Accordingly, a higher reactivity in aqueous solution is expected for the *trans* isomer, under both extracellular and intracellular conditions.

Antitumor Activity Tests. On a molar basis, *trans*-$RuCl_2(DMSO)_4$ is more toxic by a factor of 20 than *cis*-$RuCl_2(DMSO)_4$ ($LD_{0.05}$ of 37 vs. 700 mg/(kg·day)), which is in agreement with the higher reactivity expected for the trans isomer.

The results of the comparison of the antitumor activity of *cis*- and *trans*-$RuCl_2(DMSO)_4$ at equitoxic dosages are reported in Table IX. An equitoxic dosage of the clinically used cisplatin is employed as positive control.

The treatment has no statistically significant effect on primary tumor growth. On the contrary, while *cis*-$RuCl_2(DMSO)_4$ reduces the number and weight of spontaneous lung metastases to about 50% of the controls, the effect of *trans*-$RuCl_2(DMSO)_4$ on metastasis weight is slightly superior (inhibition to about 30% of the controls) but at a 20-fold lower dosage. The antimetastatic effect of the trans isomer is of the same order as that obtained with an equitoxic dosage of cisplatin. The absence of significant activity on primary tumor growth is in agreement with separate observations made with *cis*-$RuCl_2(DMSO)_4$, which indicate a strict dependence of the antitumor action on the mass of primary tumor being treated.[12]

The antimetastatic properties of the chloro and bromo trans isomers were investigated in a preliminary experiment in mice with lung tumor colonies artificially induced by iv implantations of Lewis lung carcinoma cells (Table X). The dosage used for the two isomers presents some toxicity for the host, being responsible for toxic deaths within the treated groups (37% with both complexes). Nevertheless, these results show that the efficacy of the *trans*-dichloro isomer is remarkably higher than that of the *trans*-dibromo one, indicating the influence of the halogen on the antitumor effect.

Conclusions

The different behavior of the cis and trans isomers of $[Ru(DMSO)_4X_2]$ in nonprotic solvents provides for the synthesis of homogeneous series of geometrical isomer derivatives. Moreover, their substitution kinetics in aqueous solution directly reflects on their different antitumor properties. The use of *trans*-$RuCl_2(DMSO)_4$ instead of the cis isomer allows for increased tumor toxicity at remarkably lower doses.

Our work is now directed toward the synthesis of homogeneous series of derivatives of both isomers, with the aim of improving the antitumor properties of the original complexes. Moreover, these complexes, due to their high stability towards oxidation,[29] can be used as useful model compounds to study the interactions of octahedral Ru(II) complexes with DNA and oligonucleotides.

Acknowledgment. We wish to thank Prof. M. J. Clarke (Boston College) for a helpful discussion. Financial support was provided by the Ministero Pubblica Istruzione (Rome). The ICTP (Trieste, Italy) is acknowledged for a research fellowship to W.M.A.

Registry No. *cis*-$RuCl_2(DMSO)_4$, 64376-67-6; *trans*-$RuCl_2(DMSO)_4$, 72904-47-3; *trans*-$RuBr_2(DMSO)_4$, 72904-46-2; *cis*-$RuBr_2(DMSO)_4$, 72937-89-4.

Supplementary Material Available: Tables of anisotropic temperature factors for non-hydrogen atoms (Tables XI-XIII) and positional parameters for hydrogen atoms (Tables XIV-XVI) of *cis*-$RuBr_2(DMSO)_4$, *cis*-$RuCl_2(DMSO)_4$, and *trans*-$RuCl_2(DMSO)_4$, respectively (6 pages); listings of calculated and observed structure amplitudes for *cis*-$RuBr_2(DMSO)_4$, *cis*-$RuCl_2(DMSO)_4$, and *trans*-$RuCl_2(DMSO)_4$ (36 pages). Ordering information is given on any current masthead page.

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Synthesis and Characterization of Diastereomeric (Substituted iminodiacetato)(1,2-diaminocyclohexane)platinum(II) Complexes

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Received March 4, 1988

Novel complexes of the type [Pt(DACH)(*N*-R-iminodiacetate)], wherein DACH represents (*R,S*)- and (*R,R*)-1,2-diaminocyclohexane and R represents -Me, -EtOH, and $-CH_2Ph$ groups, have been prepared, purified, and characterized by spectroscopic techniques (^1H, ^{13}C, and ^{195}Pt NMR; MS(FAB); IR) and by the measurement of selected physical properties (pH, pK_a, conductivity, and molecular weights). The data are consistent with the formation of two diastereomeric complexes in unequal proportions in which the *N*-R-iminodiacetate ligand appears to be bonded as a pseudofacial tridentate chelate. One arm of the ligand forms a stable five-membered-ring O,N-chelate while the other arm appears to be involved in ion-pair formation (zwitterion-like) involving the carboxylate anion and the formally positive Pt(II) central metal atom. It has been demonstrated indirectly that an active impurity was present in predictably inactive bulk complexes of the type PtN_3O. The need to characterize unequivocally and certify the purity of prospective antitumor complexes is emphasized.

Introduction

Among the many antitumor-active platinum(II) complexes possessing the common structure *cis*-PtA_2X_2, (1,2-diaminocyclohexane)platinum(II) complexes are of particular interest in the search for a third-generation platinum antitumor drug. Interest in these agents is the result of (1) demonstrated antitumor activity in vivo, including a selectivity based on the isomeric form of the DACH ligand employed[1] and (2) generally good dose potency but, most particularly, (3) effectiveness against cisplatin-resistant tumor systems in vitro and in vivo.[2]

Since $[PtN_3X]^+$ systems are known to be inactive,[3] preliminary reports of the antitumor activity of (*N*-alkyl-substituted iminodiacetato)(*R,R*)-1,2-diaminocyclohexane)platinum(II) complexes[4] suggested the possibility of O,O-chelation rather than the thermodynamically preferred O,N-chelation mode commonly found for metal-amino acid complexes.[5] Interest in resolving this question has led to a study of a series of novel complexes principally of the type [Pt(*R,R*-DACH)X], wherein the X group represents an *N*-alkyl-substituted iminodiacetate dianion, $R-N(CH_2CO_2)_2^{2-}$ (or *N*-R-IDA), and *R,R*-DACH denotes (-)-(*R,R*)-1,2-di-

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aminocyclohexane. Although these complexes were reported originally to exhibit extraordinary antitumor activity in several murine tumor systems, particularly the L1210 leukemia,[4] we have discovered that following purification these complexes are virtually inactive. The purpose of this paper is to discuss the synthesis, purification, and structural characterization of these novel diastereomeric complexes.

Experimental Section

Instruments and Methods. IR spectra were run as Nujol mulls, as KBr pellets, or in D_2O (with use of a rotating prism or Irtran cell) on a Nicolet FT IR (Model MX-1) spectrometer. ^1H (300 MHz), ^{13}C (75.43 MHz), and ^{195}Pt (64.40 MHz) NMR spectra were recorded on Varian XL-200 and XL-300 NMR spectrometers. All ^{13}C and ^{195}Pt NMR spectra were proton-decoupled and were obtained with *N,N*-dimethylformamide (DMF-d_7), D_2O, or 33% D_2O in H_2O as the solvent. ^{195}Pt spectra were externally referenced to and reported relative to 0.2 M K_2PtCl_4 in 0.4 M KCl. Referenced to Na_2PtCl_6 in D_2O, δ_{Pt} for K_2PtCl_4 in 0.4 M KCl is −1634. Mass spectra were run on a VG 7070 HF mass spectrometer operating in the FAB mode (xenon carrier gas). Water was used as solvent and thioglycerol as the matrix.

Elemental analyses (C, H, N, S, Cl), carried out by the Microanalysis Laboratory at Parke-Davis, were within ±0.4% of the calculated values. pK_a values for the free acids and bound *N*-R·IDA ligands were estimated by using a published procedure.[6] Conductivities were measured on a YSI Model 34 (Fisher) conductance unit in deaerated MeOH and H_2O. Optical activities were measured in MeOH (1% solutions) with a Perkin-Elmer polarimeter (Model 141). HPLC assays were carried out with a Varian 5000 high-pressure liquid chromatograph at 220 nm using (1) an Alltech cyanopropyl column (4.6 × 250 mm, 10-μm spherical packing) in the reverse-phase mode, a mobile phase of 0.005 M $NH_4H_2PO_4$ (pH 3.0) and CH_3CN (80:20), and a flow rate of 1.5 mL/min or (2) a Novapak C-18 reverse-phase column and a mobile phase of 0.05 M Na_2HPO_4 (pH 5.9). Molecular weights were determined by Galbraith Laboratories (Knoxville, TN) via vapor-phase osmometry.

