The First Stable Platinum(II) Complex of *o*-Carborane-linked Bipyridine as a Potential BNCT Reagent

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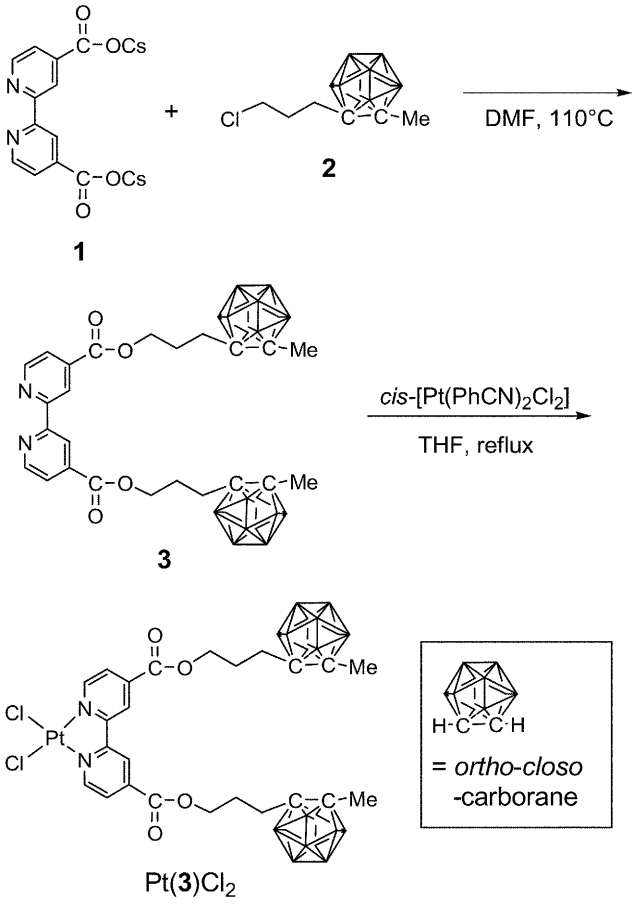
1,2-Dicarba-*closo*-dodecaborane (*o*-carborane) is one of the most stable boron clusters.[1] It is highly lipophilic, which is the required physical property in order to permeate cell membranes. Recently, a large number of compounds containing *o*-carborane have been prepared for their potential use in Boron Neutron Capture Therapy (BNCT).[2] BNCT is a bimodal cancer treatment that is currently undergoing clinical trials in several countries.[2] The therapy makes use of thermal neutrons of low kinetic energy and ^{10}B-containing drugs that are localized within malignant cells.[3] The resulting nuclear reactions with the ^{10}B nucleus ultimately lead to cell destruction in a very small volume due to the high kinetic energy (approximately 2.4 MeV) of the primary fission products ($^{7}Li^{3+}$ and $^{4}He^{2+}$). Microdosimetric calculations have shown that the radiobiological effectiveness of a capture reaction occurring in nucleus is much more effective than in cytoplasm.[4,5] With these facts in mind, a variety of organic moieties, which are known to interact with chromosomal DNA, were tethered to boron-rich moieties such as *o*-carboranes.[6] However, to date very few metal complexes have been tried as a carrier group to deliver the boron-rich compounds near to chromosomal DNA.[7,8] *cis*-Diamminedichloroplatinum(II) (cisplatin) is known to show its antitumor effects by binding to DNA of tumor cells in a covalent manner and blocking a cell proliferation.[9] Recently, Rendina et al. prepared mono- and dinuclear platinum(II)-amine complexes containing *closo*-1,2-carborane[10] or 1,7-[6] or 1,12-isomers[11] and reported their *in vitro* DNA-binding properties such as cisplatin analogs.[6]

