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Crystal Structures of Three Anticancer *cis*-[(4R,5R)- 4,5-Bis(aminomethyl)-2-alkyl-1,3-dioxolane-N,N']malonato-O,O')platinum(II) Complexes and The Model Structure of an Intrastrand DNA Adduct Obtained by Molecular Dynamics Simulations

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Cisplatin [*cis*-diamminedichloroplatinum(II)] is one of the effective anticancer agents currently available, but its clinical usefulness is limited by serious toxicity, development of acquired resistance and poor solubility in water. The title compounds, synthesized in a search for alternative active agents in SK Chemicals Ltd., show a broader spectrum of the anticancer activity, lower toxicity and higher solubility in water, and one of the compounds with an isopropyl group is currently being marketed as an intravenous drug with the brand name of 'Sunfla'.

Crystal structures of three compounds containing the (**1**) 2-methyl, (**2**) 2,2-dimethyl and (**3**) 2-isopropyl groups have been determined by the X-ray crystallographic method. All three crystals belong to monoclinic space group $P2_1$ with two molecules in the asymmetric unit. Cell parameters are a = 7.237, b = 30.704, c = 7.168 Å, β = 118.08°, V = 1405.3 Å^3 for **1**, a = 7.092, b = 30.778, c = 7.126 Å, β = 116.96°, V = 1386.3 Å^3 for **2**, and a = 7.112, b = 33.615, c = 7.135 Å, β = 116.80°, V = 1522.62 Å^3 for **3**. The molecular structures and the crystal packing modes are very similar for all three compounds. The two dependent molecules in each compound are related by pseudo twofold screw axis symmetry. Owing to this pseudo symmetry, the monoclinic cell may look like the orthorhombic cell, transformed by $\boldsymbol{a'} = \boldsymbol{a} + \boldsymbol{c}$, $\boldsymbol{b'} = \boldsymbol{a} - \boldsymbol{c}$ and $\boldsymbol{c'} = \boldsymbol{b}$, with one molecule in the asymmetric unit and space group $C222_1$. In each molecule, the Pt atom is coordinated to two O and two N atoms in a square planar structure with the coordination plane nearly parallel to the ***ac*** plane. The six-membered chelate ring involving the leaving ligand assumes a conformation intermediate between the half chair and the boat forms and the seven-membered ring involving the bidentate carrier ligand assumes the twist-chair conformation. Crystal packing consists of the extensive hydrogen-bonding networks forming the two-dimensional molecular layers and weak van der Waals interactions between these layers.

It is well known that cisplatin binds directly to DNA in various modes and the major product is the intrastrand GG adduct. In order to find the structural effect of the bulky carrier ligand, an adduct between the DNA dodecamer and **3** was modeled by molecular dynamics simulations in solvent with the periodic boundary conditions, using an initial models built based on the available cisplatinated DNA crystal structure as a guide. The resulting adduct structure is highly kinked but without any serious steric hindrances and indicates that the covalent effects of Sunfla coordination on DNA structure are very similar to those of cisplatin, though the model structure differs in the overall size and the degree of rolling of the DNA duplex from the cisplatinated DNA crystal structure.

This work was supported by a grant from the Basic Science Research Institute. YC and SWC are the recipients of the Brain Korea 21 fellowship from the Ministry of Education, Korea.