Starting Materials. (−)-1*R*,2*R*-DACH (*trans-l*-DACH) was obtained as the *d*-tartrate salt from a multicomponent amine mixture by using the direct chemical resolution method of Whitney.[7] A single recrystallization from H_2O provided a chemically and optically pure compound: $[\alpha]^{25°C}_D$ = 11.2°; mp 258 °C. Anal. ($C_{10}H_{20}N_2O_6$) C, H, N. $^{13}C\{^1H\}$ NMR (NaOD–D_2O): 27.68, 36.41, 58.85, 59.07, 76.82, 181.62 ppm. Also, 1*R*,2*R*-DACH was purchased from Strem Chemical Co. $^{13}C\{^1H\}$ NMR: 27.58, 36.25, 58.97 ppm.

1*R*,2*S*-DACH (*cis*-DACH) was obtained as the hydrosulfate by the chemical resolution method of Kidani.[8] $^{13}C\{^1H\}$ NMR: 22.97, 28.53, 52.64 ppm.

Glutaric, gluconic, and *N*-methyl-, *N*-(2-hydroxyethyl)-, and *N*-benzyliminodiacetic acids were used as purchased (Aldrich).

Deuteriated solvents and reagents (MSD Isotopes) were at least 99.8 atom %.

Synthesis of [Pt(*R*,*R*-DACH)Cl$_2$] (1). [Pt(*R*,*R*-DACH)Cl$_2$] was prepared by using an adaptation[9] of the Dhara method[10] in which NH_3 was replaced by *R*,*R*-DACH or by a solution of [*R*,*R*-DACH·H_2][*d*-tart] (tart = tartrate) containing 2 equiv of NaOH. The final product was purified by dissolution of crude **1** in DMF (~22 g/L) followed by addition of 3 volumes of 0.5 M HCl to cause recrystallization (76% yield). Anal. ($C_6H_{14}N_2PtCl_2$) C, H, N, Cl. $^{13}C\{^1H\}$ NMR (DMF-d_7): 25.00, 32.50, 63.88 ppm. $^{195}Pt\{^1H\}$ NMR (DMF-d_7): −656 ppm.

Synthesis of [Pt(*R*,*R*-DACH)SO$_4$]·H$_2$O (2). Ag_2SO_4 (2.0304 g, 6.512 mmol) in 400 mL of H_2O at 55 °C was added to a water slurry (50 mL) of compound **1** (2.47 g, 6.512 mmol), and the mixture was stirred overnight. Following filtration of AgCl, the filtrate was concentrated (rotoevaporator) and then lyophilized overnight to yield a pale yellow powder. (Larger quantities were prepared by scaling up this procedure.) Anal. ($C_6H_{16}N_2O_5SPt$) C, H, N, Cl; S: calcd, 7.16; found, 7.57. $^{195}Pt\{^1H\}$ NMR (33% D_2O in H_2O): −130, −210, −259 ppm.

[Pt(*R*,*R*-DACH)(NO$_3$)$_2$] (3). A solution of $AgNO_3$ [13.590 g (80.00 mmol) in 100 mL of H_2O] was added slowly with stirring to a 300-mL slurry of **1** (15.208 g, 40.00 mmol) in H_2O. After the reaction mixture was heated at 50 °C for 0.5 h, the slurry was cooled to ambient temperature and stirring was continued for an additional 12 h in the dark to produce a 0.1 M stock solution of $[Pt(R,R\text{-DACH})(H_2O)_2]^{2+},2NO_3^-$. Fifty milliliters of this stock solution was lyophilized under high vacuum to obtain 1.90 g of **3**. Anal. ($C_6H_{14}N_4O_6Pt$) C, H, N, Cl. $^{195}Pt\{^1H\}$ NMR (DMF-d_7): −216 ppm. $^{13}C\{^1H\}$ NMR: 64.28, 63.79, 63.47, 63.06, 31.91, 31.70, 24.81, 24.68 ppm.

[Pt(*R*,*R*-DACH)(ox)] (4; ox = Oxalate). With use of **1** as the starting material, **4** was prepared and purified according to the method of Kidani et al.[11] Anal. ($C_8H_{14}N_2O_4Pt$) C, H, N. $^{195}Pt\{^1H\}$ NMR: −361.2 ppm. $^{13}C\{^1H\}$ NMR (DMF-d_7): 167.0 (C=O), 62.88 ($C_{1,2}$), 32.27 ($C_{3,6}$), 24.86 ppm ($C_{4,5}$). $^{13}C\{^1H\}$ NMR (D_2O): 171.3 (C=O), 65.03 ($C_{1,2}$), 34.52 ($C_{3,6}$), 26.77 ($C_{4,5}$) ppm. MS(FAB): *m/e* 398.1 (M + 1). HPLC (room temperature, method 2): 6.04 min.

[Pt(*R*,*R*-DACH)(glc)$_2$] (5; glc = Gluconate). With use of the 0.1 M stock solution of $[Pt(R,R\text{-DACH})(H_2O)_2]^{2+},2NO_3^-$ from the preparation of compound **3** as the Pt(II) starting material, the synthesis of crude **5** was carried out as described by Kidani and Noji.[12] However, a totally different purification procedure than that published had to be developed to obtain a pure compound. An analytically and chromatographically pure **5** was obtained via semipreparative HPLC using a Waters C-18 reverse-phase μBondapak magnum column (9 mm o.d.). Nine consecutive runs were carried out in which the fraction containing pure **5** was frozen instantly on collection (tube immersed in a dry ice/acetone bath) and lyophilized to obtain **5**. Anal. ($C_{18}H_{36}N_2O_{14}Pt$) C, H, N. $^{195}Pt\{^1H\}$ NMR: −223 ppm. HPLC (room temperature, method 2): 5.66 min.

Synthesis of [PtA(*N*-R·IDA)] Complexes (A = DACH). The common synthetic route employed (based on eq 1) was an adaptation of the method of Harrison et al.[13] One generic procedure is described in detail; synthesis of specific complexes are referred to this procedure.

$$[PtA(SO_4)] + R\text{-}N(CH_2CO_2H)_2 + Ba(OH)_2 \xrightarrow[\text{temp}]{\text{ambient}} [PtA(N\text{-R·IDA})] + BaSO_4(s) \quad (1)$$

Solid $(HO_2CCH_2)_2N$–R was added to a 0.15–0.2 M solution of **2** in H_2O at ambient temperature. The addition of 2 equiv of $Ba(OH)_2$ solution (0.240 M) followed immediately. The reaction mixture (slurry) was filtered and the filtrate lyophilized to yield a pale yellow crude complex of [PtA(*N*-R·IDA)]. The crude product was purified via silica gel chromatography [EM Reagents silica gel 60 (70–230 mesh); ~20 mL/mmol of complex] using MeOH as eluant. A pure complex was isolated via one of the following two methods: the combined fractions were either (a) evaporated to dryness in vacuo, followed by dissolution of the residue in H_2O, filtration, and lyophilization under high vacuum, or (b) concentrated (rotoevaporator), the concentrate being poured with stirring into Et_2O to crystallize the pure colorless crystalline compound. Complexes were dried in vacuo for at least 2 h at 45 °C. Complexes prepared via this procedure were assayed by HPLC method 2.

Synthesis of [Pt(*R*,*R*-DACH)(*N*-Me·IDA)] (6). With use of the generic procedure, equimolar amounts (75.5 mmol) of $(HO_2CH_2)_2NMe$ (11.1 g), compound **2** (31.97 g), and 0.240 M $Ba(OH)_2$ (314.7 mL) gave 32.6 g (95%) of crude **6**. Isolation by method a led to recovery of 21.6 g (63%) of pure **6**. Anal. ($C_{11}H_{21}N_3O_4Pt\cdot H_2O$) C, H, N, S. IR ($cm^{-1}$): 1645, 1604 (ν(C=O), D_2O); 1654, 1614 (ν(C=O), KBr); 1403, 1326 (ν(C—O), D_2O); 1394, 1313 (ν(C—O), KBr). MS(FAB): *m/e* 455.1 (M + 1). M_r = 438 (MeOH). HPLC (retention time): 3.48 min. $pK_a \approx 2.7$. $[\alpha]^{25°C}_D$ = +61.1° (1.05% MeOH). TLC (R_f(developer)): 0.31 (MeOH), 0.53 (acetone–H_2O, 7:3). Two distinct species are observed by NMR.

Diastereomer 1. $^{195}Pt\{^1H\}$ NMR (D_2O): −714 ppm. $^{13}C\{^1H\}$ NMR (ppm, D_2O): 187.6, 175.9 (C=O); 63.8 (C_1), 65.3 (C_2); 34.7 ($C_{3,6}$); 26.7 ($C_{4,5}$); 68.2 (C_8); 68.5 (C_{10}); 53.7 (N-CH_3). ^1H NMR (ppm, D_2O): 2.35 (m, CH (C_1)); 2.4 (m, CH(C_2)); 1.4, 2.1 (m, CH_2 ($C_{3,6}$)); 1.6, 1.2 (m, CH_2 ($C_{4,5}$)); 3.8 (dd, CH_2 (C_8)); 3.5, 3.6 (dd, $^2J_{HH}$ = 15.5 Hz, CH_2 (C_{10})); 3.0 (N-CH_3).

