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Subtle Ring Size Effects on Bonding Mode. Structures and Properties of Platinum(II) Complexes Involving Sulfur-Containing Dicarboxylate Ligands

$\overline{\mathrm{S-(CH_2)}_n\mathrm{-S-C}}\mathrm{=C(COO^-)_2}$ ($n = 2, 3, 4$)

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Introduction

The platinum complexes of natural amino acids and their derivatives such as methionine, glutathione, and *S*-ethylcystein *etc.* have been of wide interest because of their biological aspects and the variety of their structural properties.[1−4] For example, the reaction of $(NH_3)_2Pt(H_2O)_2^{2+}$ with methionine afforded mixtures of O,S- and S,N-chelate isomers[5] whereas the product prepared from K_2PtCl_4 and methionine resulted in only a single S,N-chelated complex which is the thermodynamically more stable isomer.[6] In particular, the S,N-chelate of $[Pt(methionine)_2]^{2+}$ was found in the urine of patients and confirmed as a metabolite of cisplatin.[2,7] Although the bonding modes of such multidentate ligands are known from solution studies[5,6,8,9] to be sensitive to various factors, not many chemically active platinum complexes of multidentate ligands have been isolated and fully characterized by X-ray analysis.

A series of ylidenemalonates containing sulfur atoms have been used as fascinating multidentate ligands for platinum complexes in our laboratory.[10,11] These malonate-derivative ligands containing dithioether rings may coordinate to a platinum atom via one of three distinct modes of O,O′-, O,S-, or S,S′-chelation. Such a variety of chelation modes has stimulated our interest in understanding the coordination chemistry of platinum complexes. Here are reported the structural properties of new diamineplatinum(II) complexes of the sulfur-containing dicarboxylate ligands[12−14] $\overline{\mathrm{S-(CH_2)}_n\mathrm{-S-C}}\mathrm{=C(COO^-)_2}$ ($n = 2$, 1,3-dithiolan-2-ylidenemalonate (DTOYM); $n = 3$, 1,3-dithian-2-ylidenemalonate (DTAYM); $n = 4$, 1,3-dithiapan-2-ylidenemalonate (DTEYM)) exhibiting all the three coordination modes in solid state.

Experimental Section

Materials and Instrumentation. Reagent grade potassium tetrachloroplatinate(II) (Kojima), (1*R*,2*R*)-(−)-1,2-diaminocyclohexane-(DACH) (Aldrich), and aqueous ammonia (Kanto) were used as received. Esters of the DTAYM and DTEYM ligands prepared by the literature methods[12−14] were hydrolyzed with 2 equiv of potassium hydroxide in 95% ethanol at boiling temperature, and the resulting dipotassium salts were converted to barium salts by treating with $BaCl_2$. *cis*-Diamineplatinum(II) iodides were also prepared by the literature method.[10] ^1H NMR spectra were recorded on Varian Gemini 300 and 500 instruments operating at 300 and 500 MHz, respectively. Elemental analyses were performed at the Advanced Analysis Center at KIST.

Synthesis of A_2Pt(DATYM-*O,S*) (A_2 = DACH, $2NH_3$). To A_2PtI_2 (3.0 mmol) suspended in water (50 mL) was added dropwise an equimolar aqueous solution of Ag_2SO_4 (200 mL), and the reaction mixture was stirred for 4 h. After silver iodide was filtered off, the filtrate was added dropwise to a rapidly stirred aqueous solution of Ba[DTAYM]·$2H_2O$ (1.17 g, 3.0 mmol) and the reaction mixture was stirred for an additional hour. After the barium sulfate precipitated was filtered off, the resultant solution was condensed to 30 mL and then left for 2 weeks at room temperature. Pale yellow crystals of (DACH)Pt(DTAYM-*O,S*) (yield: 80.6%) and $(NH_3)_2$Pt(DTAYM-*O,S*) (yield: 65.5%) were deposited. Anal. Calcd for (DACH)Pt(DTAYM-*O,S*)·$4H_2O$: C, 26.0; H, 4.71; N, 4.67. Found: C, 26.2; H, 4.48; N, 4.71. ^1H NMR (D_2O, ppm): DACH (1.15(br, 2H), 1.35 (br, 2H), 1.60 (br, 2H), 2.10 (d, 2H), 2.30−2.60 (m, 2H)); DTAYM (2.40 (2H), 3.15 (1H), 3.28 (1H), 3.34 (1H), 3.74 (1H)).