Herein we report the preparation and characterization of the first stable platinum(II) complex containing *o*-carborane-linked bipyridine as a potential carrier group to chromosomal DNA. Carborane-linked bipyridine compound, 4,4'-(3-(1-methyl-1,2-dicarba-*closo*-dodecaborane-1-yl)carbpropoxy)-2,2'-bipyridine (**3**) was prepared by the reaction of dicesium 2,2'-bipyridine-4,4'-dicarboxylate (**1**) and 1-methyl-2-(3-chloropropyl)-*o*-carborane (**2**). (Scheme 1) 2,2'-Bipyridine-4,4'-dicarboxylic acid was converted to its cesium salt (**1**) by neutralization of the acids with aqueous Cs_2CO_3 in quantitative yield. 3-Chloropropyl-*o*-carborane (**2**) was synthesized by nucleophilic substitution of bromide ion of 1-bromo-3-chloropropane with n-butyllithium-treated 1-Me-*o*-carborane at −78 °C. The esterifiacation reaction between cesium salt of carboxylic acid and alkyl halide proceeded very slowly (3 days) at 110 °C in DMF, presumably due to very low solubility of dicesium 2,2'-bipyridyl-4,4'-dicarboxylate in DMF solvent. The crude product **3** was recrystallized from THF/Et_2O and fully characterized by ^{1}H, ^{13}C and ^{11}B NMR.[12]

Platinum complex of *o*-carborane-linked bipyridine Pt(**3**)Cl_2 was prepared by the displacement of the weakly bound benzonitrile ligands in *cis*-[$Pt(PhCN)_2Cl_2$] in THF solution by 4,4'-(3-(1-methyl-1,2-dicarba-*closo*-dodecaborane-1-yl)carbpropoxy)-2,2'-bipyridine (**3**). (Scheme 1) Without reflux heating, the complexation proceeded very sluggish, which could be ascribed to a high activation energy barrier for complexation in which the ligand acts as a



Scheme 1

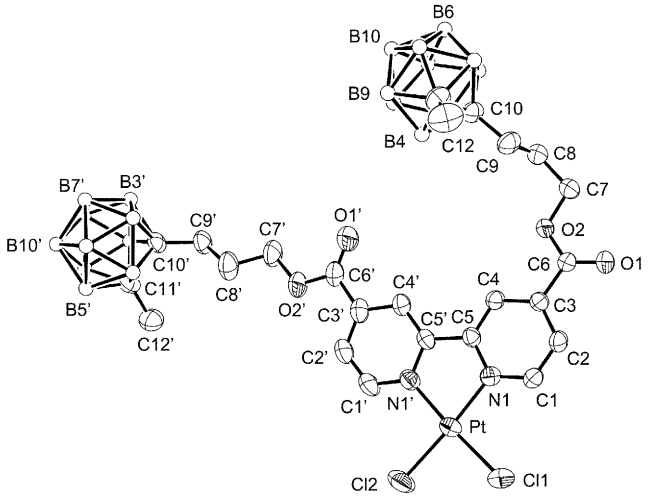


Figure 1. ORTEP drawing of Pt(**3**)Cl_2·DMF (**3**·DMF) showing the atom-numbering scheme. DMF molecule was omitted for clarity.

chelating ligand *via* two N atoms. The significant steric hindrance seems to be caused by the introduction of bulky boron cluster on each 4-position of pyridine ring, resulting in the flipping away of two nitrogen atoms in bipyridine. Pt(**3**)Cl_2 was fully characterized by various spectroscopic methods.[13] ^{195}Pt NMR spectrum showed single peak in the ranges observed for Pt(II) complexes with bipyridine derivatives.[14,15] In contrast to previously reported platinum(II) complexes containing 1-aminoalkyl-1,2-carborane ligands,[10] Pt(**3**)Cl_2 exhibited excellent stability both in solution and in the solid state. Presumably due to the high lipophilicity of incorporated carborane cages in Pt(II) complex, Pt(**3**)Cl_2 showed limited water solubility.