Diastereomer 2. $^{195}Pt\{^1H\}$ NMR (D_2O): −687 ppm. $^{13}C\{^1H\}$ NMR (ppm, D_2O): 188.1, 176.2 (C=O); 63.6 (C_1); 65.0 (C_2); 34.7 ($C_{3,6}$); 26.7 ($C_{4,5}$); 67.4 (C_8); 68.6 (C_{10}); 54.3 (N-CH_3). ^1H NMR (D_2O): 2.4 (m, CH (C_1)); 2.35 (m, CH (C_2)); 1.4, 2.1 (m, CH_2 ($C_{3,6}$)); 1.6, 1.2 (m, CH_2 ($C_{4,5}$)); 4.1, 3.8 (dd, $^2J_{HH}$(geminal) = 15.4 Hz, CH_2 (C_8)); 3.55, 3.6 (dd, $^2J_{HH}$ = 15.9 Hz, CH_2 (C_{10})); 3.1 (N-CH_3).

Synthesis of [Pt(*R*,*R*-DACH)(*N*-EtOH·IDA)] (7). With use of the generic procedure, equimolar amounts (77.95 mmol) of $(HO_2CCH_2)_2N$-CH_2CH_2OH (13.8 g), compound **2** (33.0 g), and 0.240 M $Ba(OH)_2$ (325 mL) yielded a glassy residue (unweighed), which was dissolved in 100 mL of MeOH and isolated via method b using 1 L of Et_2O. The white solid was collected by filtration, washed with Et_2O, and air-dried. Anal.

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($C_{12}H_{23}N_3O_5Pt$) C, H, N. $^{195}Pt\{^1H\}$ NMR: −675, −691 ppm. $^{13}C\{^1H\}$ NMR (ppm): 189.5, 188.9, 176.2, 176.0 (C=O); 69.23, 68.90, 68.44, 67.50, 66.76, 66.18, 66.09, 65.50, 63.62, 63.39, 62.20, 61.38, 34.67, 34.42, 26.76, 26.67. IR (cm^{-1}): 1640, 1608 (ν(C=O), D_2O); 1654, 1619 (ν(C=O), KBr); 1397, 1326 (ν(C—O), D_2O); 1386, 1312 (ν(C—O), KBr). MS(FAB): *m/e* 485.0 (M + 1). HPLC (retention time): 4.90 min. $[\alpha]^{25°C}_D$ = +48.7 (1.19% MeOH). TLC (R_f (developer)): 0.34 (MeOH), 0.53 (acetone–H_2O, 7:3).

Synthesis of [Pt(*R*,*R*-DACH)(*N*-CH_2Ph·IDA)] (8). With use of the generic procedure, equimolar amounts (78.0 mmol) of $(HO_2CCH_2)_2NCH_2Ph$ (17.4 g), compound **2** (33.0 g) and 0.240 M $Ba(OH)_2$ (324.8 mL) gave 37.9 g of a fluffy, very pale yellow solid **8** after lyophilization. Purification and isolation (method a) gave 20.9 g (50.5%) of pure colorless **8**, mp 254–258 °C dec. Anal. ($C_{17}H_{25}N_3O_4Pt$) C, H, N, S. $^{13}C\{^1H\}$ NMR (ppm): 188.7, 188.3, 176.3, 176.1 (C=O); 136.0, 135.8, 135.1, 134.2, 134.0, 132.5, 131.9, 131.6 (Ph); 69.59, 67.13, 66.67, 65.64, 65.18, 65.02, 64.86, 64.02, 63.24 (CH, 2 × CH_2, CH_2Ph); 34.76, 34.59, 26.76, 26.61. IR (cm^{-1}): 1640, 1598 (ν(C=O), D_2O); 1654, 1618 (ν(C=O), KBr); 1429 (ν(C—O), D_2O); 1394, 1316 (ν(C—O), KBr). MS(FAB): *m/e* 531.1 (M + 1). HPLC (retention time): 4.86 min. $[\alpha]^{25°C}_D$ = +47.0° (1.14% MeOH). TLC (R_f (developer)): 0.47 (MeOH), 0.78 (acetone–H_2O, 7:3).

[Pt(*R*,*R*-DACH)(glut)] (9; glut = Glutarate). With use of the generic procedure for the synthesis of [Pt(DACH)(*N*-R·IDA)] complexes, equimolar amounts (1.772 mmol) of $HO_2C(CH_2)_3CO_2H$ (0.234 g), compound **2** (0.750 g) in 20 mL of H_2O, and 10 mL of $Ba(OH)_2$ solution (0.560 g of $Ba(OH)_2·8H_2O$) yielded 0.72 g (89%). Because of limited solubility in MeOH, the complex was purified by recrystallization from hot H_2O. Anal. ($C_{11}H_{22}N_2O_4Pt$) C, H, N. $^{195}Pt\{^1H\}$ NMR (D_2O): −229 (and possible minor peak at −206) ppm.

Synthesis of N-Deuteriated Compounds. *N*-deuterio analogues of compounds **1** and **6** were prepared to locate the position of the ρ_d NH_2 deformation mode (expected to occur at ~1600 cm^{-1}) and thereby facilitate the assignment of the carboxyl group(s) absorption frequencies in these complexes.

[*R*,*R*-DACH·D_2-d_6][*d*-tart]. [*R*,*R*-DACH·H_2][*d*-tart] (2.00 g; cf. Starting Materials) was dissolved in 22 mL of D_2O at boiling temperature and then recrystallized by cooling the solution to 0 °C. (Contamination by H_2O from the atmosphere was precluded by admitting room air through a Drierite drying column during equilibration to the atmosphere.) After the mother liquor was removed by rotoevaporation, the residue was dried overnight at 40°C under high vacuum. Two additional recrystallizations from D_2O were carried out in the same manner. Following the third dissolution, the solution was frozen (dry ice–acetone) and then lyophilized under high vacuum to yield a white powder (1.93 g; 47% recovery). All operations were carried out in one flask. Comparison of the IR spectra of the product and the N–H precursor showed that deuteriation was complete.

[Pt(*R*,*R*-DACH-d_4)Cl_2]. With use of [*R*,*R*-DACH·D_2-d_6][*d*-tart], D_2O, and other starting materials and reagents (K_2PtCl_4, KI, $AgNO_3$, NaOD) that had been recrystallized from D_2O, [Pt(*R*,*R*-DACH-d_4)Cl_2] was prepared via the same procedure employed in the synthesis of **1**. The deuteriated product was not recrystallized from DMF. Anal. ($C_6H_{10}D_4N_2PtCl_2$) C, H (D), N, Cl. IR (cm^{-1}): ≃1150 (ρ_d, ND_2). MS(FAB): *m/e* 349 $((M·d_4 - Cl)^+$ or $[(M·D_3 + 1) - Cl]^{2+})$, 731 $([(2M·D_3) - Cl]^+)$.

[Pt(*R*,*R*-DACH-d_4)(*N*-Me·IDA)]. Compound **6** (0.28 g) was dissolved in 5 mL of D_2O and the solution digested at 75–80 °C for 20 min. The solution was cooled and evaporated in a rotoevaporator to give a colorless transparent film. The IR (KBr) spectrum of this film indicated that the H/D exchange was incomplete. Additional 5-mL aliquots of D_2O were added, and the heating–cooling–evaporation cycle was repeated three additional times. The sample was dried overnight at 40 °C under high vacuum after the final cycle. The residue was then dissolved in 5 mL of D_2O and lyophilized to yield quantitatively a beautifully white fluffy residue. MS(FAB): 458.2 $((M - D_4)$ or $(M + 1) - D_3)$.

Results

Syntheses. Several substituted iminodiacetate complexes of the form [Pt(DACH)(R–$N(CH_2CO_2)_2$)] were synthesized, purified (≥98% by HPLC), and characterized by various analytical and spectroscopic techniques (^1H, ^{13}C, and ^{195}Pt NMR; IR; MS (FAB)) and by measurements of selected physical properties in solution (pH, conductivity, pK_a, optical rotation). The results are presented and discussed with reference to the four relevant structures given in Figure 7 depicting O,O and O,N monomeric and/or dimeric complexes.