Anal. Calcd for $(NH_3)_2$Pt(DTAYM-*O,S*)·$2H_2O$: C, 17.4; H, 3.33; N, 5.79. Found: C, 17.8; H, 3.01; N, 5.72. ^1H NMR (D_2O, ppm): DTAYM (2.40 (2H), 3.12 (1H), 3.31 (1H), 3.42 (1H), 3.75 (1H)).

Synthesis of A_2Pt(DTEYM-*S,S′*) (A_2 = DACH, $2NH_3$). Pale yellow crystals of (DACH)Pt(DTEYM-*S,S′*) and $(NH_3)_2$Pt(DTEYM-*S,S′*) were obtained in 84.8 and 68.5% yields, respectively, using the same procedure for (DACH)Pt(DTAYM-*O,S′*). Anal. Calcd for (DACH)Pt(DTEYM-*S,S′*)·$2H_2O$: C, 29.1; H, 4.53; N, 4.85. Found: C, 29.0; H, 4.69; N, 5.10. ^1H NMR (D_2O, ppm): DACH (1.10(br, 2H), 1.35 (br, 2H), 1.60 (br, 2H), 2.00−2.15 (m, 2H), 2.50 (br, 2H)); DTEYM (2.26(m, 2H), 2.85 (m, 2H), 3.32 (m, 4H)).

X-ray Analysis of (DACH)Pt(DTAYM-*O,S*)·$4H_2O$ and **(DACH)Pt(DTEYM-*S,S′*)·$2H_2O$.** The X-ray data were collected on an Enraf-Nonius CAD 4 automatic diffractometer with graphite-monochromated Mo Kα (λ = 0.710 73 Å) at ambient temperature. The data were corrected for Lorentz and polarization effects, and empirically for absorption (azimuthal φ scans of six reflections). The structures were solved by the Patterson method (SHELXS-86) and were refined by full-matrix least-squares techniques (SHELXL-93).[15] For (DACH)Pt(DTAYM-*O,S*), all non-hydrogen atoms except two carbon atoms (C(8) and C(10)) of the DACH group and solvated molecules were refined anisotropically. The two carbon atoms of the DACH ligand were refined isotropically due to a disorder problem. The positions of the hydrogen atoms of the solvated molecules were determined in the difference Fourier map, and the remaining hydrogen atoms were placed in calculated positions. The absolute configuration of the DACH ligand was determined on the basis of the Flack absolute structure parameters and matched with the chemical need. For (DACH)Pt(DTEYM-*S,S′*), four carbon atoms (C(6), C(7), C(8), and C(9)) of the DTEYM ligand and solvated molecules were refined isotropically, and other non-hydrogen atoms were refined anisotropically. All hydrogen atoms were added at calculated positions, and hydrogen atoms of the solvated molecules were located in the difference Fourier map. Crystal parameters and procedural information corresponding to data collection and structure are given in Table 1.

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Table 1. Crystallographic Data for $(DACH)Pt(DTAYM)\cdot 4H_2O$ and $(DACH)Pt(DTEYM)\cdot 2H_2O$

	$(DACH)Pt(DTAYM)\cdot 4H_2O$	$(DACH)Pt(DTEYM)\cdot 2H_2O$
formula	$C_{14}H_{20}N_2O_4S_2Pt\cdot 4H_2O$	$C_{14}H_{22}N_2O_4S_2Pt\cdot 2H_2O$
fw	599.58	577.59
space group	$P\bar{1}$	$P2_12_12_1$
a, Å	9.762(2)	11.094(3)
b, Å	10.209(3)	12.122(2)
c, Å	10.793(2)	13.747(2)
α, deg	65.86(2)	
β, deg	84.16(2)	
γ, deg	85.31(2)	
V, Å^3	975.5(4)	1848.8(6)
Z	2	4
d_{cal}, g cm^{-3}	2.041	2.082
abs coeff, mm^{-1}	7.448	7.849
cryst size, mm	0.33 × 0.24 × 0.33	0.42 × 0.33 × 0.13
scan range	2.07−24.97	2.36−24.98
scan type	$\omega/2\theta$	$\omega/2\theta$
no. of reflns used	3175	1589
no. of params	213	204
final difference, e Å^{-3}	1.144	0.659
final R indices $\{I > 2\sigma(I)\}^a$	R1 = 0.0275 wR2 = 0.0704	R1 = 0.0322 wR2 = 0.0837
GOF on F^2	1.107	1.072

