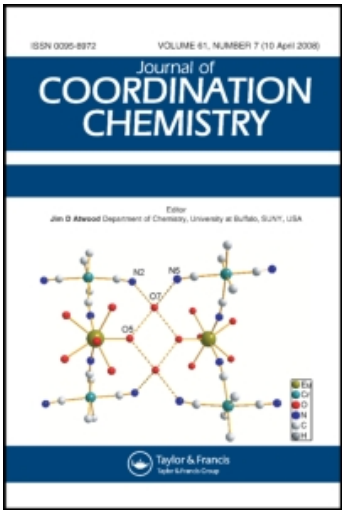

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

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To cite this Article Khokhar, Abdul R. and Lumetta, Gregg J.(1992) 'Synthesis and Characterization of *Trans-R,R-* and *Cis*-1,2-Diaminocyclohexane Platinum(II) Complexes Containing Amino Acid Ligands', Journal of Coordination Chemistry, 26: 3, 251 — 257
To link to this Article: DOI: 10.1080/00958979209409221
URL: http://dx.doi.org/10.1080/00958979209409221

J. Coord. Chem. 1992, Vol. 26. pp. 251–257
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SYNTHESIS AND CHARACTERIZATION OF *TRANS-R,R-* AND *CIS*-1,2-DIAMINOCYCLOHEXANE PLATINUM(II) COMPLEXES CONTAINING AMINO ACID LIGANDS

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(*Received 6 January 1992*)

A number of new *trans-R,R-* and *cis*-1,2-diaminocyclohexane platinum(II) complexes containing amino acid ligands has been prepared and characterized by elemental analysis, IR and ^{1}H, ^{13}C and ^{195}Pt NMR spectroscopy.

Keywords: Platinum, 1,2-diaminocyclohexane, amino acid, complexes, synthesis.

INTRODUCTION

Complexes of amino acids with platinum(II) are well known.[1] By far, the majority of these complexes contain amino acid ligands that are bound to the platinum centre in a unidentate fashion through the amino nitrogen or in a bidentate fashion though the amino nitrogen and the carboxylate group. Platinum(II) complexes containing amino acid ligands that are bound in a unidentate fashion through the carboxylate oxygen are rare. Appleton *et al.*[2] have reported the formation of *cis*-$[Pt(OCO(CH_2)_nNH_3)(OH_2)(NH_3)_2]^{2+}$ and *cis*-$[Pt(OCO(CH_2)_nNH_3)_2(NH_3)_2]^{2+}$ (n = 1, 2, or 3) complexes from the reaction of *cis*-$[Pt(OH_2)_2(NH_3)_2]$ with glycine, β-alanine or 4-aminobutyric acid. Altman and Wilchek[3] have described the synthesis of *cis-* and *trans*-$[Pt(OCOCH(NH_3)CH_2NH_3)_2Cl_2]^{2+}$. In both cases, the formation of the oxygen-bound species is contingent upon the reactions being carried out in acidic solution where the amino group is protonated.

When *cis*-$[Pt(OH_2)_2(NH_3)_2]^{2+}$ is reacted with one equivalent of glycine, *cis*-$[Pt(OCOCH_2NH_3)(OH_2)(NH_3)_2]^{2+}$ is formed along with a small amount of *cis*-$[Pt(OCOCH_2NH_3)_2(NH_3)_2]^{2+}$. Upon standing for 24 h, complete conversion to $[Pt(gly\text{-}O,N)(NH_3)_2]^{+}$ occurs. Treatment of the latter complex with an additional equivalent of glycine in alkaline solution affords *cis*-$[Pt(H_2NCH_2COO)_2(NH_3)_2]$.[4] Pivcova *et al.*[5] have reported the formation of this complex in the reaction of *cis*-$[PtCl_2(NH_3)_2]$ with glycine.

