Platinum Complexes of Vitamin C. NMR Studies on the Solution Chemistry of *cis*-Pt(diamine)(ascorbate) Complexes

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Abstract: The reaction between sodium ascorbate and *cis*-[Pt(diamine)$(H_2O)_2](NO_3)_2$, where the diamine ligand is [^{15}N]ammonia, [1,2-$^{15}N_2$]ethylenediamine (^{15}en) or 1,2-diaminocyclohexane (dach), was studied by using ^{195}Pt and ^{13}C NMR spectroscopy. The reaction between [Pt(^{15}en)$(H_2O)_2]^{2+}$ and aqueous sodium ascorbate produces two complexes of the ascorbate monoanion ($HAsc^-$) and one complex of the ascorbate dianion (Asc^{2-}) during the initial stage of the reaction ($t < 1$ h). These products are the monoascorbate complex [Pt(^{15}en)$(H_2O)(O^3$-HAsc)]$^+$, the bisascorbate complex [Pt(^{15}en)$(O^3$-HAsc$)_2$], and the ascorbate chelate [Pt(^{15}en)$(O^2,O^3$-Asc)]. The reaction ultimately produces two carbon-bound ascorbate complexes: [Pt(^{15}en)$(C^2,O^5$-Asc)] (**5**) and [Pt(^{15}en)$(C^2$-HAsc)$(O^3$-HAsc)] (**17**). The carbon-bound ascorbate ligand in the chelate **5** and the bisascorbate complex **17** is bound to platinum (at C2) through the *re* and *si* face, respectively. Analogous products are obtained in the reaction when the diamine ligand is *trans-R,R*-dach, *trans-S,S*-dach, or *cis*-dach. An additional product is observed when the reaction is run with *cis*-[Pt($^{15}NH_3)_2(H_2O)_2]^{2+}$. In this case, ammonia release, at a site trans to a C2-bound ascorbate ligand, is observed during the reaction. Correlations between the ^{195}Pt–^{15}N coupling constants and the ligand donor strength of the C2-bound ascorbate ligand are used to explain the ammonia release reaction. In each of the diamine cases, a diastereofacial selectivity for substitution at the *re* face (*re:si* = 1.5–3.3) of the ascorbate anion is observed.

In recent years, cisplatin, *cis*-[$Pt(NH_3)_2Cl_2$], has achieved widespread success in the clinic as a chemical mediator of neoplastic disease.[1-3] While cisplatin is effective in treating testicular, ovarian, and bladder carcinomas,[4] the inherent toxicity of this complex and its inability to demonstrate useful activity in treating such major forms of the disease as breast, lung, and colon cancer have stimulated the search for new platinum-based antitumor agents. Research in this field has produced a number of promising new compounds that have shown good activity in various animal tumor screens.[5] While recent clinical studies on some of these second-generation analogues have shown dramatic improvement with respect to toxicity,[6] the search for new agents that exhibit a significantly different spectrum of activity is continuing.

Recently, we reported on the synthesis and unique structural features of a new class of antitumor compounds based on *cis*-diamineplatinum(II) complexes of vitamin C.[7] These compounds, the diamineplatinum–ascorbates, are prepared from the reaction of ascorbic acid with a variety of diaminediaqua complexes of the form *cis*-[$Pt(RNH_2)_2(H_2O)_2]^{2+}$. The products of the reaction, which are obtained as either mono- or bisascorbate complexes, are structurally unique, because they contain platinum bound directly to the C2 carbon of ascorbic acid. The monoascorbate products, *cis*-[$Pt(RNH_2)_2(C^2,O^5$-ascorbate)], contain a chelating ascorbate dianion that is bound through the C2 carbon and the deprotonated O5-hydroxyl group, while the bisascorbate complexes, *cis*-[$Pt(RNH_2)_2(C^2$-ascorbate)$(O^3$-ascorbate)], contain one carbon-bound and one oxygen-bound ascorbate anion per platinum. Both types of complexes have demonstrated some degree of antitumor activity in standard preclinical animal tumor screens, with the greater activity being found among the bisascorbate analogues.[8]

Aside from demonstrating biological activity, the diamineplatinum–ascorbates are of interest from a chemical point of view. These compounds are not only the first transition-metal complexes of vitamin C to yield to complete structural characterization, they are also the first complexes to demonstrate the importance of the C2-binding site in metallo–ascorbate chemistry. An understanding of the reactions of the diamineplatinum–ascorbate system may provide insight into the nature of ascorbate interactions with other metals of biological interest. For example, a number of copper-based metalloenzymes, such as ascorbic acid oxidase, and iron-based models of peroxidase, are known to utilize ascorbic acid as a reductant.[9] In these systems, oxygen-based ascorbate chelates (bound through O2 and O3) have been proposed as intermediates. The work presented here demonstrates that ascorbic acid can form not only oxygen bound complexes with transition metals but also stable monodentate and bidentate carbon-bound species.

Experimental Section

Preparation of Compounds. All diaminediaquaplatinum(II) nitrate complexes were prepared from $K_2[PtCl_4]$ (Engelhard) by using the method of Dhara.[10] The individual *cis*- and *trans*-1,2-diaminocyclohexane (dach) isomers[11] were separated from mixed 1,2-dach (Aldrich Chemical Company) by using $NiCl_2 \cdot 6H_2O$ according to published methods.[13] The individual *trans-R,R*-dach and *trans-S,S*-dach isomers were either resolved by using tartaric acid[14] or purchased from Alfa. Isotopically

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(8) (a) Amundsen, A. R.; Stern, E. W. U.S. Patent 4457926, 1984. (b) The diamineplatinum–ascorbate complexes have been tested in a variety of in vivo animal tumor screens. The results of these studies show that while the ascorbate chelates demonstrate antitumor activity, the compounds are of relatively low potency. The bisascorbate complexes have demonstrated good antitumor activity and better potency than the *cis*-[Pt(diamine)$(C^2,O^5$-Asc)] complexes. Full details will be reported elsewhere.
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(11) Recently, some confusion with respect to the nomenclature of platinum–diaminocyclohexane complexes has occurred in the literature (see ref 12). It should be noted that the 1,2-diaminocyclohexane ligand exists in three isomeric forms: *trans-R,R-*, *trans-S,S-*, and *cis-R,S*-dach. The cis and trans nomenclature used to describe Pt–dach complexes refers to the disposition of the amine groups on the dach ring and not to cis and trans stereochemistry of the platinum(II) complex.
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labeled [^{15}N]ammonium nitrate and [1,2-$^{15}N_2$]ethylenediamine·2HCl were purchased from MSD Isotopes. Tetramethylreductic acid[15] was obtained from Polaroid. As indicated below, satisfactory elemental analyses (less than 0.4% relative error) were obtained on representative compounds by using the services of Gailbraith Laboratories, Knoxville, TN.

Preparation of *cis*-[Pt(diamine)(C^2,O^5-ascorbate)] Chelates. A general preparative route to the monoascorbate chelates involves the reaction of a diaminediaqua complex, *cis*-[Pt(diamine)$(H_2O)_2$]$(NO_3)_2$, with ascorbic acid (1–4 equiv) at pH 4–6 in water. This reaction works quite well for most diamineplatinum complexes, with yields that are a function of the specific diamine ligand. Specific examples are given below.

[Pt(*trans*-*R*,*R*-dach)(C^2,O^5-ascorbate)]·3H_2O (1). An aqueous 0.2 M solution of [Pt(*trans*-*R*,*R*-dach)$(H_2O)_2$]$(NO_3)_2$ was added to a solution which contained 2 equiv of ascorbic acid (4 M) and 2 equiv of NaOH. The resulting solution was stirred at 25 °C for 24 h under dinitrogen. The precipitate **1** was collected by filtration and recrystallized from hot (80–90 °C) water. Additional material was obtained by concentrating the filtrate. Typical yields were 65 to 70%, based on Pt. Anal. ($PtC_{12}H_{26}N_2O_9$) Pt, C, H, N.