^{a} $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. $wR2 = \sum w(F_o^2 - F_c^2)^2/\sum wF_o^4)^{1/2}$, where $w = 1/\{\sigma^2 F_o^2 + (aP)^2 + bP\}$ where $P = \{\max(F_o^2, 0) + 2F_c^2\}/3$.

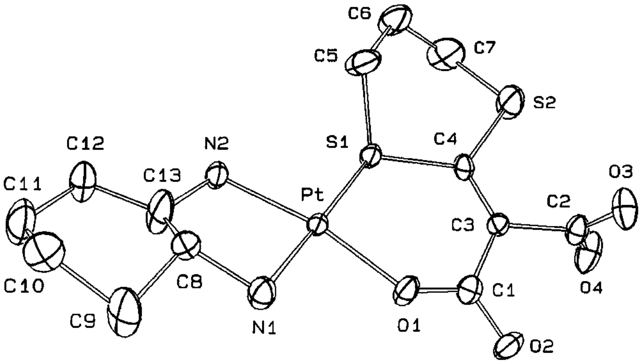

Figure 1. ORTEP drawing of $(DACH)Pt(DTAYM)\cdot 4H_2O$ showing the atomic labeling scheme and thermal ellipsoids at the 50% level.

Results and Discussion

The reaction of diamineplatinum(II) sulfate with barium salts of the appropriate dicarboxylate ligand in aqueous solution at room temperature afforded the title complexes (DACH)Pt(DTAYM) and (DACH)Pt(DTEYM), and their ammine analogs. All reactions were carried out under the same conditions. Only a single O,O′-chelate was obtained for the DTOYM in our previous work[11] and only a single O,S-chelate for DTAYM even prior to recrystallization. However, for the DTEYM complexes, (DACH)Pt(DTEYM) and $(NH_3)_2Pt(DTEYM)$, an isomeric mixture of O,S- and S,S′-chelates was afforded in the approximate mole ratios of 1:9 and 1:1, respectively, at the beginning of the preparative reaction, but the O,S-chelate isomerizes to the thermodynamically more stable S,S′-chelate on standing, which will be published separately.[16] The complexes were yellow or pale yellow crystals, which are moderately soluble in aqueous solution at room temperature.

The molecular structure of (DACH)Pt(DTAYM-*O,S*) is depicted in Figure 1, and the relevant bond distances and angles are listed in Table 2. As expected, the local geometry around the platinum(II) atom approximates to a square planar arrangement, but the most interesting feature in the molecular structure is the bonding mode of the anionic DTAYM ligand. The ligand is coordinated to the platinum atom through one of the two sulfur atoms on the dithian ring (Pt−S(1), 2.242(2)Å) and one carboxylate oxygen of the two carboxylate groups (Pt−O(1), 1.999(4)Å), whereas the platinum(II) atom in $(CPA)_2$Pt(DTOYM-*O,O′*)[11] has already been shown to be bonded via two oxygen atoms of the two carboxylate groups. In strking contrast, the DTEYM ligand in (DACH)Pt(DTEYM-*S,S′*) is coordinated to the platinum atom through two sulfur atoms (Pt−S(1), 2.282(4)Å; Pt−S(2), 2.271(3)Å) as shown in Figure 2. The DACH ligand in (DACH)Pt(DTEYM-*S,S′*) essentially remains the same as that found in (DACH) Pt(DTAYM-*O,S*). Thus, the platinum atom adopts a distorted square planar geometry. The angles N(2)−Pt−S(2) (100.7(3)°) and N(1)−Pt−S(1) (101.3(3)°) are splayed out with the concomitant closing of the bite angles N(1)−Pt−N(2) (81.8(4)°) and S(1)−Pt−S(2) (76.68(9)°). For both complexes there exist strong intermolecular hydrogen bonds between carboxylate groups and protons of neighboring amines (the shortest intermolecular distance: N(1)−O(2), 2.95 Å for (DACH)Pt(DTAYM-*S,S′*); N(1)−O(4), 2.95 Å for (DACH)Pt(DTEYM-*S,S′*)), which is probably responsible for the poor solubility of crystals compared with the crude powder product in aqueous solution.