We have been studying a series of 1,2-diaminocyclohexane(DACH) platinum(II) carboxylate complexes as potential antitumor agents.[6] During the course of this work, we have investigated a series of (*trans-R,R*-DACH) platinum(II) and (*cis*-DACH) platinum(II) complexes containing amino acid (aa) ligands. We report

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here the synthesis and spectral characterization of a series of [Pt(aa)$_2$(*trans-R,R*-DACH)][7] complexes. For ligands of the type RR'NCH(R")COO-, the coordination geometry of these complexes is a function of the substitution at the amino nitrogen. When the amino nitrogen atom is unsubstituted (R = R' = H), both amino acid ligands bind to the platinum centre through the amino nitrogen, forming complexes of the type [Pt(aa-N)$_2$(*trans-R,R*-DACH)]. However, when R or R' is not H, complexes of the type [Pt(aa-N,O)(*trans-R,R*-DACH)]$^+$[aa]$^-$ are also observed

EXPERIMENTAL

Glycine, *L*(-)-proline, *L*-serine, and barium hydroxide were supplied by Fisher Scientific Co. (Houston, TX). *L*-alanine, *L*-2-azetidinecarboxylic acid, and sarcosine were purchased from Aldrich Chemical Co. (Milwaukee, WI). *N,N*-dimethylglycine was obtained from Fluka Chemical Corp. (Ronkoukoma, NY). *Trans-R,R*-1,2-diaminocyclohexane was purchased from Morton Thikol, Inc. (Danvers, MA). *Cis*-1,2-diaminocyclohexane was purchased from Turner Labs. (The Woodlands, TX). K_2PtCl_4 was purchased from Johnson Matthey (Seabrook, NH). All chemicals obtained from commercial suppliers were used as received. [Pt(SO_4)(*trans-R,R*-DACH)].H_2O was prepared as described previously.[8]

NMR spectra were recorded on an IBM NR 200/AF NMR spectrometer. Infrared spectra were recorded in KBr pellets on a Beckman Microlab 250MX spectrophotometer. Elemental analyses were performed by Robertson Laboratories (Madison, NJ).

Synthesis of Platinum Complexes

Preparation of [*Pt(gly-N)*$_2$(trans-R,R-*DACH*)] (1)
Glycine (0.153 g, 2.04 mmol) and Ba$(OH)_2.8H_2O$ (0.322 g, 1.02 mmol) were mixed together in 50 cm^3 of water. To this solution of barium glycinate was added [Pt(SO_4)(*trans-R,R*-DACH)].H_2O (0.432 g, 1.02 mmol). After stirring for 1.5 h, the solution was filtered and evaporated to dryness yielding an off-white crystalline solid. The product was recrystallized from methanol to give pure [Pt(gly-N)$_2$*trans-R,R*-DACH)] as a white solid.

Preparation of [*Pt(pro-N)*$_2$(trans-R,R-*DACH*)] (3)
L(-)-proline (0.265 g, 2.30 mmol) was mixed with Ba$(OH)_2.8H_2O$ (0.364 g, 1.15 mmol) in 50 cm^3 of water, then [Pt(SO_4)(*trans-R,R*-DACH)].H_2O (0.488 g, 1.15 mmol) was added. After stirring for 30 min the solution was filtered and evaporated to dryness. The residue was dissolved in a small amount of water and loaded onto a Chelex-100 (Na-form) column, which had been previously neutralized by repeated washing with water. The column was eluted with 50 cm^3 of water and the resulting solution was evaporated to dryness. The crude product was collected, washed with acetone, and dried *in vacuo*. The crude product was dissolved in 2 cm^3 of methanol and filtered. Crystallization was induced by the slow addition of acetone. This resulted in pure crystals of [Pt(pro-N)$_2$(*trans-R,R*-DACH)].$2H_2O.CH_3OH$.

The other [Pt(aa)$_2$(*trans-R,R*-DACH)] and [Pt(pro-N)$_2$(*cis*-DACH)].$4H_2O$ complexes were also prepared in a similar manner. Table I lists these complexes along with elemental analyses and yields.

TABLE I
Elemental analysis data for [Pt(aa)$_2$(*trans*-*R*,*R*-DACH)].xH_2O complexes.

Complex	aa	x	Experimental (theoretical) %C	%H	%N	Yield (%)
1	gly	0	26.13(26.26)	4.88(4.86)	11.61(12.21)	82
2	azca	4	28.85(28.91)	5.50(5.90)	9.50(9.63)	45
3	pro	2*	33.80(33.50)	6.24(5.99)	9.54(9.76)	47
4	pro	4**	31.69(31.52)	6.30(6.24)	9.09(9.19)	40
5	*L*-ala	2	27.42(27.64)	5.88(5.81)	10.11(10.74)	55
6	*L*-ser	2	26.48(26.04)	5.41(5.47)	10.31(10.12)	34
7	sar	2	27.76(27.64)	5.59(5.81)	9.62(10.74)	65
8	dmgly	0	31.15(32.74)	5.82(5.90)	10.77(10.90)	58

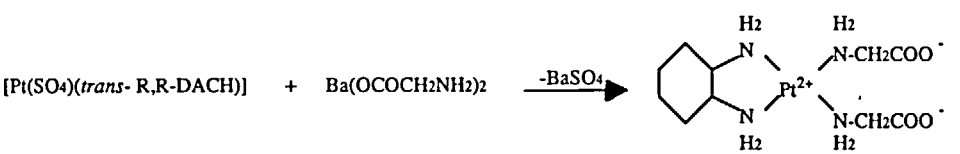
* Also contains one molecules of methanol per platinum atom. ** [Pt(pro)$_2$(*cis*-DACH)].4H_2O.

