Contribution from Research and Development,
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Platinum Complexes of Vitamin C: Reaction Chemistry of Carbon-Bound *cis*-[(Diamine)(ascorbato-C^2,O^5)platinum] Chelates

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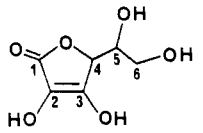
Received December 16, 1987

The reaction between a series of *cis*-[Pt(RNH_2)$_2$(ascorbato-C^2,O^5)] chelates, where (RNH_2)$_2$ is ethylenediamine (en), [1,2-^{15}N]en, ($^{15}NH_3$)$_2$, *trans*-(*R*,*R*)-, *trans*-(*S*,*S*)- or *cis*-(*R*,*S*)-diaminocyclohexane (dach), and various acids (HX = HNO_3, HCl, CH_3SO_3H) were studied in an attempt to prepare monodentate ascorbate complexes of the form *cis*-[Pt(RNH_2)$_2$(ascorbato-C^2)(L)]$^{+/0}$ (**1a**), where L is an anionic or neutral ligand such as Cl^-, ascorbate-O^3, or *S*-Me_2SO. ^{195}Pt and ^{13}C NMR studies of the reaction of the ^{15}N-labeled ascorbate chelate [Pt(^{15}en)(*C2*,*O5*-Asc)] (**1**) with aqueous acids show that, in the absence of a nucleophile, the protonated chelate [Pt(^{15}en)(*C2*,*O5*-HAsc)]$^+$ (**2**) is favored over the ring-opened complex [Pt(^{15}en)(*C2*-HAsc)(H_2O)]$^+$ (**3**). Protonation occurs at the O5 site of the ascorbate ligand, and the pK_a of the resulting complex is ~2.0 in water. While the protonated chelate **2** can be isolated from nonaqueous solvents, the complex decomposes to ascorbic acid and [Pt(^{15}en)(H_2O)$_2$]$^{2+}$ in aqueous solution. The ring-opened complex **3** was observed as an intermediate in the hydrolysis reaction of the protonated chelate **2**. Similar behavior is observed with the dach and *cis*-diammine analogues. When the ascorbate chelates are protonated in the presence of a nucleophile in aprotic solvents, ring-opened complexes of the form **1a** are obtained. In the two cases where these complexes were isolated (L = Cl^- or *S*-Me_2SO), both compounds were unstable in aqueous solutions; the chloro complex undergoes ring closure, re-forming the C2,O5 chelate, and the Me_2SO complex isomerizes to the oxygen-bound ascorbate complex *cis*-[Pt(diamine)(*O3*-HAsc)(*S*-Me_2SO)]$^+$. Ring-opened complexes of form **1a**, containing weak donors such as NO_3^-, SO_4^{2-}, $CH_3CO_2^-$, and *O3*-$HAsc^-$, are also unstable when prepared from the C2,O5 chelate. In general, the monodentate C2-bound ascorbate complexes prefer the ring-closed structure when platinum is bound to the *re* face of the ascorbate ligand.

Introduction

In previously reported studies of (diamine)platinum(II) complexes of vitamin C,[1-3] it was shown that the ascorbate anion is a multifunctional ligand capable of binding to platinum at a number of sites (C2, O2, O3, and O5) in either a monodentate or bidentate fashion. While the reaction between *cis*-[Pt(diamine)(H_2O)$_2$]$^{2+}$ complexes and sodium ascorbate initially produces a number of oxygen-bound ascorbate intermediates, the final products are two carbon-bound species: *cis*-[Pt(diamine)(*C2*,*O5*-Asc)] and *cis*-[Pt(diamine)(*C2*-HAsc)(*O3*-HAsc)]. The C2-bound ascorbate ligand in both the C2,O5 chelate and the bis(ascorbate) complex is bound to platinum, as an α-hydroxy-β-diketonate, on the rectus (*re*) and sinister (*si*) faces of the ascorbate ring, respectively. While both of these products have demonstrated antitumor activity in a number of animal tumor screens, the ascorbate chelates possess relatively low potency when compared to that of the bis(ascorbate) analogues.[3] Since the ascorbate chelates are the major products of these reactions, efforts were made to convert the chelates to ring-opened analogues of the bis(ascorbate) complexes: *cis*-[Pt(diamine)(*C2*-HAsc)L]$^{+/0}$, where L is a neutral or anionic ligand. As described in this report, we have examined the protonation reactions of the ascorbate chelates in an attempt to prepare complexes of this type by inducing ring-opening and ligand substitution reactions at the O5 site.



ascorbic acid (H_2Asc)

Experimental Section

Physical Methods. NMR spectra were recorded with a Varian XL-200 spectrometer using a 10-mm tunable probe. ^{195}Pt spectra (42.935 MHz) were typically collected by using a spectral width of 80 kHz, a pulse width of 9 μs (90°), and an acquisition time of 0.06 s. Spectra of ^{14}N-substituted complexes were processed with line broadening (200 Hz) and zero filling (32-64K). Spectra of ^{15}N-labeled platinum complexes were obtained in water by using broad-band decoupling (Waltz modulation) and were processed with line broadening (10 Hz) and zero filling (32-64K). For kinetic studies, ^{195}Pt spectra were collected at constant temperature (28 °C, with a Varian VT controller) at 8-min intervals as a function of time. ^{195}Pt spectra were referenced by using an external sample of 0.1 M $K_2[PtCl_4]$ in D_2O (-1624 ppm vs H_2PtCl_6, 1 g/3 mL of D_2O). ^{13}C NMR spectra were typically collected by using a 30° pulse (5 μs), a 12-kHz sweep width, and a 1-s acquisition time. pH measurements were made with a Corning 145 pH meter equipped with an Ingold combination electrode. NMR studies of the protonation reactions in protic solvents (H_2O, MeOH, and EtOH) were typically conducted by adding the appropriate acid to 100-300 mg of ascorbate chelate in 3 mL of solvent and acquiring ^{195}Pt or ^{13}C spectra of the resulting products.