Spectral Studies. ^{195}Pt NMR. Studies of [Pt(DACH)(*N*-R·IDA)] complexes by ^{195}Pt NMR were carried out to help elucidate the nature of the Pt–ligand bonding (O,O or O,N bonding) and to assess the stability of these complexes in aqueous solution. Studies were carried out in D_2O or D_2O–H_2O (1:2) mixtures at Pt(II) concentrations of ~0.1 M. Complexes **6** and **8** were studied as both a function of temperature (20, 50, 80 °C) and pH (5.7, 7.4, 8.0). A summary of the chemical shift data is presented in Table I. Two broad resonance peaks (450 Hz at half-peak height at 20 °C), separated by only 11–27 ppm, were observed for each complex, indicating the presence of two closely related Pt(II) complexes. On the basis of integrated peak areas, the ratios of the upfield–downfield components in **6** and **7** are 1.4 and 1.1, respectively. ^{195}Pt NMR spectra of **6** and **8**, recorded as a function of temperature (Figure 1, **6**), show that while each set of peaks (Table I) is shifted slightly upfield (from $PtCl_6^{2-}$) as the temperature is raised the doublets showed little or no tendency to coalesce over the 20–80 °C temperature range studied.

Table I. ^{195}Pt and ^{13}C NMR Spectral Data

species	$^{195}Pt^a$ δ	$^{195}Pt^a$ Δδ	^{13}C δ(C=O)
[Pt(*R*,*R*-DACH)(*N*-R·IDA)]			
R = Me (**6**)	−687, −714	27	188.1, 187.6; 176.2, 175.9
R = EtOH (**7**)	−675, −691	16	189.5, 188.9; 176.2, 176.0
R = CH_2Ph (**8**)			
20 °C	−661, −672	11	188.7, 188.3; 176.3, 176.1
50 °C	−670, −681	11	
80 °C	−684, −694	10	
[Pt(*R*,*S*-DACH)(*N*-R·IDA)]			
R = Me	−674, −703	29	187.8, 187.4; 176.2, 176.1
R = CH_2Ph	−646, −669	23	188.3, 188.2; 176.4, 176.1
N-Me·IDA			172.0[b]
N-EtOH·IDA			173.4[c]
N-CH_2Ph·IDA			182.0[c]

[a] Referenced to 0.2 M K_2PtCl_4 in 0.4 M KCl (referenced to Na_2PtCl_6, $\delta_{Pt}(K_2PtCl_4)$ = −1634). [b] D_2O. [c] NaOD–D_2O.

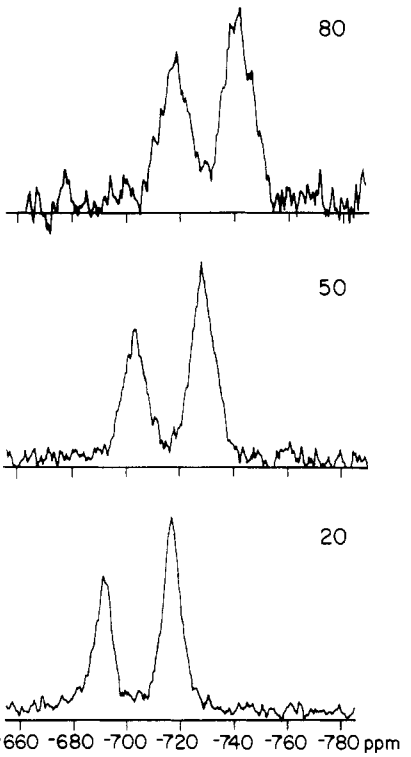
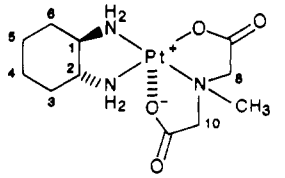


Figure 1. ^1H-decoupled ^{195}Pt NMR spectra (64.40 MHz) of [Pt(*R*,*R*-DACH)(*N*-Me·IDA)] in D_2O as a function of temperature (20, 50, 80 °C). Spectra are referenced to 0.2 M K_2PtCl_4 in 0.4 M KCl (δ_{Pt} for K_2PtCl_4 referenced to Na_2PtCl_6 in D_2O is −1634 ppm).

Table II. ^1H and ^{13}C NMR Data for the Diastereomers of [Pt(*R*,*R*-DACH)(*N*-Me·IDA)] (**6**)



position	^{13}C		^1H		
	config 1[a]	config 2	config 1[a]	config 2	mult
1	63.8	63.6	2.35	2.4	m
2	65.3	65.0	2.4	2.35	m
3, 6[b]	34.7	34.7	1.4, 2.1	1.4, 2.1	m
4, 5[b]	26.7	26.7	1.2, 1.6	1.2, 1.6	m
8	68.2	67.4	3.8 (s)	4.1, 3.8 (16.4)[c]	dd
10	68.5	68.6	3.5, 3.6 (15.5)[c]	3.55, 3.6 (15.9)[c]	dd
N-Me	53.7	54.3	3.0[d]	3.1[d]	s

[a] Configuration 1 has higher population. [b] No distinction is made between protons at positions 4, 5 or at positions 3, 6. [c] $^2J_{HH}$ geminal coupling (Hz) in parentheses. [d] Platinum coupling is not resolved at 20 °C due to CSA (~16 Hz for $^3J_{Pt-NCH_3}$) at 80 °C).

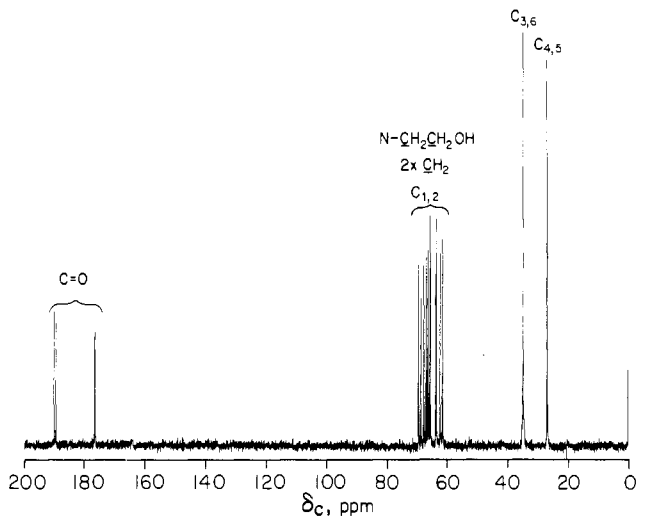


Figure 2. ^1H-decoupled ^{13}C NMR spectrum (75.43 MHz) of [Pt(*R*,*R*-DACH)(*N*-EtOH·IDA)] in D_2O at 20 °C.

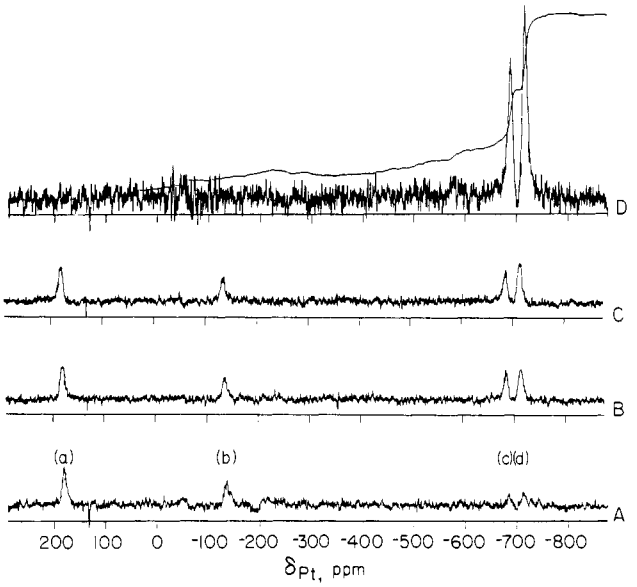


Figure 3. ^{195}Pt NMr spectra (64.40 MHz) of the reaction mixture in eq 1 as a function of time after mixing: (A) 41 min; (B) 93 min; (C) 138 min. Spectrum D is of pure **6**. Assignments: (a) $[Pt(R,R\text{-DACH})(\mu\text{-O(H/D)})]_2^{2+}$; (b) $[Pt(R,R\text{-DACH})(\mu\text{-O(H/D)})]_3^{3+}$; (c, d) doublet for pure **6**.

When the samples held at 80 °C were cooled to 20 °C, their spectra were identical with those recorded at the start of the heating cycle (20 °C). Since samples were maintained at each temperature for 40 min during data accumulation, one can conclude from the unchanged spectra that the complexes are quite stable in H_2O. Studies of the effect of pH on **8** indicate that the spectra of **8** were virtually unaffected over the pH range 5.7–8.0.

^{13}C NMR. Studies of **6–8** and selected reference complexes, **1–4**, by ^{13}C NMR were carried out in D_2O or DMF-d_7. With use of **6** as a complex representative of the series, DEPT analysis,[14] two-dimensional proton–carbon correlation spectroscopic studies,[15] and studies of the formation of the [Pt(*R*,*R*-DACH)(*N*-R·IDA)] complexes (via ^{13}C and ^{195}Pt NMR) were carried out (vide infra). Selected chemical shift data (δ) appear in Tables I and II, and the remainder of the ^{13}C data are tabulated under the appropriate complex in the Experimental Section.