RESULTS AND DISCUSSION

When [Pt(SO_4)(*trans*-*R*,*R*-DACH)].H_2O is added to an aqueous solution of barium glycinate, [Pt(gly-N)$_2$*trans*-*R*,*R*-DACH)] (**1**) is formed along with barium sulfate (scheme I). The precipitated barium sulfate can be removed by filtration and the solution evaporated to give **1**, which can be purified by recrystallization from methanol.

The structure of **1** is one in which the *trans*-*R*,*R*-DACH ligand is bound in a bidentate fashion and the two glycine ligands are bound to platinum through the amino nitrogen atoms, thus giving a square planar arrangement around the metal centre. Support for this structure comes from various NMR spectroscopic data. The 200 MHz proton NMR spectrum of **1** in D_2O displays a sharp singlet at 3.12 ppm due to the methylene protons of the glycinate ligands. This singlet is accompanied by platinum satellites (^3J(Pt,H) = 37 Hz), although these are broadened because of chemical shift anisotropy at this high magnetic field.[9]

The $^{13}C\{^1H\}$ NMR spectrum of a D_2O solution of **1** displays resonances characteristic of the *trans*-*R*,*R*-DACH ligand: $\delta C\gamma$ 23.76, δC_β 32.01 and δC_α 61.36 ppm, and the *cis*-DACH ligand: δC_γ 20.00, γC_β 26.59, and δC_α 59.03 (relative to 1,4-dioxane, 66.50 ppm). The glycinate methylene carbon resonates at 40.11 ppm and a single carbonyl peak is observed at 175.59 ppm. The latter is characteristic of a free



Scheme I

carboxylate ion,[10] thus supporting the above structure where the carboxylate groups are not bound to platinum.

The final piece of NMR evidence comes from the platinum-195 NMR spectrum, which displays a single peak at −2856 ppm (relative to Na_2PtCl_6). This chemical shift is indicative of a square planar platinum(II) complex in which all four ligands are nitrogen donors.[4,11] This is further confirmed by an experiment in which the glycine nitrogen atoms are labelled as nitrogen-15 (I = 1/2). In this case, the platinum resonance is no longer a singlet, but rather is split into a triplet owing to coupling to nitrogen-15 ($^1J(Pt,^{15}N) = 329$ Hz). The magnitude of this coupling is typical for complexes in which the ligand *trans* to the nitrogen-15 labelled ligand is also a nitrogen donor (*trans-R,R*-DACH in this case).[11] For comparison, the ^{195}Pt NMR spectral data for *cis*-[Pt(gly-$^{15}N)_2(^{15}NH_3)_2$] can be cited.[4] This complex displays a triplet of triplets at Pt-2661 ppm with a $^1J(Pt,^{15}N)$ of 312 Hz for the glycinato ^{15}N. These data are consistent with that obtained for **1**.

The infrared spectrum (KBr) of **1** is also consistent with the structure depicted in scheme I. The spectrum displays a pattern that is typical for free carboxylate ions: $\nu_a(COO^-)$ 1580 cm^{-1} and $\nu_s(COO^-)$ 1390 cm^{-1} (compare to sodium glycinate: $\nu_a(COO^-)$ 1555 cm^{-1} and $\nu_s(COO^-)$ 1402 cm^{-1}). If the glycine carboxylate groups were bound to platinum, a pattern in which $\nu_a(COO^-) > 1600\,cm^{-1}$ and $\nu_s(COO^-) < 1380\,cm^{-1}$ would be expected.[12]

Reactions analogous to that depicted in scheme I can be carried out for a number of different amino acids (see Table I). In all cases, except where aa = sar (CH_3NHCH_2COOH) or dmgly ($(CH_3)_2NCH_2COOH$, *vide infra*, the amino acid binds to platinum(II) through the amino nitrogen atom exclusively, as is evidenced by various spectroscopic data (Tables II–IV). The binding of the amino acid ligands through the amino nitrogen is consistent with the already demonstrated affinity of platinum(II) for nitrogen as opposed to oxygen donors.[1]

