IN SILICO INSIGHTS INTO DNA-BINDING OF RUTHENIUM(II)-ARENE ANTICANCER COMPOUNDS

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The discovery of cisplatin as an anticancer drug led to considerable interest in metallopharmaceuticals. Problems remain associated with their use, including general toxicity, drug resistance and low selectivity. Recently, organometallic ruthenium(II) arene complexes showed there potential to overcome this drawback. Rational design requires a detailed understanding of structure-property relationships at an atomistic level.

We performed classical MD and mixed QM/MM Car-Parrinello MD simulations[1] to rationalize the binding mode of two series of anti-cancer ruthenium(II) arene complexes to double-stranded DNA (dsDNA). The bifunctional RAPTA [Ru(η^6-arene)X_2(PTA)] (**1**)[2] (PTA=1,3,5-triaza-7-phosphatricyclo [3.3.1.1] decane) and the monofunctional [Ru(η^6-p-cymene)Xen] (**2**)[3-4] series of compounds were both bound to the dsDNA sequence d(CCTCTG*G*TCTCC)/d(GGAGACCAGAGG), where G* is guanosine that binds to the ruthenium compounds through its N7 atom. As reference, the same sequence was also simulated without any drug and in its canonical, unperturbed B-DNA form.

The local and global structural modifications of dsDNA upon complexation were analysed in detail. In particular the induced "bending angle" of dsDNA, which is thought to be a trigger for apoptosis, is investigated in depth.
The differences of the DNA-interaction-properties between the two series of compounds as well as with respect to the canonical B-DNA are discussed and linked to experimental observations. In particular, an atomistic description of a Watson-Crick base-pair break upon binding of **2** to dsDNA is proposed, that has been recently suggested on the bases of experimental results.[5]

Fundamental differences between binding of **1** or **2** to single stranded DNA (ssDNA) or dsDNA are rationalized.[6]

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