Examination of a typical ^{13}C NMR spectrum for complexes **6–8** (Figure 2, **7**) shows that the number of ^{13}C resonances observed is twice that expected for a single complex. This indicates that each (chromatographically pure) complex contains two spectrally distinct components. For instance, inspection of the carbonyl region for **7** (Figure 2) reveals the presence of two different carboxyl groups characterized by two sets of doublets at 189.5, 188.9 and 176.2, 176.0 ppm. Whereas only slight chemical shift differences ($\Delta \leq 0.5$ ppm) exist within a doublet, significantly larger differences ($\Delta \simeq 12$ ppm) separate the two types of C=O resonances. The carboxyl group at higher field (δ_C = 176.2 and 176.0) has a shift similar to that of the ionized form of the free ligand, which is expected to occur several ppm downfield of the un-ionized acid (δ_C = 173.4 in D_2O; Table I).[16]

In closely related studies of the $[Pt(^{15}NH_3)_2(N\text{-Me-IDA-}O,N)]^+$ complex ion in solution (the complex was not isolated, Appleton et al.[17] assigned the two observed carbonyl resonances to coordinated (185.6 ppm) and uncoordinated (171.6 ppm) carboxylate groups. The double sets of resonances observed for [Pt(DACH)(*N*-R·IDA)] complexes is consistent (and expected) either with the presence of (1) diastereomers arising from O,N-chelation involving a prochiral N group with the Pt(*R*,*R*-DACH) moiety possessing a 2-fold rotational axis of symmetry or, to a lesser extent, with the presence of (2) rotamers arising out of O,O-chelation and existing in conformations placing the –NR group above or below the square plane of the platinum(II) complex (vide infra).

Reaction Profile for the Formation of [Pt(*R*,*R*-DACH)(*N*-R·IDA)]. The formation of [Pt(*R*,*R*-DACH)(*N*-R·IDA)] com-

(14) Sorenson, O. W.; Donstrup, S.; Bildose, H.; Jackson, H. J. *J. Magn. Reson.* **1984**, *55*, 347.
(15) Box, A. D.; Morris, G. A. *J. Magn. Reson.* **1984**, *42*, 51.
(16) Breit-Maier, E.; Voelter, W. *^{13}C-NMR Spectroscopy*; Monographs in Modern Chemistry 5; Verlag Chemie: New York, 1978; p 171.
(17) Appleton, T. G.; Hall, J. R.; Ralph, S. F. *Inorg. Chem.* **1985**, *24*, 673–677.

Table III. ^{195}Pt NMR Chemical Shift Data for Complexes Relevant to the Formation of [Pt(*R*,*R*-DACH)(*N*-R-IDA)] Complexes

complex	chem shift (δ_{Pt})[a]	ref
$[Pt(R,R\text{-DACH})(H_2O)_2]^{2+}$	−238	19
$[Pt(R,R\text{-DACH})(D_2O)_2]^{2+}$	−264	20
$[Pt(R,R\text{-DACH})(\mu\text{-OD})]_2^{2+}$	172	20
$[Pt(R,R\text{-DACH})(\mu\text{-OD})]_3^{3+}$	−123	20
$[Pt(R,R\text{-DACH})(OD)_2]$	−162	20
$[Pt(^{15}N\text{-en})(H_2O)_2]^{2+}$ [c]	−276	19
$[Pt(^{15}N\text{-en})(H_2O)(ONO_2)]^{+}$	−295	19
$[Pt(R,R\text{-DACH})SO_4]$ (**2**)	130, −210, −259	*d*
$[Pt(R,R\text{-DACH})(NO_3)_2]$ (**3**)[b]	−216	*d*
[Pt(*R*,*R*-DACH)(ox)] (**4**)	−223	*d*
[Pt(*R*,*R*-DACH)(glut)] (**9**)	−229 (−206)	*d*
$[Pt(R,R\text{-DACH})(glc)_2]$ (**5**)	−223	*d*
$[Pt(R,R\text{-DACH})Cl_2]$ (**1**)	−656; −653	*d*; 25

[a] Chemical shift data reported relative to 0.2 M K_2PtCl_4 in 0.4 M KCl (δ_{Pt} for K_2PtCl_4 referenced to Na_2PtCl_6 (in D_2O) is −1634 ppm). [b] DMF-d_7. [c] en = ethylenediamine. [d] This work.

plexes (eq 1) was monitored (for R = Me) as a function of time in D_2O–H_2O (1:2) at ambient temperature via ^{195}Pt and ^{13}C NMR. The purpose of these studies was to look specifically for evidence for the initial formation of an O,O-chelate and/or its subsequent conversion to an O,N-chelate. Five minutes after the reagents were mixed, $BaSO_4$(s) was filtered and the filtrate examined by ^{195}Pt NMR over the +200 to −800 ppm range at 41, 93, and 138 min after mixing. (Reported times are the midpoints of the data collection interval.) As indicated in Figure 3, the product profile is virtually unchanged over the entire monitoring period (~3 h); i.e., the same four peaks centered at ~180, −130, −687, and −714 ppm were observed in all three scans. The major product, **6**, isolated in the reaction (characterized by δ_{Pt} = −687 and −714) is formed immediately, not as a byproduct of a later reaction. Judging from the data of Ismail and Sadler[18] and Hollis et al.,[19] both components, a and b (Figure 3), are clearly Pt(*R*,*R*-DACH) complexes involving Pt–O-bonded ligands (H_2O and/or OH^-). As an aid to the assignment of these peaks, spectra were obtained for $[Pt(R,R\text{-DACH})SO_4]$($\delta_{Pt}$ = −132 (minor), −210, and −257), the starting material used in the syntheses of the [Pt(*R*,*R*-DACH)(*N*-R-IDA)] complexes, and the apparent single product (δ_{Pt} = 153; unchanged after 60 h) of the reaction (eq 2)

$$[PtA(SO_4)] + Ba(OH)_2 \rightarrow [Pt(R,R\text{-DACH})(OH)_2] + BaSO_4(s) \quad (2)$$

obtained in the absence of the *N*-Me-IDA ligand (A = *R*,*R*-DACH). The ^{195}Pt shift for component b (Figure 3) is essentially the same as that for the minor component (δ_{Pt} = −132 ppm, aquation product) of $[Pt(R,R\text{-DACH})SO_4]$, and the ^{195}Pt shift for component a ($\delta_{Pt} \simeq 180$) is comparable in shift value to that for the stable product of reaction 2, presumably $[Pt(R,R\text{-DACH})(OH)_2]$. Neither component contains a bound carboxy group, as δ_{Pt} values for representative (carboxylato)platinum(II) complexes are generally more upfield (Table III), e.g., [Pt(*R*,*R*-DACH)(glut)] (−223 ppm), $[Pt(R,R\text{-DACH})(glc)_2]$ (−229 ppm), and [Pt(*R*,*R*-DACH)(ox)] (−361 ppm). On the basis of the above data and the spectral data of Gill and Rosenberg,[20] components a and b respectively are most likely the bridged hydroxy dimer (δ_{Pt} = 172) and trimer (δ_{Pt} = −123) species $[Pt(R,R\text{-DACH})(OH)]_n$ (n = 2, 3).

Results of monitoring essentially the same reaction mixture by ^{13}C NMR at 49 and 140 min after mixing corroborate the ^{195}Pt NMR observations. Only five signals were observed in the carbonyl region (δ_C = 188.5, 187.7, 176.4, 176.1, and 173.7). The first four signals correspond to those of pure **6**, and the fifth (173.7 ppm) is due to the unbound *N*-Me-IDA ligand. Thus, from ^{13}C NMR as well as ^{195}Pt NMR studies, there is no evidence that a Pt–carboxylate species is formed under the preparative conditions employed (the pH of the reaction mixture was ~7). Appleton et al. have reported[17] the formation of the transient (carboxylato)platinum(II) complex *cis*-$[Pt(^{15}NH_3)_2(O_2CCH_2NCH_2CO_2H)(H_2O)]^+$ by ^{15}N–^{195}Pt NMR spectral studies at pH 1.5. However, the authors note than even at this low pH the rate of conversion to the O,N-chelated form was appreciable.

Table IV. Infrared, Mass Spectroscopic, and Physicochemical Data for [Pt(*R*,*R*-DACH)(*N*-R-IDA)] Complexes

property	R = Me	R = HOEt	R = $PhCH_2$
IR ν(C=O), cm^{-1}			
D_2O	1645, 1604	1640, 1608	1640, 1598[a]
KBr	1654, 1614	1654, 1619	1654, 1618
IR ν(C—O), cm^{-1}			
D_2O	1403, 1326	1397, 1326	1429 sh[b]
KBr	1394, 1313	1386, 1312	1394, 1316
MS(FAB) (M + 1), amu	455.1	485.0	531.1
M_r obsd (calcd)	438 (454)		476 (530)
HPLC			
purity, %	99.5	98.8	97.8
retention time, min	3.48	4.9	4.96
TLC R_f (MeOH)	0.31	0.34	0.47
solubility, mg/g of solvent			547 (MeOH), 344 (DMF)
apparent pK_a[c]			
complex	2.7		2.6
ligand (free)	2.5, 9.6		2.7, 8.9
optical rotation, $[\alpha]^{25°C}_D$, deg (MeOH)	+61.1 (1.05%)	+48.7 (1.19%)	+47.0 (1.14)

[a] ν(C=O) and ν(C—O) values for free ligand: 1730, 1653, 1458 cm^{-1}. [b] Unresolved shoulder. [c] Approximate values.

