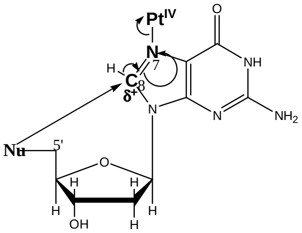
Mechanism and Kinetics of Oxidation of Guanosine Derivatives by Pt(IV) Complexes

Sunhee Choi, Richard B. Cooley, Adelina Voutchkova, Chin Hin Leung,
Livia Vastag, Darcy E. Knowles, Adam M. Beard

Department of Chemistry and Biochemistry, Middlebury College, Middlebury, VT 05753

Platinum complexes are biologically important for their anticancer activities. The interaction of DNA with Pt^{II} complexes has been extensively studied by many research groups. Pt^{IV} complexes are kinetically inert and their reaction with DNA was not generally expected. However our lab discovered that Pt^{IV} complexes with highly electron-withdrawing and bulky ligands have high reduction potentials and high reactivity toward 5'-GMP. Furthermore, a Pt^{IV} complex, *trans*-Pt(*d,l*)(1,2-$(NH_2)_2C_6H_{10}$)Cl_4, [$Pt^{IV}Cl_4$(dach)], which has a high reduction potential, oxidizes 5'-dGMP, 3'-dGMP and 5'-d[GTTTT]-3'. The proposed mechanism involves Pt^{IV} binding to N7 of the guanosine moiety followed by nucleophilic attack of a 5'-phosphate or 5'-hydroxyl oxygen to C8 of G and an inner-sphere, two-electron transfer to produce cyclic (5'-O-C8)-G and Pt^{II} complex. The identity of the final oxidized G depends on the hydrolysis rate of the cyclic intermediate. The cyclic phosphodiester intermediate formed from [Pt^{IV}]/5'-dGMP is hydrolyzed to 8-oxo-5'-dGMP. However the cyclic ether intermediate formed from [Pt(IV)]/3'-dGMP (or 5'-d[GTTTT]) does not hydrolyze, and the cyclic form is the final oxidation product. The Pt^{IV} complex simply binds to N7 of the G moiety in cGMP, 9-Mxan, 5'-d[TTGTT]-3' and 5'-d[TTTTG]-3' without further redox reaction. The results indicate that a nucleophilic group at the 5' position is required for the redox reaction between guanosine and the Pt^{IV} complex.



The kinetic curves of the reaction of Pt^{IV} with dGMP exhibits autocatalysis because the redox reaction generates Pt^{II} species and the substitution reaction is Pt^{II} catalyzed. The kinetic curves will be analysed using eq. (1) to obtain kinetic data which we hypothesize will depend on the Pt^{IV} reduction potentials and the guanosine structures.

$$A_t = A_\infty + (A_o - A_\infty)\frac{\alpha e^{-\alpha t}}{[\alpha - \beta(1 - e^{-\alpha t})]} \qquad \text{eq. (1)}$$