Reaction of [Pt(SO_4)(*trans-R,R*-DACH)] with barium sarcosinate results in the formation of two platinum-containing products (Scheme II). The major species (**7**) is that in which both sarcosinate ligands are bound to platinum through the amino nitrogen. This complex is analogous to **1** and its spectral features are similar to that of **1** (Tables II–IV). In addition to **7**, a small amount of **9** is formed. In **9**, one sarcosinate ion is bound to platinum in a bidentate fashion, while the other is not bound to platinum; **9** appears in the platinum-195 NMR spectrum as a singlet at

TABLE II

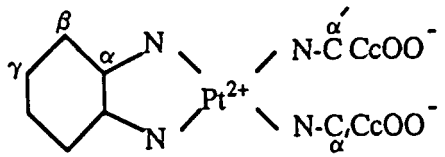
Infrared spectroscopic data for [Pt(aa-N)$_2$(*trans-R,R*-DACH)] complexes.

	aa	$\nu_a(COO^-)$, cm^{-1}	$\nu_s(COO^-)$, cm^{-1}
1	gly	1580	1390
2	azca	1590	1409
3	pro	1604	1379
4	pro*	1597	1379
5	*L*-ala	1600	1408
6	*L*-ser	1605	1402
7	sar	1595	1388

* [Pt(pro)$_2$(*cis*-DACH)].4H_2O.

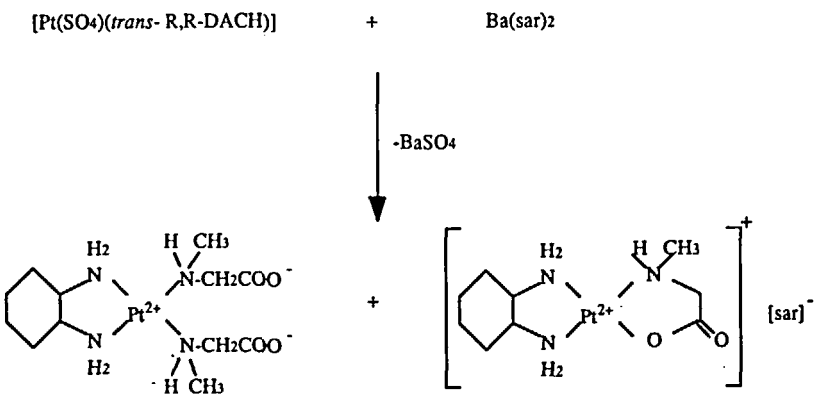
TABLE III

$^{13}C\{^1H\}$ and $^{195}Pt\{^1H\}$ NMR data for [Pt(aa-N)$_2$(*trans-R,R*-DACH)] complexes.



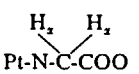
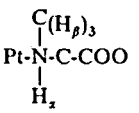
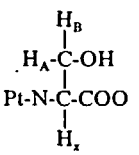
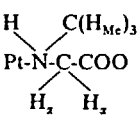
	aa	$\delta C_{\alpha'}$	δC_c	δC_α	δC_β	δC_γ	δC_{other}	δPt
1	gly[a,c]	49.11	175.59	61.36	32.01	23.76		−2856
2	azca[a,d]	68.35	176.65	62.55	33.65	25.44	29.27 68.22	−2866
3	pro[a,d]	69.46	177.39	62.56	33.46	25.50	25.01 30.46 53.54	−2812
4	pro[a,d,e]	69.51	177.56	59.03	26.59	20.00	25.07 30.49 53.74	−2766
5	*L*-ala[a,c]	57.00	178.88	61.26	31.93	23.70	20.02	−2852
6	*L*-ser[a,c]	f	175.28	f	31.98	23.73	61.37 62.21 63.07	−2851
7	sar[b,d]	43.20	174.51	61.59	33.36	25.48	62.48	−2790

[a] $^{195}Pt\{^1H\}$ NMR spectrum recorded for aqueous solution; referenced to Na_2PtCl_6 (0.00 ppm) in D_2O. [b] $^{195}Pt\{^1H\}$ NMR spectrum recorded for CH_3OH solution; referenced to Na_2PtCl_6 (0.00) ppm) in D_2O. [c] $^{13}C\{^1H\}$ NMR spectrum recorded for D_2O solution; referenced to external 1,4-dioxane (66.50 ppm). [d] $^{13}C\{^1H\}$ NMR spectrum recorded for CD_3OD solution; referenced to the solvent peak at 49.00 ppm. [e] [Pt(pro-N)$_2$(*cis*-DACH)]. [f] Cannot make specific assignments.