Table 2. Selected Bond Lengths (Å) and Bond Angles (deg) for $(DACH)Pt(DTAYM)\cdot 4H_2O$ and $(DACH)Pt(DTEYM)\cdot 2H_2O$

$(DACH)Pt(DTAYM)\cdot 4H_2O$		$(DACH)Pt(DTEYM)\cdot 2H_2O$	
Pt−S(1)	2.242(2)	Pt−S(1)	2.282(4)
Pt−O(1)	1.999(4)	Pt−S(2)	2.271(3)
Pt−N(1)	2.038(5)	Pt−N(1)	2.08(1)
Pt−N(2)	2.046(5)	Pt−N(2)	2.06(1)
S(1)−C(4)	1.780(6)	S(1)−C(4)	1.80(1)
S(1)−C(5)	1.814(7)	S(1)−C(5)	1.821(2)
S(2)−C(7)	1.768(9)	S(2)−C(4)	1.79(1)
S(2)−C(7)	1.768(9)	S(2)−C(8)	1.83(2)
C(3)−C(4)	1.340(9)	C(3)−C(4)	1.33(2)
O(1)−Pt−S(1)	95.3(1)	S(1)−Pt−S(2)	76.6(1)
N(1)−Pt−O(1)	85.8(2)	N(2)−Pt−S(2)	100.7(3)
N(1)−Pt−N(2)	83.7(2)	N(1)−Pt−S(1)	101.3(3)
N(2)−Pt−S(1)	95.2(2)	N(1)−Pt−N(2)	81.8(4)
S(1)−C(10)−S(2)	115.2(3)	S(1)−C(4)−S(2)	103.6(5)
C(4)−S(1)−C(5)	100.8(3)	C(4)−S(1)−C(5)	102.6(6)
C(4)−S(2)−C(7)	103.7(3)	C(4)−S(2)−C(8)	102.7(6)

The bonding fashions of the O,O′-, O,S- and S,S′-chelation of the title complexes represented in Chart 1 are irrespective of

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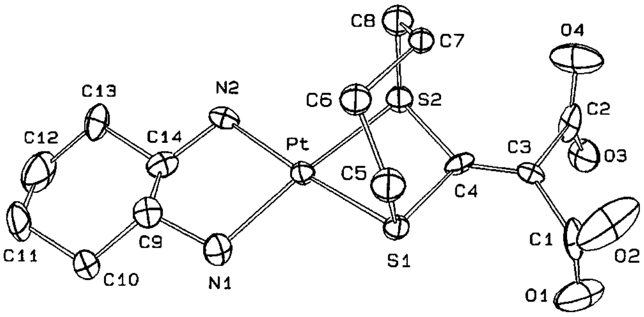
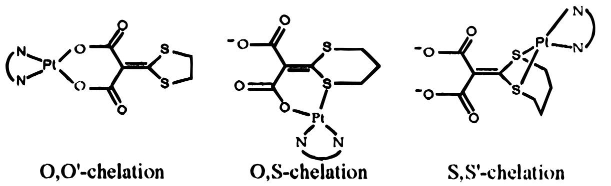
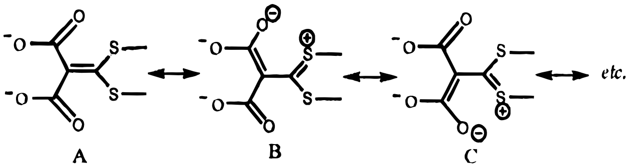


Figure 2. ORTEP drawing of (DACH)Pt(DTEYM)·$2H_2O$ showing the atomic labeling scheme and thermal ellipsoids at the 50% level.