[Pt(*trans*-*S*,*S*-dach)(C^2,O^5-ascorbate)]·2H_2O (2). A 0.2 M solution of [Pt(*trans*-*S*,*S*-dach)$(H_2O)_2$]$(NO_3)_2$ was mixed with 2 equiv of ascorbic acid and NaOH, as described above. After 24 h the solution was concentrated under reduced pressure. Crystals of [Pt(*trans*-*S*,*S*-dach)(C^2,O^5-ascorbate)] were obtained by evaporating the solution under a N_2 stream. This isomer has a much higher aqueous solubility (~18 mg/mL) than that of the *R*,*R* isomer **1**. Yields of up to 40% were obtained by successive filtration and evaporation. Anal. ($PtC_{12}H_{24}N_2O_8$) Pt, C H, N.

[Pt(*cis*-dach)(C^2,O^5-ascorbate)]·3H_2O (3) and (4). Two isomeric forms of the ascorbate chelate were obtained from the reaction of [Pt(*cis*-dach)$(H_2O)_2$]$(NO_3)_2$ and sodium ascorbate. When this reaction was conducted as described for **1**, a white precipitate was obtained after 24 h. This solid, which contained both isomeric forms of the [Pt(*cis*-dach)(C^2,O^5-ascorbate)] chelate, was obtained in 60% yield from successive filtration and evaporation steps. The two isomeric forms, **3** and **4**, were identified by using analytical HPLC (see below). Compounds **3** (t_R = 1.52 min) and **4** (t_R = 1.78 min) were separated by dissolving 1.5 g of the mixture in 23 mL of ethylene glycol, and filtering the resulting solution into 50 mL of water. The solution was cooled to 3 °C for 1 h, and the resulting white precipitate **3** was collected by filtration. The filtrate was poured into 500 mL of acetone, and after 5 h at 0 °C, the resulting precipitate **4** was collected by filtration. Both solids were washed with water and acetone and dried under vacuum (yield, 0.7 g of **3** and 0.4 g of **4**). A separation of >90%, as judged by HPLC, was obtained by using this method. **3** and **4**: Anal. ($PtC_{12}H_{26}N_2O_9$) Pt, C, H, N.

[Pt(^{15}en)I_2]. An aqueous solution (0.1 M) of $K_2[PtCl_4]$ was treated with 4.1 equiv of KI (saturated) and stirred for 15 min at 25 °C. An aqueous solution containing [1,2-$^{15}N_2$]ethylenediamine·2HCl (1 equiv, 2 M) and KOH (2 equiv) was added to the resulting $K_2[PtI_4]$ solution. After 1 h, the [Pt(^{15}en)I_2] precipitate was collected by filtration and washed extensively with water and ethanol. The solid was dried under vacuum (yield, 95%).

[Pt(^{15}en)(C^2,O^5-ascorbate)]·3H_2O (5). A 0.2 M solution of [Pt(^{15}en)$(H_2O)_2$]$(NO_3)_2$ (4.4 mmol) was treated with 8.8 mmol ascorbic acid, and the pH of the solution was adjusted to 5.4 (pH meter) with 2 N NaOH. The solution was placed under dinitrogen, and after 24 h a crystalline precipitate **5** was collected by filtration. A 52% yield of **5** was obtained after washing the solid with water and drying under vacuum.

***cis*-[Pt($^{15}NH_3$)$_2I_2$].** A 0.2 M solution of freshly prepared $K_2[PtI_4]$ was treated with 2 equiv (2.5 g) of $^{15}NH_4NO_3$ and 2 equiv of KOH dissolved in 10 mL water. After 2 h the *cis*-[Pt($^{15}NH_3$)$_2I_2$] was filtered and washed with water and ethanol. The solid was dried under vacuum (92% yield).

***cis*-[Pt($^{15}NH_3$)$_2$(C^2,O^5-ascorbate)]·2H_2O (6).** The ^{15}N-labeled diammine complex **6** was prepared by using the method described for compound **5**. Yields of 20–40% were obtained. Anal. ($PtC_6H_{16}N_2O_8$) Pt, C, H, N.

[Pt(*trans*-dach)(TMRA)]·2H_2O (7). Racemic [Pt(*trans*-dach)$(H_2O)_2$]$(NO_3)_2$ (10 mmol in 60 mL water) was mixed with 20 mmol of tetramethylreductic acid and 10 mmol of NaOH (1 M). The resulting solution was stirred for 3 h and filtered to remove a grey precipitate. The grey solid was stirred in 200 mL of methanol and filtered, and the filtrate was allowed to evaporate in air. The resulting white solid was collected by filtration and washed with methanol (yield 1.9 g). Anal. ($PtC_{15}H_{30}N_2O_5$) Pt, C, H, N.

[Pt(^{15}en)(TMRA)]·2H_2O (8). An aqueous solution of [Pt(^{15}en)$(H_2O)_2$]$(NO_3)_2$ (1 mmol in 4 mL) was added to a solution of TMRA (2 mmol) and NaOH (2 mmol) in 1 mL of water. The desired product, which precipitated from solution, was redissolved by adding methanol and heating (45 °C). Upon cooling, crystals of the TMRA chelate **8** precipitated from solution. The white solid was collected by filtration, washed with water, and vacuum dried (yield 69%). Anal. ($PtC_{11}H_{24}N_2O_5$) Pt, C, H, N.

HPLC Methods. Analytical and preparative HPLC studies were conducted with a Waters HPLC system by using a 6000A pump equipped with an extended flow pump-head and a 440 UV–vis detector. Analytical samples were run in water (isocratic) at a flow rate of 6 mL/min by using a Novapak C_{18} radial compression column (Z module). A Whatman partisil-10 ODS-3 column (4 mL/min flow rate) and a Siemens fraction collector (Model ES-1) were used for preparative separations. Peaks were monitored at 254 nm.

Spectral Measurements. NMR spectra were recorded with a Varian XL-200 spectrometer by using a 10-mm tunable probe (20–80 MHz). ^{195}Pt spectra (42.935 MHz) were collected by using a 70° pulse (9 μs) and a 0.06 s acquisition time with a spectral width of 80 kHz (9.6k data points). Spectra of ^{14}N-substituted complexes were processed by using line broadening (200 Hz) and zero filling (32k). ^{195}Pt spectra of ^{15}N-labeled complexes were obtained in water, to avoid line broadening due to N-deuteriation, with use of broad-band ^{1}H-decoupling (Waltz modulation). A line broadening of 10 Hz with 32k zero filling was used to process ^{195}Pt spectra of ^{15}N-labeled complexes. ^{195}Pt spectra were referenced by using an external sample of 0.1 M $K_2[PtCl_4]$ (in D_2O) at −1624 ppm. The position of the $K_2[PtCl_4]$ was measured relative to H_2PtCl_6 (1 g/3 mL of D_2O) at 0 ppm. ^{13}C spectra were typically collected by using a 30° pulse (5 μs), a 12-kHz sweep width, and a 1-s acquisition time. APT,[16] DEPT,[17] and HETCOR[18] experiments were conducted by using standard Varian software.