Two-Dimensional Proton–Carbon Correlation Spectroscopy and DEPT Analysis. DEPT analysis (for assignment of carbon multiplicities) and two-dimensional proton–carbon correlation spectroscopic studies of **6** were carried out to facilitate the complete assignment (Table II) of all protons and carbon atoms for each of the two spectrally distinct components (diastereomers). In this analysis, it was assumed that the spectrally distinct components were diastereomers having the structures III and IV (Figure 7, vide infra). Essentially all proton and carbon assignments have been confirmed except that no distinction has been made between the protons on $C_{4,5}$ and on $C_{3,6}$. Final assignments for the methylene protons, C_8 (δ_H = 4.1, 3.8) and C_{10} (δ_H = 3.55, 3.6), were made on the basis of the data of Appleton et al.[17] for the $[Pt(NH_3)_2(N\text{-Me-IDA})]^+$ cation, for which the less shielded methylene protons were assigned the higher shift values (δ_H). However, it is not known which set of data corresponds to which component (diastereomer).

Infrared Spectra. Infrared spectra of **6**–**8** in D_2O and KBr show a characteristic pattern of six absorption bands over the 2000–1200-cm^{-1} range (Table IV). As an example, the absorption bands for **6** occur (in D_2O) at 1645 (s), 1604 (s), 1457 (w), 1403 (ms), 1326 (ms), and 1256 (w) cm^{-1}. The excellent correspondence between the number and frequencies of the bands in D_2O vs those in KBr (Table IV) indicates that little or no H/D exchange occurred in D_2O during the time required to obtain the spectra. Absence of a strong absorption band near ~1730 cm^{-1}, characteristic of a free (un-ionized) $-CO_2H$ group (ν(C=O)) as in Pt(II) glycino complexes,[21] shows unequivocally that neither of the two carboxylate groups exists in the free acid form. The strong and sharp bands at 1645 and 1604 cm^{-1} are consistent with ν(C=O)

(18) Ismail, I. M.; Sadler, P. J. In *Platinum, Gold, and Other Metal Chemotherapeutic Agents*; Lippard, S. J., Ed.; ACS Symposium Series 209; American Chemical Society: Washington, DC, 1983; Chapter 8, pp 173–180.
(19) Hollis, L. S.; Stern, E. W.; Amundsen, A. R.; Miller, A. V.; Doran, S. L. *J. Am. Chem. Soc.* **1987**, *109*, 3602.
(20) Gill, D. S.; Rosenberg, B. *J. Am. Chem. Soc.* **1982**, *104*, 4598–4604.
(21) Nakamoto, K. *Infrared and Raman Spectra of Inorganic and Coordination Compounds* 3rd ed.; Wiley: New York, 1978; p 310.

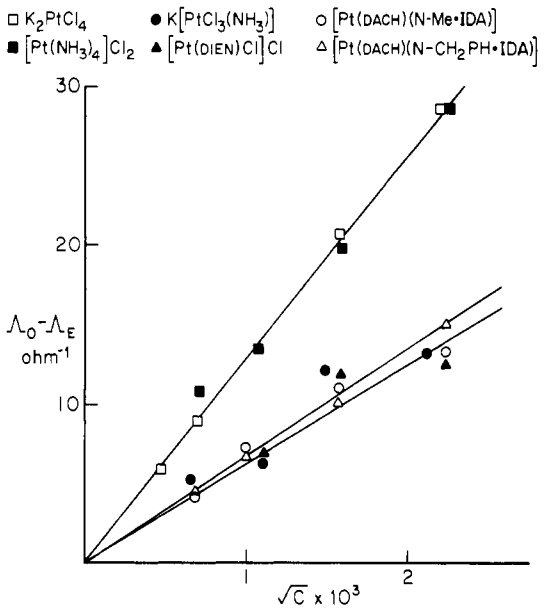


Figure 4. Plots of the limiting minus the equivalent conductance ($\Lambda_0 - \Lambda_E$) vs the square root of the concentration (M), $C^{1/2}$, for the complexes [Pt(*R*,*R*-DACH)(*N*-R•IDA)] (**6** and **8**) and selected 1:1 and 2:1 electrolytes in H_2O at 25 °C. DIEN represents diethylenetriamine.

for a chelated carboxyl group (1630 cm^{-1} for $[Pt(NH_3)_2$(gly-*N*,*O*)]$^+$) and a free (ionized) carboxylate group as in *trans*-[Pt-$(NH_3)_2$(gly-*N*)$_2$], respectively (gly = glycine). IR studies of [Pt(*R*,*R*-DACH-d_4)(*N*-Me•IDA)] and [Pt(*R*,*R*-DACH-d_4)Cl_2] support these assignments since (1) the 1645- and 1604-cm^{-1} bands are essentially unchanged on N-deuteriation and (2) the $-NH_2$ deformation mode (ρ_d, NH_2), which absorbs in the carboxyl region, shows only a weak but broad absorption band at ~1530 cm^{-1}. Thus, the IR data clearly establish the presence of two types of carboxyl groups.

MS(FAB) and Molecular Weight Determinations. The mass spectra of complexes **6**–**8** (Table IV) show base peaks corresponding to the (M + 1) species. Molecular weights determined in MeOH for the [Pt(*R*,*R*-DACH)(*N*-R•IDA)] complexes **6** and **8** and for the O,O-chelate complex [Pt(*R*,*R*-DACH)(glut-*O*,*O*)] (**9**) show values (Table IV) of 438 (calculated 454), 476 (calculated 530), and (not listed) 425 (calculated 439), respectively. Taken together, the data provide conclusive evidence that the complexes are monomeric in solution.

Conductivity Studies. The conductivity of the [Pt(*R*,*R*-DACH)(*N*-R•IDA)] complexes in solution were measured to assess both the solution stability and the electrolytic nature of these complexes in solution. Measurements were made in H_2O and MeOH under dinitrogen gas at concentrations of 10^{-3}–10^{-4} M for complexes **6** and **8** and for selected 1:1 and 1:2 reference electrolytes. Slopes of plots of $\Lambda_0 - \Lambda_E$ vs $C^{1/2}$ for **6** and **8** (Figure 4) in H_2O were found to be comparable to those for the 1:1 electrolytes [Pt(dien)Cl]Cl and $K[Pt(NH_3)Cl_3]$. Thus, [Pt(*R*,*R*-DACH)(*N*-R•IDA)] complexes behave essentially as 1:1 electrolytes in H_2O. Similar measurements in MeOH (Figure 5) establish that **6** and **8** are essentially nonconductors as compared to Bu_4NBr and Me_4NI.

pH and conductivity data for **6** (expressed as molar conductance, Λ_M) are illustrated in Figure 6. Plots of pH and Λ_M vs −log [concentration (M)] for **6** are curvilinear and consistent with those expected for a weakly basic electrolyte. As a point of comparison, the pH of a 0.1 M solution of **6** (by extrapolation of the pH curve in Figure 6) is close (9.4) to the pH (8.9) of a 0.1 M solution of NaO_2CCH_3.[22]

pK_a Determinations. Apparent pK_a values were determined for complexes **6** and **8** (and their respective free ligands) (Table IV) in order to determine which functional group (carboxylate

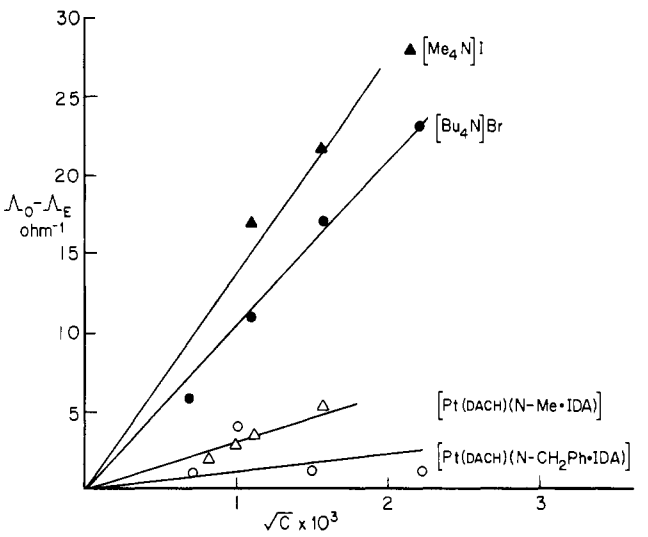


Figure 5. Plots of the limiting minus the equivalent conductance ($\Lambda_0 - \Lambda_E$) vs the square root of the concentration (M), $C^{1/2}$, for the [Pt(*R*,*R*-DACH)(N-*R*-IDA)] complexes (**6** and **8**) and Me_4NI and Bu_4NBr in MeOH at 25 °C.

