4P069

QM/MM Study of Piano-Stool Ru(II) Complexes Interacting with DNA

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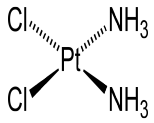
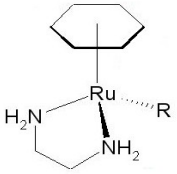
Introduction



Cisplatin

Piano-stool Ru(II) complexes are interesting for their promising anti-cancer activity against some type of tumours. In medical practice is up to the present days abundantly used a successful chemotherapeutic drug cisplatin (*cis*-diammine-dichloroplatinum(II)) but unfortunately this drug has also many side effects and cancer cells can get resistance to it. Reaction mechanism of cisplatin was studied intensively and is quite well known now. The drug enters cancer cell by passing through cell membrane, activation reaction proceeds when one or both chlorine is interchanged by water molecule and after that the complex interacts with DNA. Position N7 on guanine is especially preferred. Crucial is creation of bridge between two adjacent guanines and consequent deformation of DNA which is mortal for the cell.



Ru(II) Piano-Stool Complex

After success of cisplatin research of anti-cancer drugs concerned mainly on transition metal complexes. Besides titanium and rhodium complexes are ruthenium compounds intensively studied both experimentally and theoretically in these days. Several Ru(III) and Ru(II) complexes exhibit antitumoral and/or antimetastatic activity. This computational study is concern on complex $[(\eta^6\text{-benzene})Ru^{II}(en)Cl]^+$ and its interaction with DNA. Experimentally is known that this complex form strong monofunctional adduct with DNA and similarly to cisplatin the N7 position on guanine is preferred as binding site. We have shown that also computationally from energy point of view in our previous QM study [1].

Purpose of our study is to describe interaction of $[(\eta^6\text{-benzene})Ru^{II}(en)Cl]^+$ complex with DNA and compare it with interaction of cisplatin. Because of similarities in behaviour of these two complexes we would like to find out if also Ru(II) complex causes deformation of DNA and if so how does it do it. Is binding to one guanine only sufficient enough for blocking transcription of DNA? Is there any possibility of creation of intrastrand cross-link like cisplatin does? How does an arene ligand interact with DNA and why complexes with bigger arene ligand (biphenyl, dihydro- and tetrahydroantracene) have stronger biological activity? We will try to answer these questions by QM/MM computational simulations and present some up-to-date results here.

Theory

QM/MM methodology can be used for studying large molecular system which can be divided into two region: small core which is described by QM level of theory and the rest that can be parametrized by MM force field. There is several ways how to calculate total energy of such divided system and how to treat mutual interaction of these two regions. We use subtractive scheme for total energy: $E_{\mathrm{QM/MM}}(S) = E_{\mathrm{MM}}(S) + E_{\mathrm{QM}}(I+L) - E_{\mathrm{MM}}(I+L)$

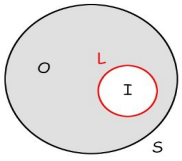


Fig. 1:QM/MM parts

Electrostatic interaction between QM and MM region is calculated by electronic embedding approach, i.e. atomic point-charges from MM part are included in QM Hamiltonian and wave function is polarized as a result. If there is a chemical bond between QM and MM part dangling atoms are saturated by hydrogens. Position of these hydrogens (link atoms) is forced to be on cut bond in specified distance in order to remove artificially added degrees of freedom.

We use our own implementation which is based on U. Ryde's code ComQum [2]. It is an interface for standard QM and MM software packages used for energy and force calculation. Optimization methods (SD, CG, L-BFGS) and molecular dynamics (Velocity Verlet) are part of this code.

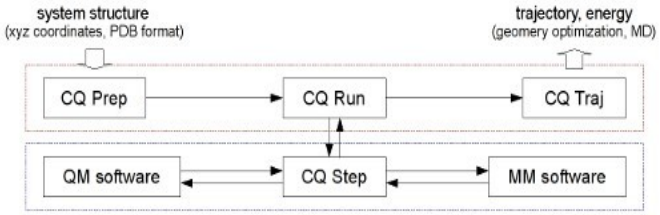


Fig. 2: ComQum modules diagram

Computational details

As we want to study deformation changes on DNA helix our model has to include at least several nucleic base pairs. For the beginning we built model consisting of 10 base-pair DNA oligonucleotide with sequence 5'-AATGGGACCT-3' (standard B-DNA structure parameters, Watson-Crick base-pairing) and $[(\eta^6\text{-benzene})Ru^{II}(en)H_2O]^+$ complex. All system is electrically neutralized by 18 Na^+ cations and surrounded by explicit water molecules.

The computational model is divided into two regions which are described at different level of molecular theory as is usual for QM/MM approach. Central part of the model including Ru(II) complex and two nearest guanines connected by deoxyribose and phosphate group is the most important part of the model and is described by DFT(B3LYP)/6-31G(d)/6-31++G(2df,2pd) implemented in Gamess. Rest of the system is parametrized by Amber FF96.

Results

Structure of reactant and product of reaction when Ru(II) complex is bound to guanine N7 in DNA were fully optimized and compared with geometries from previously done QM study [1]. Phosphate groups interact electrostaticaly with charged Ru(II) complex and that leads to structure distortion and stabilization. Stabilization effect has also hydrogen bond between oxygen O6 on guanine and hydrogen on ethylendiammine. Distance between central Ru cation and N7 nitrogen on guanine is shorten from 2.35 Å in QM calculation to 2.26 Å calculated by QM/MM. Also reaction energy is lowered from -7.53 kcal/mol [1] by several kcal/mol. From these first results it seems that interaction of Ru(II) complex with guanine is underestimated in QM calculations as result of lacking electrostatic interaction with phosphate groups. Also steric effects of molecular surrounding has influence on the structure. Detailed analysis of bonding energies, molecular orbitals and charge densities will be presented.

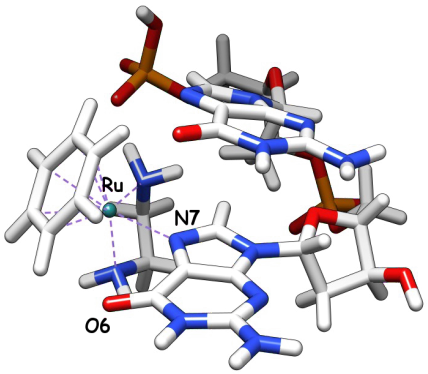


Fig. 3: QM core of the product structure

References

[1] Futera, Z.; Klenko, J.; Sponer, J.E.; Sponer, J.; and Burda, J.V.: *J. Comput. Chem.* **30**, 2009, p1758-1770.
[2] Ryde, U.: *J. Comput.-Aided Mol. Design* **10**, 1996, p153-164.