Chart 1



Scheme 1



amine coligands, but we have found that antitumor activity of these platinum complexes is greatly dependent not only on amine coligands but also on bonding modes of the anionic leaving groups, which will be published separately.[16]

Such variable coordination modes of the title complexes may be explained in terms of the sulfur-containing ring size effect and affinity of platinum(II). It is well known that platinum(II) ion, a soft acid, generally prefers a sulfur donor atom, a soft base, to an oxygen donor, a hard base. However, in the present case the donor strength of the sulfur atom in the ligand seems to be dramatically changed presumably owing to the resonance effect shown in Scheme 1.

As a matter of fact, the four carbon and two sulfur atoms in the scheme are nearly in a plane (Tables S10 and S11), irrespective of the ring size, but the contribution of the resonance structures B and C *etc.* seems to decrease with the expansion of the sulfur-containing ring size due to the gradual breaking of the coplanar character of the ring. For illustration, the five-membered dithiolan ring is almost planar,[11] but the two carbon atoms adjacent to sulfur both in the six-membered dithian and in the seven-membered dithiepane rings are out of the above resonance planes to different degrees (Tables S10 and S11) resulting in suppression of the contribution of the lone pair π-electrons to the resonance structures. For instance, the two adjacent carbon atoms C(5) and C(7) on the dithian ring deviate from the resonance plane approximately by 1.13 and 0.27 Å, respectively, and C(5) and C(8) on the dithiepane ring by 1.67 and 1.77 Å, respectively. Bond lengths may also provide concrete evidence on the contribution of the resonance structures. The order of C=C bond lengths of the DTOYM (1.374(9)Å), DTAYM (1.340(9) Å), and DTEYM (1.33(2) Å) coordinated to platinum is consistent with the expected degree of resonance. It seems not to be meaningful to compare the C=C bond lengths of these ligands with different platinum coordination sites, but in the title complexes different bonding modes or even different metals may not influence significantly the C=C bond length. Of course, if we compare the DTAYM and DTEYM complexes, no distinguishable C=C bond lengths and the similar degree of deviations of the two carbon atoms adjacent to sulfur from the resonance plane for the DTAYM and DTEYM ligands imply that the degree of contribution of the resonance structures B and C *etc.* may be not significantly different from each other. However, the C=C bond length of the DTOYM ligand being considerably longer than a normal double bond (1.33 Å)[17] along with its ring planarity is indicative of a significant resonance effect. As a result, while the donor ability of sulfur atoms in the dithiolan ring is remarkably decreased due to the resonance effect resulting in only O,O′-chelation of the DTOYM ligand with diamineplatinum(II) cation, the basicity of sulfur atoms in the dithiepane ring seems to be barely retained, resulting in S,S′-chelation of the DTEYM ligand. The DTAYM ligand with a six-membered dithian ring may be a rare borderline case in which the donor ability of sulfur atoms is almost comparable to that of its carboxylate oxygen atoms. Of course, the dithian ring is less favorable for S,S′-chelation than the dithiepane ring in terms of ring strain, which may not, however, be a crucial factor. For instance, O,S-chelation is always sterically feasible also with the DTOYM and DTEYM ligands, bu the stable O,S-chelated form was isolated only with the DTAYM ligand.

In conclusion, the present ligands are a unique noninnocent system. For the title complexes, the three striking bonding modes were prominently observed and dramatically controlled by subtle ring size effects. Such a variety of bonding modes discloses that the electronic properties of the ligand may considerably change due to geometrical factors. Understanding various factors controlling the bonding mode should be done prior to molecular design of new platinum compounds that exhibit desirable biological activities.

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Supporting Information Available: Details of X-ray experiments, atomic coordinates, anisotropic thermal parameters, lists of bond lengths and angles, hydrogen atom parameters and least-squares planes for (DACH)Pt(DTAYM-*S,O*) and (DACH)Pt(DTEYM-*S,S′*) (11 pages). Ordering information is given on any current masthead page.

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