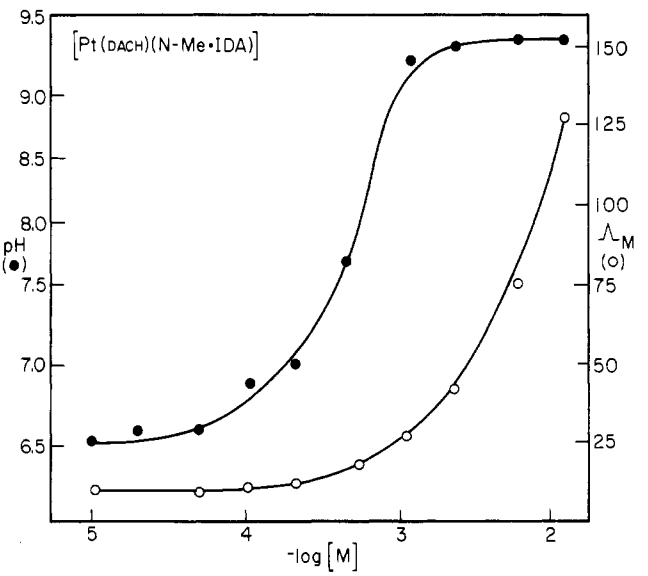


Figure 6. Plots of pH and molar conductance, Λ_M, for [Pt(*R*,*R*-DACH)(*N*-Me•IDA)] (**6**) in H_2O at 25 °C.

or amine) was bound to the Pt(II) central metal atom. The complexes were titrated with both acid ($HClO_4$) and base (NaOH) and the free *N*-R•IDA compounds with base. Single pK_a values (~2.7) were obtained for **6** and **8**, and two pK_a values were obtained for the *N*-Me (2.5 and 9.6) and *N*-CH_2Ph (2.7 and 8.9) IDA (free) ligands. Published data for $HN(CH_2CO_2H)_2$ quote values of pK_{a_1} and pK_{a_2} of 2.98 and 9.89, respectively.[23]

Obtaining a single pK_a of 2.7 for the complexes is consistent with the idea that the complex is an O,N-chelate in which the second carboxylate group is unbound and exists (ionized) as a free basic anion. Appleton et al.[17] proposed this basic structure for the complex *cis*-[Pt($^{15}NH_3$)$_2$(*N*-Me•IDA)]X (not isolated), in which the uncoordinated carboxylate group would be expected to be protonated under the acidic conditions employed.

Measurement of Other Physicochemical Properties. As was apparent in initial attempts to purify the crude complexes by various recrystallization techniques, the complexes exhibit high solubility in protic solvents (H_2O, alcohols, amides). Solubilities in DMF and MeOH, e.g., are 344 and 547 mg/g of solvent, respectively, for complex **8**. R_f values by TLC show the trend $-CH_2Ph$ > −EtOH > Me. Quantitative HPLC assays of **6**–**8**

(22) *The Merck Index*, 9th ed.; Merck: Rahway, NJ, 1976; p 1107.

(23) Reference 22, p 651.

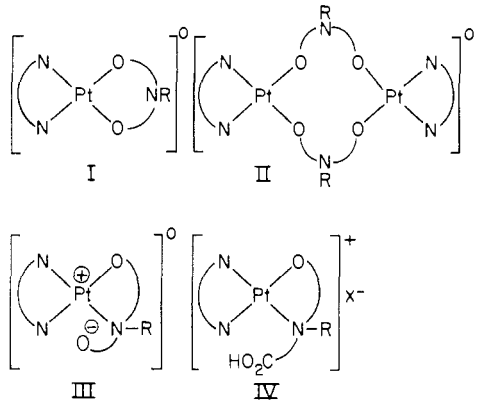


Figure 7. Generalized potential structures of [Pt(*R,R*-DACH)(*N*-R·IDA)] complexes.

indicate that the purity of these complexes is 99.5, 98.8, and 97.8%, respectively (cf. Table IV).

Discussion

Four general structures were considered as possibilities for the structure of [Pt(DACH)(*N*-R·IDA)] complexes (Figure 7). All four structures appeared plausible initially for the following reasons. Consideration of structures I and II, monomeric and dimeric O,O-bonded chelates, respectively, appeared warranted since only an O,O-chelate could have accounted for the preliminary antitumor activity reported for these complexes (vide infra). Apart from the antitumor activity argument, II also appeared reasonable because its close counterpart in the diammine–platinum(II) system (in which the glutarate dianion is the bridging ligand) is known to exist in the solid state, at least, as verified by a single-crystal X-ray structural determination.[24] However, the solution stability of this 16-membered-ring complex is questionable. Related structures III and IV were a priori the most likely candidates because of the high thermodynamic stability of Pt(O,N-chelate) complexes.

Apart from differences in the type of donor atom chelate, inspection of the structures indicates that different electrolytic properties would be observed for I and II (neutral) than for IV (1:1 electrolyte) or III (analogous to a zwitterion). MS(FAB) and molecular weight data alone, which have established that [Pt(*R,R*-DACH)(*N*-R·IDA)] complexes are monomeric in solution, were sufficient to eliminate II from further consideration. The strongest evidence in support of I is that the complexes are monomeric and would be expected to behave as weak electrolytes in solution, as is observed, by virtue of the free basic nitrogen atom. Additional support for I is derived from the possible existence of rotamers arising from two orientations of the *N*-R·IDA ligand placing the –NR (or just R) group above or below the PtN_2O_2 square plane. If these rotamers are stable on the NMR time scale at 20 °C, one would expect to see doublets in the ^{13}C NMR spectra for each of the carbonyl groups (but not as great a difference between the two sets of doublets) as is experimentally observed. However, it is not clear as to whether the rotamers (invertamers) would be spectrally distinct entities under the experimental conditions employed, particularly over the 20–80 °C temperature range studied. In any case, neither the ^{13}C nor the ^{195}Pt NMR signals show any tendency to coalesce at 80 °C as would not be expected for signals from rapidly exchanging rotamers. Thus, the lack of coalescence is better understood in terms of structures III and IV wherein coalescence of signals would require high-energy-demanding Pt–O and Pt–N bond-breaking processes to occur. Other arguments weighing against structure I are as follows. The experimentally observed pK_a values (~2.7) are consistent with the presence of a free carboxylate group and not with that of a free amine (for which a pK_a value of 8–10 would be expected). On the basis of the chemistry of mixed-ligand complexes of Pt(II), an eight-membered-ring O,O-chelate would be expected to be unstable in H_2O at 80 °C for 0.5 h (as was not the case for **6** and **8**) and show spectral evidence of hydrolytic degradation. (The minor peak at –209 ppm in the ^{195}Pt NMR solution spectrum of [Pt(*R,R*-DACH)(glut)] (**9**) is probably an aquo species resulting from hydrolytic degradation (aquation) at only 20 °C. Complex **9** is presumed to be an example of an eight-membered O,O-chelate complex.) Also, at 80 °C in solution the free basic nitrogen donor atom would be expected to displace readily one of the carboxyl groups in bringing about a change in the mode of chelation from O,O to O,N.

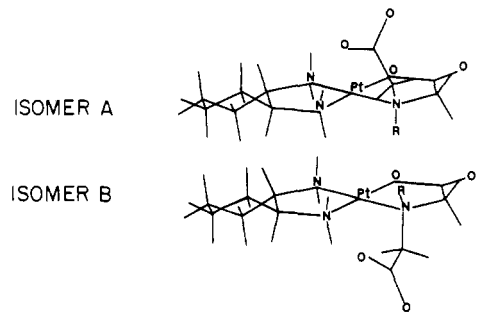


Figure 8. Graphic depiction of the structures of the [Pt(*R,R*-DACH)(*N*-R·IDA)] diastereomers.