Results and Discussion

^{195}Pt NMR spectroscopy is perhaps the single most useful technique that can be employed to monitor the course of the diamineplatinum–ascorbate reaction. The reactions can be conducted directly in the NMR tube, and the products can be identified and quantified as a function of time. Typically, the kinetics of the platinum substitution reactions in this system are slow enough to allow convenient spectral measurements. The high receptivity of the ^{195}Pt nucleus, the broad chemical shift range, and the predictable nature of the chemical shifts upon ligand substitution provide an excellent means for product characterization.[19] Furthermore, ^{15}N-labeling of the diamine ligand provides additional information by permitting measurement of both the multiplicity of the ^{195}Pt–^{15}N splitting pattern and the coupling constant $J(^{195}Pt-^{15}N)$. The magnitude of $J(^{195}Pt-^{15}N)$ is a particularly useful aid to structural characterization since it is directly related to the donor properties of the ligands bound to platinum.[20–25] The effect of both the trans and cis influence of donor ligands on the $J(^{195}Pt-^{15}N)$ coupling constant has recently been investigated by Appleton et al.[21] By using this type of information in platinum complexes of the form *cis*-[Pt($^{15}NH_2R$)$_2$(X)(Y)]$^{n+}$, it is possible to distinguish between species that have very similar donor ligands (X and Y). In this manner, Appleton[24] was able to identify the three mononuclear species, *cis*-[Pt($^{15}NH_3$)$_2$$(H_2O)_2$]$^{2+}$, *cis*-[Pt($^{15}NH_3$)$_2$$(O_2CCH_3)(H_2O)$]$^+$ and *cis*-[Pt($^{15}NH_3$)$_2$$(O_2CCH_3)_2$], that are obtained with two similar

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(15) Abbreviations: TMRA, tetramethylreductic acid; Asc, ascorbate dianion; HAsc, ascorbate monoanion; O_d, general oxygen donor; C_d, general carbon donor.

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Table I. ^{195}Pt NMR Data, Chemical Shifts (ppm), and $^{195}Pt-^{15}N$ Coupling Constants (Hz) for Complexes Relevant to the "Pt(^{15}en)(ascorbate)" Reaction

compound	chem shift[a]	J	J'
$[Pt(^{15}en)(H_2O)_2]^{2+}$ Deprotonation Products[b]			
$[Pt(^{15}en)(H_2O)_2]^{2+}$ (pH 2) (**9**)	−1910	421	
$[Pt(^{15}en)(H_2O)(NO_3)]^{+}$ (**10**)	−1929		
$[Pt_2(^{15}en)_2(H_2O)_2(\mu\text{-}OH)]^{3+}$ (**11**)	−1829	424[c]	373[d]
$[Pt_2(^{15}en)_2(\mu\text{-}OH)_2]^{2+}$ (**12**)	−1480	366	
$[Pt_3(^{15}en)_3(\mu\text{-}OH)_3]^{3+}$ (**13**)	−1770	~330	
Pt(^{15}en)(ascorbate) Reaction Products			
bisoxygen donors			
$[Pt(^{15}en)(H_2O)_2]^{2+}$ (**9**)	−1911	420	
$[Pt(^{15}en)(H_2O)(O^3\text{-HAsc})]^{+}$ (**14**)	−1838	422[c]	385[e]
$[Pt(^{15}en)(O^3\text{-HAsc})_2]$ (**15**)	−1780	390	
$[Pt(^{15}en)(O^2,O^3\text{-Asc})]$ (**16**)	−1712	363	
carbon–oxygen donors			
$[Pt(^{15}en)(C^2,O^5\text{-Asc})]$ (**5**)	−2634	347[f]	253[g]
$[Pt(^{15}en)(C^2\text{-HAsc})(O^3\text{-HAsc})]$ (**17**)	−2663	400[e]	237[g]
$[Pt(^{15}en)(O^2,O^3\text{-TMRA})]$ (**8**)	−1806	360	

[a] Chemical shifts measured relative to H_2PtCl_6 (1 g/3 mL of D_2O) at 0 ppm. [b] Deprotonation products were prepared by adjusting an aqueous solution of $[Pt(^{15}en)(H_2O)_2](NO_3)_2$ (0.25 M) to pH 5 with 1 N NaOH. [c] trans to H_2O. [d] trans to OH. [e] trans to O3. [f] trans to O5. [g] trans to C2.

oxygen donors (H_2O and acetate), even though each has a very similar chemical shift.

The diamineplatinum–ascorbate reaction was studied under various conditions with use of a number of different diamine ligands. Since a variety of products are obtained in these reactions, ^{15}N-labeled diamineplatinum complexes were prepared to aid in product characterization. In general, the major products formed during these reactions were the same for each diamine examined. Various platinum to vitamin C ratios (1:1 to 1:4) and initial pH adjustments (pH 4–6) were studied. Typically, these changes had some effect on the product distribution and the kinetics of the reactions, but, in general, the studies outlined below were representative of the diamineplatinum ascorbate reaction in this window of stoichiometry and pH.

Reaction of $[Pt(^{15}en)(H_2O)_2](NO_3)_2$ with Ascorbic Acid. When the reaction of $[Pt(^{15}en)(H_2O)_2]^{2+}$ with 2 equiv of sodium ascorbate is followed as a function of time by using ^{195}Pt NMR, two distinct classes of species are observed. As shown in Figure 1, the diamineplatinum species are grouped, based on donor type, into the bisoxygen donor (−1600 to −1900 ppm) and the carbon–oxygen donor (−2500 to −2700 ppm) regions of the spectrum. The relative concentration of the various species in each region is found to change as a function of time. Within the first 60 min of the reaction, the predominant species in solution are bisoxygen-bound complexes of the general form $[Pt(^{15}en)(O_d)_2]^{n+}$. As the reaction proceeds over the next few hours, the concentration of the carbon–oxygen-bound species, complexes of the general form $[Pt(^{15}en)(C_d)(O_d)]$, increases at the expense of the bisoxygen-bound species. In the final stage of the reaction (after 36 h) the carbon–oxygen-bound components are the only species remaining in solution.

Four major oxygen-bound intermediates are observed in the early stage of the reaction. The ^{195}Pt chemical shift and $^{195}Pt-^{15}N$ coupling constant data for these species are presented in Table I. For comparative purposes, ^{195}Pt NMR data were obtained on a number of deprotonation products of the $[Pt(^{15}en)(H_2O)_2]^{2+}$ system.[25,26] These complexes, which include the monohydroxo-bridged dimer $[Pt_2(^{15}en)_2(H_2O)_2(\mu\text{-}OH)]^{3+}$ (**11**), the dihydroxo-bridged dimer $[Pt_2(^{15}en)_2(\mu\text{-}OH)_2]^{2+}$ (**12**), and the trihydroxo-bridged trimer $[Pt_3(^{15}en)_3(\mu\text{-}OH)_3]^{3+}$ (**13**), are generated in solution by adding base to aqueous $[Pt(^{15}en)(H_2O)_2]^{2+}$. The relationship between ^{195}Pt chemical shift, $^{195}Pt-^{15}N$ coupling constant and the donor properties of the oxygen-based ligands in

