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Syntheses, Crystal Structures, and Antitumor Activities of the Optically Isomeric Mandelate Chelates, Mandelato(trans-1,2-diaminocyclohexane)platinum(II)

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The four optical isomers of mandelato(trans-1,2-diaminocyclohexane)platinum(II) have been prepared. The X-ray crystal structure analyses of a pair of diastereomer have confirmed that the skeletal configuration of (R)- or (S)-mandelic acid has been retained on the chelation of platinum(II). Preliminary animal test against mice leukemia L1210 has been carried out using these compounds.

Since the discovery of antineoplastic activity of cis-dichlorodiammine-platinum(II),[1] wide varieties of platinum complexes have been prepared in search of less toxic antitumor agents.[2,3] In the process of ameriolation, 1,2-diaminocyclohexane(dach) was reported as a potent ligand(carrier ligand).[4-6] The ligand, dach, was separated or resolved into three isomers, and their isomeric platinum complexes showed the antitumor activities sharply distingnished from each other.[7] Such a discrimination is supposed to derive from DNA recognitions of the incoming platinum(II) species. This point of view leads to one of the most important subjects in the drug design; the chiralities of the carrier ligand. Further emphasis should be put on the fact that the anionic ligands(leaving groups) in the platinum complexes also have the considerable influences on the antitumor activities[8,9] and would play the important roles to the drug metabolism. Accordingly the special regard will be paid to not only chiralities of the carrier ligands but those of the leaving groups.

Recently Totani et al. have reported the syntheses of a series of (glycolato-O,O')platinum(II) complexes.[10] The complexes have a novel chelate ring structure. By using the optically active mandelate(md) as a leaving group instead of glycolate, a chiral point will be brought about in the vicinity of platinum(II).

We report here the preparation, the first structure determination and antitumor activities of the mandelate chelates, mandelato(trans-1,2-diaminocyclohexane)platinum(II) (Fig.1).

The complexes 1-4 were synthesized by the modification of the literature method (Scheme 1).[10] The dihydroxo complex was neutralized by addition of the equivalent amount of mandelic acid. The procedure results in the five-membered chelation of platinum(II). The neutralization is relatively slow process: after

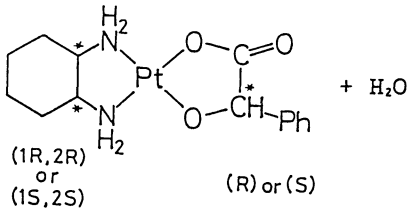
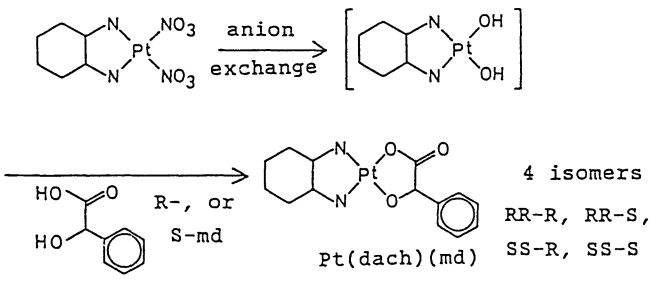


Fig. 1. Proposed Structure of [Pt(dach)(md)]·H_2O.
1 (1R,2R)-(R) 2 (1R,2R)-(S)
3 (1S,2S)-(R) 4 (1S,2S)-(S)



Scheme 1.

overnight standing of the reaction mixture at room temperature, oily material was only obtained while the heating of the aqueous solution at 60 °C for several hours gives the crystalline solid. However, at higher temperature (>80 °C), the solution gradually turned red. The coloring indicates a partial decomposition of the platinum(II) alkoxide. The solid products were purified by recrystallization from water.[11]

Among the four optical isomers, a pair of diastereomers, 1 and 2, were applied to X-ray crystal structure analysis.[12]

The molecular structure of 1, i.e., the crystallographically independent unit, is shown in Fig.2. In crystals, two complexes and two water molecules form rather discrete clusters; the two independent complexes are related by pseudo 2-fold axis. Their coordination planes are approximately perpendicular to each other. The configurations of the ligands are retained in comparison with the corresponding free amine or acid. The RR-dach has λ-gauche chelate conformation. The mandelate ligand shows bidentate chelation to the platinum atom with carboxylate and alcoholate. Though several mandelate transition metal complexes have been reported, their mandelate groups are bound to the metals using only carboxylate oxygens.[13,14] Thus the complex 1 is the first example of the mandelate chelate. This type of five-membered chelation has been proposed to glycolatoplatinum(II) in solution, but the solid state structure is unknown to date. The phenyl group of mandelate rises up to the axial direction to the coordination plane. Such a direction is possibly resulted from the crystal packing. Consequently the R-md has δ-gauche conformation in the solid state.