As regards structures III and IV, the method of synthesis precludes the X group from being anything except OH^- as is substantiated by the elemental analytical data. If X is OH^-, this is tantamount to having III. The high solubility of [Pt(DACH)(*N*-R·IDA)] complexes in protonic solvents can be rationalized easily for III and IV, and to a lesser extent for I and II, in terms of H-bonding interactions involving the solvent with the basic N atom in I and II and with the ionized and un-ionized carboxyl groups in III and IV, respectively. Theoretically, III becomes IV in the presence of 1 mol of HX (e.g., $HClO_4$) and thus can be viewed as the conjugate base of IV. All the experimental data obtained are consistent with III as the structure of the [Pt(*R,R*-DACH)(*N*-R·IDA)] complexes and, in particular, ^{195}Pt NMR data (showing the presence in solution of two closely related species) and ^{13}C NMR data (establishing the presence of two species possessing two different carboxylate groups and closely agreeing with the data of Appleton and co-workers). Since the Pt(*R,R*-DACH) moiety possesses a 2-fold rotational axis of symmetry, the formation of an O,N-chelate, III, generates inner diastereomers by virtue of the prochiral N atom. A schematic drawing of these diastereomers is depicted in Figure 8. Chirality in the bound ligand is a prerequisite to the formation of diastereomers. It is likely that the free carboxylate group is associated with the positive platinum(II) center, forming an internal ion pair and taking on the appearance of a facial tridentate ligand.[26] pH and conductivity measurements indicate that the carboxylate group is dissociated (from Pt(II)) to a certain extent but not protonated to an appreciable extent since no evidence of a free CO_2H (un-ionized) group was observed by ^{13}C NMR or IR spectroscopy. As alluded to earlier in the text, this basic structure, III, was first proposed by Appleton et al.[17] for the complex cation *cis*-[Pt($^{15}NH_3$)$_2$(*N*-Me·IDA)]$^+$, for which diastereomers cannot exist.

Conclusions

On the basis of the results of spectroscopic and physicochemical studies we conclude that [Pt(DACH)(*N*-R·IDA)] complexes incorporate the *N*-R·IDA ligand as an O,N- rather than an O,O-chelate and that these complexes exist as spectroscopically defined diastereomeric pairs.

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(26) Preliminary results of molecular modeling studies of III (using complex **6**) suggest that an appreciable H-bonding interaction exists between the dangling carboxylate group and one proton on each of the two $-NH_2$ groups of the *R,R*-DACH ligand, which would be expected to enhance the stability of the ion-pair interaction.

The lack of antitumor activity of [Pt(DACH)(*N*-R·IDA-*O*,*N*)] complexes is consistent with a key structure–activity criterion,[3,27] which states that diam(m)ineplatinum(II) complexes must possess a pair of cis (reactive) leaving groups in order to exhibit antitumor activity. Since diam(m)ineplatinum(II) complexes incorporating an O,N-chelating ligand possess only one labile site, the lack of activity of these PtN_3O-type complexes is fully expected and would have been predicted had the structures of the complexes been known prior to biological testing.

The decision to evaluate the antitumor properties of the original homogeneous complexes was made under the presumption that the complexes were pure (based principally on elemental analyses). However, it has been demonstrated indirectly that an active impurity was present in the inactive [Pt(DACH)(*N*-R·IDA)] bulk materials. In retrospect, although these studies were very interesting, the research would not have been initiated were it known that the complexes were impure. This situation (which is perhaps more common in the Pt cancer chemotherapy field than is realized) underscores the need to characterize unequivocally and certify the purity of prospective antitumor complexes before any antitumor testing is initiated, especially when such complexes are derived directly from antitumor-active precursors or starting materials such as $[Pt(DACH)SO_4]$ and $[Pt(DACH)Cl_2]$. The use of selected spectroscopic techniques and/or reverse-phase HPLC analyses in evaluating the purity of new complexes is highly recommended.

It has been estimated that an impurity level of $[Pt(DACH)SO_4]$ of ≤5% could account for the activity observed for the original crude [Pt(DACH)(*N*-R·IDA)] complexes. We speculate that the active component(s) in the original crude samples tested is most likely derived from $[Pt(DACH)SO_4]$ (as an aquation and/or oligomeric product) or is even perhaps $[Pt(DACH)(OH)_2]$.

Acknowledgment. We acknowledge the invaluable assistance of the Microanalysis, Spectroscopy, and Chromatography groups at Parke-Davis and helpful discussions with Dr. L. Marzilli, Emory University.

Registry No. **1**, 61848-66-6; **2**, 62011-40-9; **3**, 66900-68-3; **4**, 61825-94-3; **5**, 82310-65-4; **6** (diastereomer 1), 116558-19-1; **6** (diastereomer 2), 116558-20-4; **7**, 111556-05-9; **8**, 111556-07-1; **9**, 97313-10-5; *N*-Me(IDA), 4408-64-4; *N*-CH_2Ph(IDA), 3987-53-9; [*R*,*R*-(DACH)D_2-d_6][*d*-tart], 116407-31-9; [*R*,*R*-(DACH)H_2][*d*-tart], 116407-32-0; [Pt(*R*,*R*-DACH-d_4)Cl_2], 116407-33-1; [Pt(*R*,*R*-DACH-d_4)(*N*-Me(IDA))], 116407-34-2; [Pt(*R*,*S*-DACH)(*N*-Me(IDA))], 116407-35-3; [Pt(*R*,*S*-DACH)(*N*-CH_2Ph(IDA))], 116407-36-4; D_2, 7782-39-0; ^{195}Pt, 14191-88-9.

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Thiolato–Technetium Complexes. 1. Synthesis and Characterization of Bis(tertiary diphosphine)technetium(III) Complexes Containing Methanethiolato Ligands. Single-Crystal Structural Analyses of *trans*-$[Tc^{III}(SCH_3)_2(DMPE)_2]CF_3SO_3$ and *trans*-$[Tc^{III}(SCH_3)_2(DEPE)_2]PF_6$, Where DMPE = 1,2-Bis(dimethylphosphino)ethane and DEPE = 1,2-Bis(diethylphosphino)ethane

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Received May 24, 1988

The Tc(III) methanethiolato complexes *trans*-$[Tc(SCH_3)_2D_2]^+$, where D is either 1,2-bis(dimethylphosphino)ethane (DMPE) or 1,2-bis(diethylphosphino)ethane (DEPE), have been synthesized and characterized. Preparation of these complexes from $[Tc^V(O)(OH)D_2]^{2+}$ utilizes excess $NaSCH_3$ as reductant and ligand. The X-ray crystal structures of both title complexes are examined. *trans*-$[Tc(SCH_3)_2(DMPE)_2]CF_3SO_3$, chemical formula $TcS_3P_4F_3O_3C_{15}H_{38}$, crystallizes in the triclinic space group $P\bar{1}$ with a = 7.9615 (13) Å, b = 9.3019 (7) Å, c = 18.5029 (16) Å, α = 88.093 (7)°, β = 89.686 (11)°, γ = 88.188 (11)°, V = 1368.8 (3) Å^3, and Z = 2. The final weighted R value is 0.032. The coordination complex is approximately octahedral with average Tc–P = 2.428 Å (range 2.422 (2)–2.434 (2) Å), Tc–S = 2.300 Å (range 2.298 (2)–2.302 (2) Å), and S–C = 1.842 Å (range 1.837 (7)–1.847 (7) Å). *trans*-$[Tc(SCH_3)_2(DEPE)_2]PF_6$, chemical formula $TcS_2P_5F_6C_{22}H_{54}$, crystallizes in the monoclinic space group $P2_1/c$ with a = 11.0724 (13) Å, b = 11.2450 (11) Å, c = 14.1331 (14) Å, β = 107.957 (8)°, V = 1674.0 (3) Å^3, and Z = 2. The final weighted R value is 0.022. This complex is also nearly octahedral with average Tc–P = 2.449 Å (range 2.4399 (8)–2.4584 (7) Å), Tc–S = 2.3025 (5) Å, and S–C = 1.821 (4) Å. In both structures the Tc atom occupies an inversion center. The visible spectra of these *trans*-$[Tc(SCH_3)_2D_2]^+$ complexes in acetonitrile show sulfur-to-technetium charge-transfer bands at 16 810 and 28 490 cm^{-1} for D = DMPE and at 16 610 and 28 830 cm^{-1} for D = DEPE. Cyclic voltammetric measurements in *N*,*N*-dimethylformamide show two reversible reduction couples corresponding to Tc(III/II) and Tc(II/I) at −0.550 and −1.72 V vs Ag/AgCl for D = DMPE and −0.554 and −1.81 V vs Ag/AgCl for D = DEPE. The absorption spectra and cyclic voltammograms are compared with those of other *trans*-$[TcD_2X_2]^+$ complexes with X = Cl, Br, −NCS and are discussed in terms of the relative strengths of the σ and π interactions between Tc and the ligating S and P atoms.

Introduction

The development of the inorganic chemistry of technetium, including especially the synthesis and characterization of new classes of low-valent complexes, has been driven largely by the preeminence of the isotope ^{99m}Tc in diagnostic nuclear medicine.[4-6] Gratifyingly, applications of the principles and techniques of inorganic chemistry have successfully progressed the aims of nuclear medicine and have generated several new and clinically useful ^{99m}Tc organ imaging agents.[6,7] This laboratory continues to develop new classes of low-valent technetium complexes with the dual goals of elucidating their fundamental inorganic chemistry and evaluating the potential use of their ^{99m}Tc analogues in diagnostic nuclear medicine.

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0020-1669/88/1327-4113$01.50/0