Dynamic Studies of Biomolecule Platination by UV-Spectroscopy: New Tricks for the Old Dog

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Several compounds of platinum, e.g. cisplatin and carboplatin, display strong cytostatic acitvity and are potent anticancer drugs, widely used in clinics. Extensive studies of mechanism of action of platinum drugs and platinum-induced DNA damage were held in last decades. Yet transport and early steps of platinum drug transformation in living organisms remain elusive. Evidence appeared, that platinum drug distribution and activation *in vivo* is not passive, but is greatly assisted by proteins, especially copper transporters [1]. Though platination of pure DNA is a well studied process, the relative rates of reactions with therapy target (DNA), and toxicity and side targets (proteins) are poorly studied, and many controversies remain. The characterization of these processes is important, as they should directly affect structure-activity relationships and may be used for design of more potent and less toxic metal-based drugs.

Platinum concentrations in biologically relevant systems are small, the reactions are relatively fast and biomolecules may be large, so the number of methods applicable to kinetic studies is limited. Spectroscopy in UV-region (absorption, circular dichroism (CD)) is among the simplest methods, suitable for such studies. But platinum drugs do not have any intense, typical UV-bands in solutions are broad and spectral changes are highly correlated. So UV-spectroscopy is rarely used for quantitative kinetic studies of platination reactions, because of low accuracy of obtained data. In the present work we developed a method, that allows to determine the number of intermediate stages and rate constants more accurately. It is based on transformation of the set of spectra, resembling primary component analysis (PCA). PCA-like method was verified on simulated and real problems and displayed properties, superior to simple methods, typically used in UV-spectroscopy kinetic studies. We studied the reactions of sulfur-containing (S-donor) biomolecules with cisplatin and new chiral platinum complexes, and platination of DNA in the presence of competing S-donor molecules by UV- and CD-spectroscopy and PCA-like approach. The results show, that typical rates of DNA damage in the absence and in the presence of S-donor biomolecules are of the same order. But the amount of DNA damage is very variable, up to complete blocking of platination. It depends mostly on the nature of S-donor, DNA/sulfur ratio and ion concentrations in the solution.

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[1] Safaei R. Role of copper transporters in the uptake and efflux of platinum containing drugs. // Cancer Lett. **234**, 1 (2006) :Pp. 34-39.