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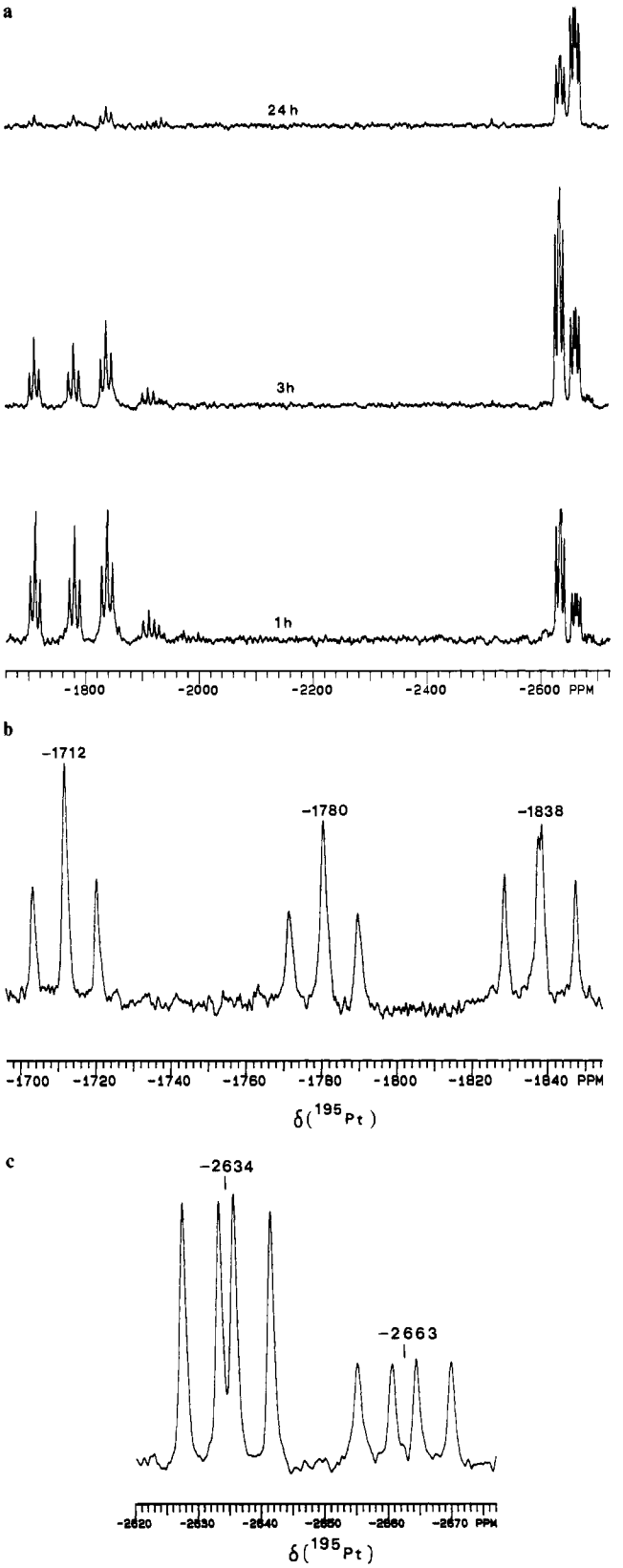


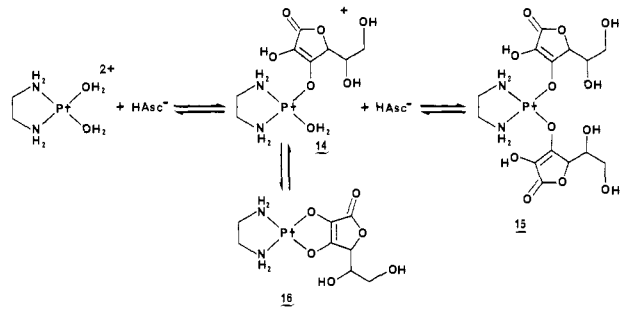
Figure 1. (a) ^{195}Pt spectra of the reaction between 1 mmol of $[Pt(^{15}en)(H_2O)_2]^{2+}$ and 2 mmol of sodium ascorbate in 4 mL of water taken at 1, 3, and 24 h. (b) Enlargement of the oxygen-donor region of spectrum 1a (at 1 h) showing inequivalent ^{15}N-splitting of the ^{195}Pt resonance centered at −1838 ppm. The three sets of signals arise from the monoascorbate complex $[Pt(^{15}en)(H_2O)(O^3\text{-HAsc})]^{+}$ (**14**) at −1838 ppm, the bisascorbate complex $[Pt(^{15}en)(O^3\text{-HAsc})_2]$ (**15**) at −1780 ppm, and the ascorbate chelate $[Pt(^{15}en)(O^2,O^3\text{-Asc})]$ (**16**) at −1712 ppm. (c) Enlargement of the carbon–oxygen donor region of spectrum 1a (at 1 h), showing the signals for the carbon-bound ascorbate chelate $[Pt(^{15}en)(C^2,O^5\text{-Asc})]$ (**5**) at −2634 ppm and the bisascorbate complex $[Pt(^{15}en)(C^2\text{-HAsc})(O^3\text{-HAsc})]$ (**17**) at −2663 ppm.

this system compares favorably with the previously reported analysis of the deprotonation reactions of *cis*-$[Pt(^{15}NH_3)_2(H_2O)_2]^{2+}$ [22-26] This information can be used to develop reasonable assignments for the oxygen-bound intermediates in the diamineplatinum–ascorbate reactions.

In the beginning of the ascorbate reaction, before the mixture of $[Pt(^{15}en)(H_2O)_2]^{2+}$ and ascorbic acid is treated with sodium hydroxide, one major and two minor species are observed in the ^{195}Pt spectrum. At this low pH (1.2), the main species in solution is unreacted $[Pt(^{15}en)(H_2O)_2]^{2+}$. The ^{195}Pt resonance of $[Pt(^{15}en)(H_2O)_2]^{2+}$ appears as a triplet (due to the coupling of two equivalent ^{15}N nuclei) at −1911 ppm, with a ^{195}Pt–^{15}N coupling constant of 421 Hz. The magnitude of the coupling constant is related to the donor properties of both the water and diamine ligands. A number of studies[27] suggest that ^{195}Pt–^{15}N coupling constants are strongly influenced by the Fermi contact contribution to the spin–spin interaction. As a result, the coupling constants are, for the most part, directly proportional to the *s*-character of the Pt and N bonding orbitals.[27] The relationship between the coupling constants and the donor properties of various diamine ligands in *cis*-$[Pt(diamine)(H_2O)_2]^{2+}$ complexes is consistent with this mechanism of spin–spin coupling. With a stronger σ-donor such as ethylenediamine,[28] the coupling constant is approximately 30 Hz larger than that found with *cis*-$[Pt(^{15}NH_3)_2(H_2O)_2]^{2+}$. The second major factor that influences the magnitude of $J(^{195}Pt$–$^{15}N)$ relates to the donor properties of the trans oriented ligands (X and Y) in diamine complexes of the form *cis*-[Pt(diamine)(X)(Y)].[20-25] The X and Y ligands exert both a cis and trans influence on $J(^{195}Pt$–$^{15}N)$. While there are a number of factors involved in this interaction,[21] a simplified view of the relationship between J and the donor strength of X and Y is applicable in most cases. Weak trans donors, such as H_2O or oxygen-based ligands, lead to larger coupling constants (J = 350–430 Hz), and strong donors such as sulfur- or carbon-based ligands lead to smaller coupling constants (J = 200–300 Hz). This general trend is observed among the various products of the diamineplatinum–ascorbate reactions.