The diastereomer 2 has the structural features analogous to 1. Both ligands, RR-dach and S-md, have λ-gauche conformations. A pair of diastereomers 1 and 2 have a typical square planar coordination except rather small N-Pt-N and O-Pt-O angles due to the five-membered chelation.

Between the alcoholates and the water molecules, strong hydrogen bonds are formed. The hydrogen bonding patterns of both isomers resemble to each other, but the hydrogen-bond distribution in 2 within the distance 2.95 Å is more frequent than that in 1. The slight difference in hydrogen-bond distribution indicates that 2 is more ionic than 1. Actually solubilities of diastereomers are different from each other. The complex 2 (15.3 mg/ml H_2O at 26 °C) is more

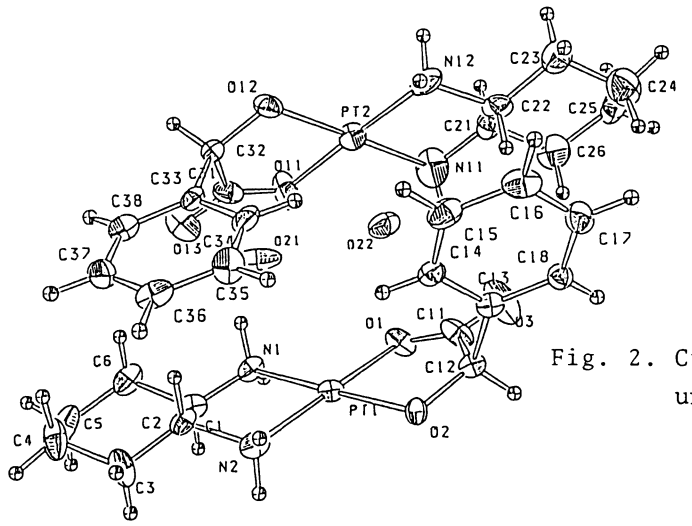


Fig. 2. Crystallographyically independent unit of 1. View along b-axis.

soluble than 1 (7.8 mg/ml H_2O). The experimental fact supports the above speculation.

Historically the platinum alkoxides are believed to be unstable,[15] and few examples have been reported so far.[16-18] In complexes 1-4, the metal alkoxide bond may be stabilized by five-membered chelation.

The results of animal test against mice leukemia L1210 are listed in Table 1. The complexes show antitumor activities to a certain extent but the activities are not so high. On the other hand, the toxixities are greatly reduced, compared to cis platin. The four optical isomers exhibit differences in antitumor activities. The complex 1 is effective in a wide range of dose amount where its enantiomer 4 shows no activity. The antitumor activity of 1 is similar to that of 2, but toxic dose is different.

Table 1. Antitumor Activity against Mice Leukemia L-1210

Isomer	T/C(%)					
	Dose (mg/kg)					
	400	200	100	50	25	12.5
1	Toxic	126 P	190 P	162 P	137 P	109
2	138 P	160 P	132 P			
3	126 P	156 P	108			
4	Toxic	124	114			

10^5 cells/mouse were transplated i.p. into CDF1 mice (6 mice/group) and samples were administered i.p. on day 1, 5, and 9. From the mean survival times of treated (T) and control (C) mice, T/C values are calculated as indicators of the activity. T/C value over 125 was evaluated as antitumor active and indicated with P.

All these facts together demonstrate that the chiralities of not only the carrier ligands but of leaving groups influence the antitumor activities of the complexes.

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11) Elemental analyses Found: 1 C, 35.16; H, 4.65; N, 5.86. 2 C, 35.37; H, 4.62; N, 5.86%. 3 C, 35.09; H, 4.53; N, 5.81%. 4 C, 35.23; H, 4.62; N, 5.75%. Calcd. for $C_{14}H_{22}N_2O_4Pt$: C, 35.22; H, 4.64; N, 5.87%.
12) Crystallographic data 1: Fw=477.43, monoclinic, $P2_1$, a=11.778(2); b=10.930(2); c=12.217(2) Å, β=90.71(2)°, V=1572.6(9) Å^3, Z=4, D_x=2.02; D_m=1.99 g cm^{-3}, R=0.042, wR=0.039 for 3053 reflections. 2: Fw=477.43, monoclinic, $P2_1$, a=11.886(1); b=10.623(2); c=12.104(1) Å, β=92.98(1)°, V=1526.3(6) Å^3, Z=4, D_x=2.08, D_m=2.06 g cm^{-3}, R=0.042, wR=0.052 for 3219 reflections. Details of the X-ray structure analysis are reported in the following: T. K. Miyamoto, K. Okude, K. Maeda, H. Ichida, Y. Sasaki, and T. Tashiro, submitted to Bull. Chem. Soc. Jpn.
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