Molecular structure of Pt(**3**)Cl_2·DMF was determined by X-ray diffraction[16] and an ORTEP view of Pt(**3**)Cl_2·DMF was presented in Figure 1. The Pt(II) complex possesses a square planar coordination geometry with the two chloride atoms trans to the diimine N atoms.[17] The Pt-N distances of 2.007 and 2.011 Å and N-Pt-N bond angle of 80.6° agree well with values found for other Pt(II) diimine complexes.[18,19] The Pt-Cl bond distance (2.288 and 2.290 Å) and Cl-Pt-Cl bond angle (88.77°) are very similar to the corresponding values of [Pt(bu_2bpy)Cl_2].[18] Except for the substituents at 4,4'-positions of bipyridine, the molecule is remarkably planar. The average deviation from planarity of PtN_2Cl_2 is only 0.02 Å. The angle between the least-squares planes of the two pyridine subunits is only 4.0° and both two average pyridine rings form dihedral angles of 5.0° with the PtN_2Cl_2 coordination plane. The bond lengths and angles of *o*-carboranes are consistent with other corresponding values and are unremarkable.[7,20,21]

In conclusion, we prepared the first platinum(II) complex of carborane-containing bipyridine for potential use in boron neutron capture therapy. The complex was fully characterized by various spectroscopic methods including ^{195}Pt NMR spectroscopy and was found to be very stable both to air and to moisture. X-ray crystallographic structure determination revealed that the complex possesses square planar coordination geometry and the molecule is remarkably planar.

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Supplementary Material Available. Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre (Deposition No. CCDC 261762). These data can be obtained free of charge via *www.ccdc.cam.ac.uk/data_request/cif*, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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12. Compound **3**: 29% yield. ^{1}H NMR (300 MHz, DMF-d_7, 363 K): δ 8.99 (d, J = 4.9 Hz, 2H), 8.95 (d, J = 1.5 Hz, 2H), 8.01 (dd, J = 4.9, 1.5 Hz, 2H), 4.49 (t, J = 6.2 Hz, 4H), 2.67 (m, 4H), 2.23 (s, 6H), 2.13 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, DMF-d_7, 363 K): δ 165.3, 156.9, 151.1, 139.5, 123.7, 120.3, 79.7, 77.2, 65.1, 32.1, 29.2, 23.1. ^{11}B{^{1}H} NMR (96.3 MHz, DMF, 363 K): δ –5.4, –6.5, –11.1.
13. Pt(**3**)Cl_2: 81% yield. ^{1}H NMR (400 MHz, DMF-d_7): δ 9.82 (d, J = 6.1 Hz, 2H), 9.15 (d, J = 1.8 Hz, 2H), 8.37 (dd, J = 6.1, 1.8 Hz, 2H), 4.54 (t, J = 6.3 Hz, 4H), 2.69 (m, 4H), 2.24 (s, 6H), 2.15 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, DMF-d_7): δ 163.9, 158.2, 150.3, 141.2, 128.1, 124.8, 79.6, 77.3, 66.0, 31.9, 29.3, 23.2. ^{11}B{^{1}H} NMR (96.3 MHz, DMF): δ –6.5, –11.1. ^{195}Pt NMR (64.5 MHz, DMF): δ –2286. IR (KBr, cm^{-1}): 3083 w, 2972 w, 2580 vs, 1737 s, 1645 s, 1413 m, 1317 m, 1253 s, 1133 m, 1018 m, 891 w, 762 m.
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16. Crystal data for Pt(**3**)Cl_2·DMF: $C_{27}H_{51}B_{20}Cl_2N_3O_5Pt$, M = 979.90, triclinic, space group $P\bar{1}$ (No. 2), a = 11.490(3) Å, b = 12.995(3) Å, c = 16.211(2) Å, α = 79.16(2)°, β = 87.56(2)°, γ = 68.03(2)°, V = 2203.6(8) Å^3, Z = 2, d_{calc} = 1.477 g/cm^3, F(000) = 972, 7169 unique, 523 parameters, R_1 = 0.0365, wR_2 = 0.0920 (6398, $I > 2\sigma(I)$), GOF = 1.117. Data were collected on an Enraf-Nonius CAD4TSB diffractometer using graphite-monochromated Mo-K$_\alpha$ radiation. The structure was solved by Patterson method and Fourier methods and refined by full-matrix least squares based on F^2 using SHELXS 86 and SHELXL 93.
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