The two minor components that are present in the reaction under acidic conditions can be assigned as monoaqua species of the form $[Pt(^{15}en)(H_2O)(O_d)]^+$. One of these components is the mononitrato complex, $[Pt(^{15}en)(H_2O)(NO_3)]^+$, which is also present before ascorbic acid is added to the solution. An analogous mononitrato complex is observed[23] in aqueous solutions of *cis*-$[Pt(^{15}NH_3)_2(H_2O)_2](NO_3)_2$. Typically, the ^{195}Pt spectrum of the *cis*-$[Pt(diamine)(H_2O)(NO_3)]^+$ complex appears as a doublet of doublets, due to the inequivalent oxygen donors. However, under the conditions of this experiment, the intensity of the mononitrato resonance was too small (<1% of the intensity of the $[Pt(^{15}en)(H_2O)_2]^{2+}$ resonance) to resolve the individual coupling constants. The second minor component appears in the ^{195}Pt spectrum as a weak doublet of doublets centered at −1835 ppm. On the basis of chemical shift and coupling constant data, we assign this quartet to the O3-bound monoascorbate complex $[Pt(^{15}en)(H_2O)(O^3\text{-HAsc})]^+$ (**14**, see Table I). The nonequivalent coupling constants of 385 and 422 Hz are in the range expected for ^{15}N trans to an oxygen-bound ascorbate and a water ligand, respectively.[20-25] These values are similar to those observed for the monoacetate complex,[23] *cis*-$[Pt(^{15}NH_3)_2(H_2O)(O_2CCH_3)]^+$. While the site of attachment on the ascorbate ring could not be confirmed by additional spectroscopic measurements due to the low concentration and the transitory nature of this species, the O3-binding site is the most likely based on the pK_a values of ascorbic acid (O3, pK_a = 4.17 and O2, pK_a = 11.7).[29] It is interesting to note that the monoascorbate complex **14** is present

Scheme I

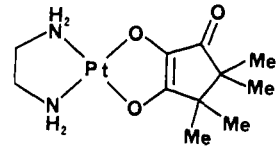


at low concentration (~2% of the total platinum) even at low pH.

When the pH of the solution is raised by adding 1 equiv of sodium hydroxide per equivalent of ascorbic acid, the diaqua complex **9** becomes a minor component within 10 min. Within the first hour of the reaction, three major sets of ^{195}Pt resonances are observed in the oxygen-donor region of the spectrum adjacent to the residual diaqua related signal (see Figure 1b). One of these is the doublet of doublets (−1838 ppm) from the monoascorbate complex $[Pt(^{15}en)(H_2O)(O^3\text{-HAsc})]^+$ (**14**). While this set of resonances is similar to that expected from the monohydroxo-bridged dimer **11**, it is unlikely that this complex would form under these conditions (pH 4) where the pH is less than that required to deprotonate the diaqua complex (pK_{a1} 6.1–6.5).[24,26] Furthermore, the concentration of this component after pH adjustment is dependent on the initial platinum to sodium ascorbate mole ratio, with **14** predominating at lower sodium ascorbate to platinum ratios (1–2 equiv per Pt). With higher ratios (2–4 equiv per Pt), the intensities of the remaining two sets of resonances, centered at −1780 and −1712 ppm, increase at the expense of the intensity of the monoascorbate multiplet at −1838 ppm. The resonances at −1780 and −1712 ppm are symmetric triplets with ^{195}Pt–^{15}N coupling constants of 390 and 363 Hz, respectively.

As the concentration of sodium ascorbate is increased, the product distribution among the oxygen-bound species is expected to shift toward the bis-O3-ascorbate complex **15**. Since the intensity dependence of the triplet at −1780 ppm behaves in this manner, this multiplet is assigned to the bis-O3-ascorbate complex, $[Pt(^{15}en)(O^3\text{-HAsc})_2]$ (**15**). The chemical shift and coupling constant data are consistent with this assignment. The symmetry of the triplet suggests that the two oxygen donors are equivalent, and the coupling constant (J = 390 Hz) is similar to that observed in the monoascorbate complex **14**. Furthermore, the relatively constant change in the chemical shift per ascorbate substitution (60–70 ppm per ascorbate ligand, in going from **9** to **14** to **15**) is characteristic of the additive nature of substitution shifts in ^{195}Pt NMR.[20,21]

The remaining triplet in the oxygen-donor region (−1712 ppm) of the spectrum has a ^{195}Pt–^{15}N coupling constant of 363 Hz. This value is significantly smaller than that observed for ^{15}N trans to an ascorbate anion bound to Pt, in a monodentate fashion, through O3 (385–390 Hz). Since this component could be the O2,O3-ascorbate chelate $[Pt(^{15}en)(O^2,O^3\text{-Asc})]$, a model compound of a related enediol chelate was prepared for comparative purposes. Tetramethylreductic acid (TMRA) was chosen as an ascorbate model since the redox properties of this molecule are known to be similar to those of vitamin C.[30] The enediol functionality of TMRA provides a binding site that is similar to the enediol binding site of ascorbic acid. The $[Pt(^{15}en)(O^2,O^3\text{-TMRA})]$ complex **8**,



8

(27) (a) Motschi, H.; Pregosin, P. S. *Inorg. Chim. Acta* **1980**, *40*, 141. (b) Motschi, H.; Pregosin, P. S.; Venanzi, L. M. *Helv. Chim. Acta* **1979**, *62*, 667. (c) Pregosin, P. S.; Omura, H.; Venanzi, L. M. *J. Am. Chem. Soc.* **1973**, *95*, 2047.

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(29) Radford, T.; Sweeney, J. G.; Iacobucci, G. A.; Goldsmith, D. J. *J. Org. Chem.* **1979**, *44*, 658.

(30) Clarke, M. J. *Comments Inorg. Chem.* **1984**, *3*, 133.

which was prepared by the reaction of $[Pt(^{15}en)(H_2O)_2](NO_3)_2$ with TMRA (pH = 4–5), was characterized by using ^{195}Pt and ^{13}C NMR and elemental analysis. The ^{195}Pt spectrum of **8** appears as a triplet at −1806 ppm with a $^{195}Pt-^{15}N$ coupling constant of 360 Hz. Since this coupling constant is very similar to that observed for the triplet at −1712 ppm (J = 363 Hz), we believe that this species is the O2,O3-ascorbate chelate [Pt-(^{15}en)(O^2,O^3-Asc)] (**16**). The reaction sequence involving the oxygen-bound species is summarized in Scheme I.

After the initial stage of the reaction, the concentration of the three oxygen-bound ascorbate complexes **14–16** decreases as a function of time. These intermediates remain as major components in solution only during the first few hours of reaction. As the reaction proceeds, two sets of resonances appear, with increasing intensity, in the carbon–oxygen donor region of the ^{195}Pt spectrum. These products are carbon-bound ascorbate complexes of the form $[Pt(^{15}en)(C_d)(O_d)]^{n+}$. The ^{195}Pt multiplet centered at −2634 ppm (Figure 1c, Table I) arises from the C2,O5-bound ascorbate chelate [Pt(^{15}en)(C^2,O^5-Asc)] (**5**). This product, which can be isolated from solution as a crystalline precipitate, was characterized by using ^{13}C NMR and elemental analysis. The results of these studies show that **5** is structurally analogous to the *cis*-dach complex [Pt(*cis*-dach)(C^2,O^5-Asc)] (**3**), whose structure was determined by using X-ray crystallography.[7] The ascorbate ligand in both **3** and **5** is bound to the platinum, as a dianion, through the C2-carbon and the O5-hydroxyl group, which is deprotonated. As the two $^{195}Pt-^{15}N$ coupling constants in **5** suggest, the carbon donor (C2) exerts a much greater trans influence than the oxygen donor (O5). The coupling constant for ^{15}N trans to the C2-carbon (253 Hz) is much smaller than that trans to the O5-oxygen (347 Hz). $^{195}Pt-^{15}N$ coupling constants in the 230–270 Hz range are generally found opposite ligands that have a large trans influence,[20,21] such as sulfur and carbon donors. The enhanced trans influence[31] of the C2-bound ascorbate ligand also is clearly seen in the X-ray crystallographic studies of the [Pt(*cis*-dach)(C^2,O^5-Asc)] analogue.[7] In this complex, the Pt–N bond that is trans to C2 is 0.05 (1) Å longer than the corresponding bond length trans to O5. As discussed below, the weakening of the Pt–N bond trans to C2 in the case of the diammine complex, *cis*-$[Pt(^{15}NH_3)_2(C^2,O^5$-Asc)], can lead to ammonia release at this site.

