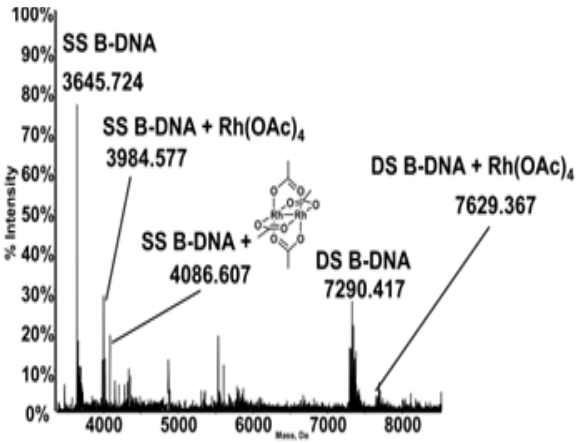
3. Mass spectrometry



Deconvoluted ESI-MS mass spectra of B-DNA

Deconvoluted ESI-MS mass spectra of B-DNA with dirhodium tetraacetate in a 1:5 DNA to complex ratio **(incubation 5 h).**





Deconvoluted ESI-MS mass spectra of B-DNA with dirhodium tetraacetate in a 1:5 DNA to complex ratio **(incubation 24 h).**

Conclusions

- ✓ The results of this work reported the first crystal structure of an adduct formed upon reaction of a dirhodium paddlewheel complex, $[Rh_2(\mu\text{-}O_2CCH_3)_4]$, and a DNA duplex model system.

- ✓ The present data also indicate that dirhodium tetraacetate reacts with DNA **differently from cisplatin**: the Rh-Rh center binds to the N7 atom of an adenine, at the axial position, instead of the N7 atom of a guanine.

- ✓ These results support the idea that dirhodium compounds are able to bind to DNA and provide new insights for the understanding of the molecular basis of the antitumor activity of dirhodium tetracarboxylates.

Acknowledgments

We gratefully acknowledge the Elettra Synchrotron staff for their assistance during data collection.

Elettra Sincrotrone Trieste