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

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Platinum complexes are biologically important for their anticancer activities. The interaction of DNA with PtII complexes has been extensively studied by many research groups. PtIV complexes are kinetically inert and their reaction with DNA was not generally expected. However, our lab discovered that PtIV complexes with highly electron-withdrawing and bulky ligands have high reduction potentials and high reactivity toward 5'-GMP. Furthermore, a PtIV complex, trans-Pt(d,l)(1,2-(NH2)2C6H10)Cl4, [PtIVCl4(dach)], which has a high reduction potential, oxidizes 5'-dGMP, 3'-dGMP and 5'-d[GTTTT]-3'. The proposed mechanism involves PtIV 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 PtII complex. The identity of the final oxidized G depends on the hydrolysis rate of the cyclic intermediate. The cyclic phosphodiester intermediate formed from [PtIV]/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 PtIV complex simply binds to N7 of the G moiety in cGMP, 9-Mxan, 5'-d[TGTGT]-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 PtIV complex.

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

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A_t = A_\infty + (A_0 - A_\infty) \frac{\alpha e^{-\alpha t}}{[\alpha - \beta (1 - e^{-\alpha t})]} \quad \text{eq. (1)}
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