The second multiplet in the carbon–oxygen donor region of the ^{195}Pt spectrum consists of a doublet of doublets centered at −2663 ppm. This signal arises from the platinum complex that is formed when the metal binds to the opposite diastereotopic face of the ascorbate ligand (at C2). As expected, the reactive diaqua complex, $[Pt(^{15}en)(H_2O)_2]^{2+}$ can bind to the prochiral C2-carbon from either the *re* or *si* face of the ascorbate ring (see Figure 2). When the platinum binds to the *re* face, the hydroxyl group at O5 is properly positioned for ring closure, which results in the formation of the C2,O5-ascorbate chelate **5**. However, when the platinum binds to C2 through the opposite face, ring closure is not possible since the exocyclic glycol chain (containing O5) is positioned away from the metal on the opposite side of the ascorbate ring. Since ring closure is geometrically prohibited when platinum is bound to the *si* face, the remaining binding site on platinum, which contains a reactive ligand (H_2O), is available for further reaction with a second ascorbate anion when excess sodium ascorbate is present. The ^{195}Pt resonances, from the resulting bisascorbate complex [Pt(^{15}en)(C^2-HAsc)(O^3-HAsc)] (**17**), are those centered at −2663 ppm (see Figure 1c). The values of the $^{195}Pt-^{15}N$ coupling constants for **17** are 237 Hz for the nitrogen trans to C2 and 400 Hz for the nitrogen trans to O3. These values are consistent with the proposed formulation of **17** (see Table I). As discussed below, ^{13}C NMR studies of the dach analogues of the bisascorbate complex confirm this assignment.

A plot of the intensity of the ^{195}Pt resonance of both *re* and *si* isomers of C2-bound ascorbate complexes **5** and **17** as a function of time is shown in Figure 3. During the first 200 min of the reaction, the concentration of both complexes increases with time. The *re* to *si* ratio, based on the ^{195}Pt signal intensities,[32] remains constant at 1.6:1 during this period of the reaction. These results show that the reaction is stereoselective for the face of the as-

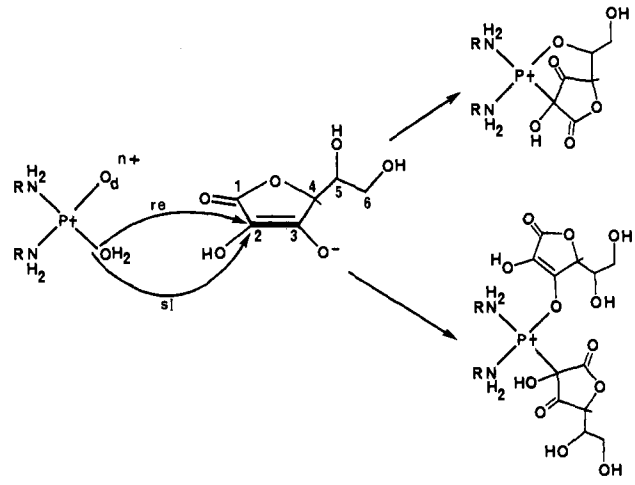

Figure 2. Diagram of platinum binding to the *si* and *re* face of the ascorbate anion at the C2-carbon showing the products of the reaction. Platinum binding at the *re* face leads to ring closure through attachment at O5, while ring closure is prevented when platinum binds to the *si* face of the ascorbate anion.

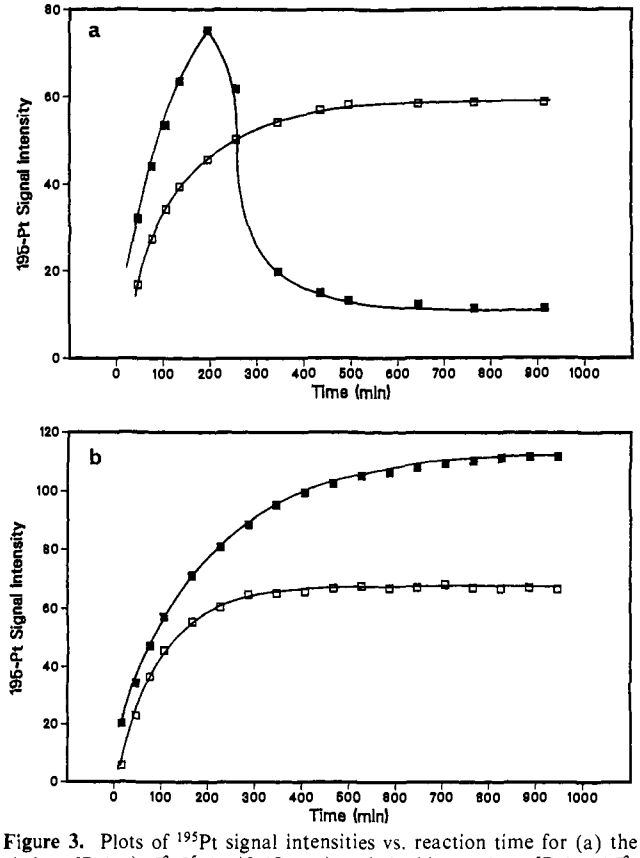

Figure 3. Plots of ^{195}Pt signal intensities vs. reaction time for (a) the chelate [Pt(en)(C^2,O^5-Asc)] (**5** = ■) and the bisascorbate [Pt(en)(C^2-HAsc)(O^3-HAsc)] (**17** = □) components of the "Pt(en)(ascorbate)" reaction (1 mmol of Pt + 4 mmol of sodium ascorbate in 4 mL of D_2O) and (b) the chelate [Pt(*trans*-*S*,*S*-dach)(C^2,O^5-Asc)] (**32** = ■) and the bisascorbate [Pt(*trans*-*S*,*S*-dach)(C^2-HAsc)(O^3-HAsc)] (**33** = □) components of the "Pt(*trans*-*S*, *S*-dach)(ascorbate)" reaction (1 mmol of Pt + 4 mmol of sodium ascorbate in 4 mL of D_2O).

(31) Appleton, T. G.; Clark, H. C.; Manzer, L. E. *Coord. Chem. Rev.* **1973**, *10*, 335.

(32) Signal intensities of ^{195}Pt resonances for ^{14}N-substituted compounds were used to gauge relative concentrations. The relaxation times of the *si* and *re* bound ascorbate complexes are short enough (0.012–0.018 s) to allow useful comparison of peak heights.