Scheme II

TABLE IV
Proton NMR data* for [Pt(aa-N)$_2$(*trans-R,R*-DACH)] complexes.

	aa	Solvent	Proton NMR data	
1		D_2O	δH_z 3.12 (s)	$^3J(Pt,H)=37$
5		D_2O	δH_z 3.28 (q) δH_β 1.23 (d)	J = 6.4
6		D_2O	δH_z 3.35 δH_A 3.89 δH_B 3.69	$J_{AB}=11.8$ $J_{AX}=3.6$(or 5.6) $J_{AB}=5.6$(or −3.6)
7		CD_3OD	δH_z 3.34 (s) δH_{Me} 2.61 (s)	

* Chemical shifts are referenced to the HDO peak at 4.67 ppm or the CD_3OD quintet at 3.30 ppm. All coupling constants are given in Hz.

−2374 ppm. This downfield shift for **9**, as compared to **7** (δPt −2790 ppm), is consistent with a structure in which there are three nitrogen-donor ligands bound to platinum(II).[4,12] Because **9** is only a minor product as compared to **7**, peaks due to this complex are difficult to discern in its proton or carbon-13 NMR spectra. Separation of **7** and **9** has not been achieved to date.

When the amino nitrogen atom is further substituted, the [Pt(aa-N,O)(*trans-R,R*-DACH)]$^+$[aa]-species becomes more dominant. For example, when [Pt(SO_4)(*trans-R,R*-DACH)] reacts with Ba(dmgly-N,O)(*trans-R,R*-DACH)]$^+$[dmgly]$^-$ (**10**) is formed exclusively. No evidence for the formation of [Pt(dmgly-N)$_2$(*trans-R,R*-DACH)] has been obtained. Like **9**, compound **10** displays a singlet at −2337 ppm in its platinum-195 NMR spectrum. The $^{13}C\{^1H\}$ NMR spectrum of a CD_3OD solution of **10** displays resonances for two different carboxylate carbons: The uncoordinated carboxylate carbon appears at 176.62 ppm and the coordinated carboxylate carbon at 183.66 ppm. The methyl groups for the free *N,N*-dimethylglycinate ion are magnetically equivalent on the NMR time scale. In the $^{13}C\{^1H\}$ NMR spectrum, these methyl carbons appear at 67.99 ppm, while in the ^1H NMR (CD_3OD) spectrum, the corresponding methyl protons resonate at 2.37 ppm. In contrast, the two methyl groups bound to the coordinated amino group are not magnetically equivalent. This is indicated by the appearance of peaks at 63.81 and 64.34 ppm in the carbon-13 NMR spectrum and singlets at 2.89 and 2.93 ppm in the proton NMR spectrum. Similarly, the two methylene protons for the free dmgly ion

are magnetically equivalent, giving rise to a singlet at 3.04 ppm in the proton NMR spectrum, whereas for the chelated dmgly ligand, the methylene protons are split into an AB pattern (δH_A 3.67, δH_B 3.51 ppm, $J_{AB} = 15.7$ Hz).

The presence of alkyl substituents on the amino nitrogen atom should cause the amino group to be more basic than the unsubstituted analogue, and thus the substituted amino groups should be better donor ligands than the unsubstituted varieties.[13] Yet, substitution of the amino nitrogen results in less bonding of the amino nitrogen to platinum; that is, species are observed in which one of the amino acid ligands is bound in a bidentate fashion through the amino nitrogen and a carboxylate oxygen. This would suggest that, in these cases, one amino acid ligand binds to platinum in a bidentate fashion in order to relieve steric strain.

ACKNOWLEDGEMENTS

This work was supported by grant no. CA41581 from the National Cancer Institute.

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7. The following abbreviations are used throughout the text: aa = amino acid; *trans-R,R*-DACH = *trans-R,R*-1,2-diaminocyclohexane; H(gly) = glycine; H(azca) = *L*-2-azetidinecarboxylic acid; H(pro) = *L*(-)-proline; H(*L*-ala) = *L*-alanine; H(*L*-ser) = *L*-serine; H(sar) = sarcosine; H(dmgly) = *N,N*-dimethylglycine.
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