Table II. ^{195}Pt NMR Data, Chemical Shifts (ppm), and ^{195}Pt–^{15}N Coupling Constants (Hz) for the "*cis*-Pt($^{15}NH_3$)$_2$(ascorbate)" Reaction Products

compound	chem shift[a]	J	J'
Bisoxygen Donors			
cis-[Pt($^{15}NH_3$)$_2$(H_2O)$_2$]$^{2+}$	−1582	392	
cis-[Pt($^{15}NH_3$)$_2$(H_2O)(NO_3)]$^+$	−1595	403[b]	378[c]
cis-[Pt($^{15}NH_3$)$_2$(H_2O)(O^3-HAsc)]$^+$ (**18**)	−1530	400[b]	357[d]
cis-[Pt($^{15}NH_3$)$_2$(O^3-HAsc)$_2$] (**19**)	−1492	358	
cis-[Pt($^{15}NH_3$)$_2$(O^2,O^3-Asc)] (**20**)	−1398	338	
Carbon–Oxygen Donors			
[Pt($^{15}NH_3$)(H_2O)(C^2,O^5-Asc)] (**21**)	−2206	410[e]	
[Pt($^{15}NH_3$)(O^3-HAsc)(C^2,O^5-Asc)]$^-$ (**22**)	−2163	362[e]	
cis-[Pt($^{15}NH_3$)$_2$(C^2,O^5-Asc)] (**6**)	−2506	316[e]	220[f]
cis-[Pt($^{15}NH_3$)$_2$(C^2-HAsc)(O^3-HAsc)] (**23**)	−2485	371[d]	195[f]
cis-[Pt($^{15}NH_3$)$_2$(O^2,O^3-TMRA)] (**24**)	−1506	330	

[a] Chemical shifts measured relative to H_2PtCl_6 (1 g/3 mL of D_2O) at 0 ppm. [b] trans to H_2O. [c] trans to NO_3. [d] trans to O3. [e] trans to O5. [f] trans to C2.

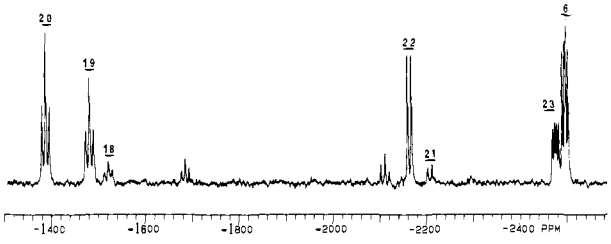

Figure 4. ^{195}Pt spectrum of the reaction between *cis*-[Pt($^{15}NH_3$)$_2$(H_2O)$_2$]$^{2+}$ (1 mmol/4 mL of H_2O) and sodium ascorbate (2 mmol) taken at 1 h.

corbate ring that is able to bind to the platinum in a bidentate fashion. Selectivity of this type, where a transition-metal complex shows preferential diastereofacial coordination, has been observed in a number of organometallic reactions.[33] As the reaction continues beyond 200 min, the chelated-ascorbate complex **5** precipitates from solution, while the bisascorbate complex **17** continues to increase in concentration and ultimately becomes the major Pt-containing species in solution. With diamine complexes that form a fairly insoluble ascorbate chelate, such as the [Pt(*trans-R,R*-dach)(C^2,O^5-Asc)] analogue, isolated yields of up to 67% are obtained. The selectivity ratio for the *re* face appears to depend on the diamine ligand employed in the reaction. Further studies on this aspect of the reaction are in progress.

Reaction of *cis*-[Pt($^{15}NH_3$)$_2$(H_2O)$_2$](NO_3)$_2$ with Ascorbic Acid. The reaction of *cis*-[Pt($^{15}NH_3$)$_2$(H_2O)$_2$](NO_3)$_2$ with sodium ascorbate produces a distribution of products that is very similar to that found for the "Pt(^{15}en)(ascorbate)" reaction. The ^{195}Pt chemical shift and coupling constant data for the various products formed in this reaction are presented in Table II. As shown in Figure 4, the diammine–ascorbate reaction produces four products in the oxygen-donor region (−1300 to −1800 ppm) of the ^{195}Pt NMR spectrum. Three of these signals result from the same oxygen-bound ascorbate species that were observed in the "Pt(^{15}en)(ascorbate)" reaction. The ordering of the ^{195}Pt chemical shifts among these complexes, *cis*-[Pt($^{15}NH_3$)$_2$(H_2O)(O^3-HAsc)]$^+$ (**18**), *cis*-[Pt($^{15}NH_3$)$_2$(O^3-HAsc)$_2$] (**19**), and *cis*-[Pt($^{15}NH_3$)$_2$(O^2,O^3-Asc)] (**20**), and the relationship between the ^{195}Pt–^{15}N coupling constants and the trans influence of the O3- and O2,O3-bound ascorbate ligand is also maintained in this series. The reduced value of the coupling constant (338 Hz) for the O2,O3-ascorbate chelate **20** agrees well with the value (330 Hz) found for the TMRA model compound *cis*-[Pt($^{15}NH_3$)$_2$(O^2,O^3-TMRA)] (**24**). The time-dependent behavior of the concentration of **18**, **19**, and **20** during the course of the reaction also parallels that found in the ethylenediamine case. Again, the oxygen-bound ascorbate complexes, which are the predominant Pt species at the beginning of the reaction, gradually disappear with time while the carbon-bound species go on to become the final products of the reaction. The fourth oxygen-bound complex, which is seen in the ^{195}Pt spectrum at −1695 ppm, is not observed in the corresponding ethylenediamine reaction. The identity of this minor component of the reaction remains unknown.

One major difference in the product distribution is found when comparing diammine and ethylenediamine–ascorbate reactions. This difference is evident when the upfield regions of the respective ^{195}Pt spectra (Figures 1 and 4) are examined. In the diammine reaction, a group of new resonances is observed in the −2100 to −2300 ppm region of the spectrum. These peaks consist of a prominent doublet at −2163 ppm, flanked by two smaller sets of resonances. While the identity of the small triplet at −2120 ppm is of unknown origin, the main doublet arises from a chelated ascorbate species that has lost ammonia. The loss of ammonia, which occurs trans to the carbon donor of the C2,O5-bound ascorbate ligand, produces two products of the form [Pt($^{15}NH_3$)(O_d)(C^2,O^5-Asc)]$^{-/0}$. These complexes contain either a water ligand (**21**, small doublet at −2206 ppm) or an ascorbate anion (**22**, large doublet at −2163 ppm) in the O_d site. Exchange is expected to occur at the site trans to the strong carbon donor, based on established mechanisms of ligand substitution processes in square-planar platinum(II) complexes.[34] Recent SCF calculations,[35] performed on the *cis*-[Pt(NH_3)$_2$(C^2,O^5-Asc)] molecule, suggest that exchange of the ammine ligand trans to C2 is favored based on calculated Pt–N bond energies. The calculated Pt–N bond energies of 15 kcal/mol (trans to C2) and 36 kcal/mol (trans to O5) also indicate that the ^{195}Pt–^{15}N coupling constants (220 and 316 Hz, respectively) are a reasonable measure of Pt–N bond strength. Independent ^{15}N NMR studies of the reaction confirm that ammonium ion is released in solution. Furthermore, ^{195}Pt NMR studies of the ammonia release reaction show that the doublet at −2206 ppm is produced when an isolated sample of the ascorbate–chelate **6** is heated in water. The monoammine complex **21**, as formed during the reaction or directly from **6**, decomposes to Pt^0 upon standing in aqueous solution. Additional studies of the ammonia release reaction are in progress.

The time dependent behavior of the concentration of the remaining two carbon-bound ascorbate products of the reaction is also different in the diammine case. A plot of ^{195}Pt signal intensity for the chelate *cis*-[Pt($^{15}NH_3$)$_2$(C^2,O^5-Asc)] (**6**) and the bisascorbate complex *cis*-[Pt($^{15}NH_3$)$_2$(C^2-HAsc)(O^3-HAsc)] (**23**) as a function of reaction time shows that a smooth increase in concentration of both components occurs to the equilibrium point (~10 h). Precipitation of the chelate **6** is not observed in this case, as a result of its higher aqueous solubility. The stereoselectivity ratio (*re:si* = 3.3) of the reaction at equilibrium, as judged by the ^{195}Pt signal intensity, is approximately twice that observed in the ethylenediamine–ascorbate case.

Reaction Chemistry of the "Pt(dach)(ascorbate)" System. As discussed in our initial report,[7] the number of products obtained in this reaction is reduced when the starting [Pt(dach)(H_2O)$_2$]$^{2+}$ complex is prepared from one of the three individual dach isomers, *cis*-dach, *trans-R,R*-dach, or *trans-S,S*-dach.[11] Consequently, to sort out the chemistry in this case, three individual reactions were studied with use of resolved [Pt(dach)(H_2O)$_2$]$^{2+}$ starting materials. The important aspects of these studies are outlined below.

The reaction between [Pt(*trans-R,R*-dach)(H_2O)$_2$]$^{2+}$ and sodium ascorbate was examined in detail. For the most part, the products are analogous to those found in the ethylenediamine–ascorbate reaction. While coupling constants were not obtained (^{15}N-labeled dach was not used), the chemical shifts of the various products of this reaction (see Table III) are closely related to those of the respective ethylenediamine analogues. The time profile of the oxygen-bound and carbon-bound ascorbate complexes is also

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(34) Atwood, J. D. *Inorganic and Organometallic Reaction Mechanisms*; Brooks/Cole: Monterey, CA, 1985; pp 46–74.

(35) Basch, H.; Krauss, M.; Stevens, W. J. *Inorg. Chem.* **1986**, *25*, 4777.

Table III. ^{195}Pt NMR Data for Complexes Relevant to the "Pt(dach)(ascorbate)" Reaction

compound	chem shift (ppm)
[Pt(*trans*-*R*,*R*-dach)$(H_2O)_2]^{2+}$	−1872
[Pt(*trans*-*R*,*R*-dach)$(H_2O)(O^3$-HAsc)$]^+$ (**25**)	−1795
[Pt(*trans*-*R*,*R*-dach)$(O^3$-HAsc$)_2]$ (**26**)	−1737
[Pt(*trans*-*R*,*R*-dach)$(O^2,O^3$-Asc)] (**27**)	−1667
[Pt(*trans*-*R*,*R*-dach)$(C^2,O^5$-Asc)] (**1**)	−2622
[Pt(*trans*-*R*,*R*-dach)$(C^2$-HAsc$)(O^3$-HAsc)] (**28**)	−2644
[Pt(*trans*-*S*,*S*-dach)$(H_2O)(O^3$-HAsc$)]^+$ (**29**)	−1787
[Pt(*trans*-*S*,*S*-dach)$(O^3$-HAsc$)_2]$ (**30**)	−1730
[Pt(*trans*-*S*,*S*-dach)$(O^2,O^3$-Asc)] (**31**)	−1664
[Pt(*trans*-*S*,*S*-dach)$(C^2,O^5$-Asc)] (**32**)	−2606
[Pt(*trans*-*S*,*S*-dach)$(C^2$-HAsc$)(O^3$-HAsc)] (**33**)	−2630

[a] Chemical shifts measured relative to H_2PtCl_6 (1 g/3 mL of D_2O) at 0 ppm.

similar to that found in the ethylenediamine case. The stereoselectivity ratio (*re*:*si* = 2.4) in the initial phase of the reaction is slightly larger than observed in the ethylenediamine–ascorbate reaction (*re*:*si* = 1.6), and the precipitation point is sooner (150 min), as a result of the lower solubility of the [Pt(*trans*-*R*,*R*-dach)$(C^2,O^5$-Asc)] chelate **1**. One main benefit of using the dach ligand lies in the desirable HPLC behavior of the carbon-bound products. The bulky dach ligand produces longer retention times on C_{18}-based reversed phase columns, providing the means for separating the chelate **1** from the bisascorbate complex [Pt(*trans*-*R*,*R*-dach)$(C^2$-HAsc$)(O^3$-HAsc)] (**28**) on a preparative scale.

A number of ^{13}C and ^{1}H NMR experiments were performed on [Pt(*trans*-*R*,*R*-dach)$(C^2,O^5$-Asc)] (**1**) and [Pt(*trans*-*R*,*R*-dach)$(C^2$-HAsc$)(O^3$-HAsc)] (**28**) in an attempt to confirm the structural assignment for the bisascorbate complex. The proton spectrum of the ascorbate–chelate **1**, in Me_2SO-d_6, contains three well-resolved signals from the ascorbate protons, H4 (d, 4.01), H5 (t, 3.90), and H6 (d, 3.18). These resonances were used in conjunction with HETCOR and DEPT experiments to provide ^{13}C assignments for each of the [Pt(diamine)$(C^2,O^5$-Asc)] chelates. A complete listing of the ^{13}C NMR data, obtained on these complexes and on the bisascorbate complex **28**, is presented as Supplementary Material (Table S1). There are two points of interest that relate to these studies. First, when platinum binds to the C2 and O5 positions of the ascorbate anion, the position of the C2 resonance shifts upfield by an average of 48 ppm. The opposite effect is observed at the C1, C3, and C5 positions which shift downfield by 25, 20, and 17 ppm, respectively. Second, the ^{13}C spectrum of **28** shows two sets of ascorbate resonances, with chemical shift values that are consistent with the presence of C2- and O3-bound ascorbate ligands.

An interesting isomerization reaction occurs when an isolated sample of [Pt(*trans*-*R*,*R*-dach)$(C^2$-HAsc$)(O^3$-HAsc)] (**28**) is allowed to stand in aqueous solution. As shown by HPLC and ^{195}Pt NMR studies, **28** slowly converts to chelate **1** with loss of 1 equiv of ascorbic acid. We are presently studying this reaction, which presumably involves a *si* to *re* isomerization and a ring closure step for the C2-bound ascorbate ligand, in an attempt to determine if this process involves dissociation of the platinum–carbon bond.

The diamineplatinum–ascorbate reaction was conducted in an analogous fashion by using resolved *cis*- and *trans*-*S*,*S*-dach ligands. In most respects, the reaction profiles for these two isomers are similar to those described above. In the case of the "Pt(*trans*-*S*,*S*-dach)(ascorbate)" reaction, the two carbon-bound species form at comparable rates and with a similar diastereofacial preference (*re*:*si* = 1.5, see Figure 3b). The main difference between the *trans*-*R*,*R*- and the *trans*-*S*,*S*-dach reactions lies in the solubility of the respective [Pt(dach)$(C^2,O^5$-Asc)] chelates. The *trans*-*S*,*S*-complex is approximately 10 times more soluble than the *R*,*R*-isomer, and as a result, this product does not precipitate from solution during the reaction. A similar product distribution is obtained with the *cis*-dach isomer. However, in this case two isomeric forms of the chelate and the bisascorbate complex are produced as a result of the asymmetry of the *cis*-dach ligand.[7]

Conclusion

In contrast to a recent report[36] on "Pt(dach)(ascorbate)" complexes which presents a simplified view of the chemistry of this system, we have identified, by using multinuclear NMR and HPLC techniques, a variety of different products in this reaction. The chemistry of the diamineplatinum(II) ascorbate system is quite complex, with the distribution of products being a function of amine ligands, reagent stoichiometry, pH, and time. Oxygen binding at O2 and O3 of the ascorbate anion is kinetically favored while carbon binding at C2 is thermodynamically favored and accounts for essentially all of the products seen at long reaction times. The stereoselectivity displayed by platinum in attacking the ascorbate ligand at the C2 carbon and the apparent influence of amine ligand on the magnitude of this effect as well as the isomerization from *si* to *re* binding are novel observations and the subject of ongoing studies.

Supplementary Material Available: ^{13}C and ^{1}H NMR data for the ascorbate complexes relevent to this study (3 pages). Ordering information is given on any current masthead page.

(36) Hacker, M. P.; Khokhar, A. R.; Brown, D. B.; McCormack, J. J.; Krakoff, I. H. *Cancer Res.* **1985**, *45*, 4748.