HPLC studies were conducted by using a Waters Delta-Prep 5000 instrument, operating in the analytical mode. Samples were typically run in water (isocratic) at a flow rate of 6 mL/min with use of a Novapack C_{18} radial compression column (Z module), and peaks were monitored at 254 nm.

Abbreviations: dach, 1,2-diaminocyclohexane; *R*,*R*-dach, *trans*-(*R*,*R*)-dach; *S*,*S*-dach, *trans*-(*S*,*S*)-dach; ^{15}en, [1,2-^{15}N]ethylenediamine; H_2Asc, ascorbic acid.

Compound Preparation. All (diamine)platinum-ascorbate chelates were prepared from the reaction of the corresponding *cis*-[Pt(diamine)(H_2O)$_2$](NO_3)$_2$ complex with sodium ascorbate by using previously described methods.[2] Isotopically labeled [1,2-^{15}N]ethylenediamine dihydrochloride was purchased from MSD Isotopes, and all other reagents were obtained from commercial sources. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

[Pt(*R*,*R*-dach)(*C2*,*O5*-HAsc)](MeSO$_3$) (11). The methanesulfonate salt of the protonated chelate was prepared by reacting 1.0 g of [Pt(*R*,*R*-dach)(*C2*,*O5*-Asc)]·3H_2O (**10**) with 0.123 mL of methanesulfonic acid in 15 mL of ethanol (distilled over Mg, under dinitrogen). The platinum complex **10** was purified, by recrystallization from water, and dried under vacuum at 40 °C before use. The chelate dissolved rapidly upon addition of the methanesulfonic acid, and the product (**11**) was obtained as a white hygroscopic precipitate after cooling the solution to 4 °C overnight (yield 250 mg after drying under vacuum).

The protonated chelate was also generated in situ by adding 1-2 equiv of concentrated acid (HCl, HNO_3, $HClO_4$, or H_2SO_4) to the chelate in aqueous solution (~50-100 mg/mL of H_2O). While the complex was unstable under the low-pH conditions required for protonation, it was possible, as discussed below, to use ^{195}Pt and ^{13}C NMR to identify the protonated chelate and to follow its decomposition reaction.

[Pt(*R*,*R*-dach)(*C2*-HAsc)Cl] (12). The ring-opened chloro-ascorbate complex was prepared by treating [Pt(*R*,*R*-dach)(*C2*,*O5*-Asc)]·3H_2O (250 mg in 3 mL of DMF-d_7) with 0.03 mL of $MeSO_3H$ and stirring the resulting mixture for 5 min at room temperature. After the solution was filtered to remove any undissolved material, 19 mg of LiCl was added to the filtrate. The resulting solution was stirred for 20 min and then poured into 40 mL of acetone-diethyl ether (1:1). The light yellow

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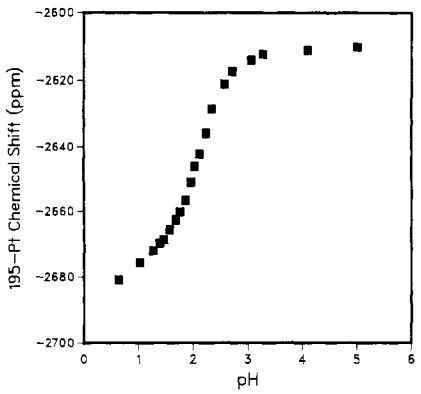

Figure 1. ^{195}Pt NMR titration curve for the reaction of [Pt(*S,S*-dach)(*C2,O5*-Asc)] (**6**; 45 mg in 3 mL of H_2O) with 2 M HNO_3.

precipitate was collected by filtration and dried under vacuum (yield 120 mg).

The chloro–ascorbate complex converts to the ascorbate-C^2,O^5 chelate **10** when it is placed in water. This reaction was followed by HPLC (retention times: 1.5 min for **12** and 2.0 min for **10**) and ^{195}Pt NMR. The chloro–ascorbate complex also forms as a transient species when **10** is treated with 1–2 equiv of HCl in aqueous solution. The final product of this reaction was identified as [Pt(*R,R*-dach)Cl_2] by using ^{195}Pt and ^{13}C NMR.

[Pt(*R,R*-dach)(*C2*-HAsc)(S-Me_2SO)]($MeSO_3$) (14). [Pt(*R,R*-dach)(*C2,O5*-Asc)]·3H_2O (2.5 g) was suspended in 40 mL of Me_2SO and treated with 0.33 mL of methanesulfonic acid. After 5 min at room temperature, the solution was poured into 450 mL of acetone–diethyl ether (1:2). After 1 h, the product was collected by filtration and washed with diethyl ether (yield 2.3 g, after vacuum drying).

The ring-opened complex was also generated by dissolving **10** in Me_2SO and adding 1–2 equiv of concentrated acid, such as H_2SO_4 or HNO_3. Under these conditions, the ring-opened complex was stable for short periods of time ($t_{1/2} \approx 1$ h).

[Pt(*R,R*-dach)(*O3*-HAsc)(*S*-Me_2SO)]($MeSO_3$) (17). A 1.0-g sample of **14** was dissolved in 30 mL of methanol and stirred for 18 h at room temperature under N_2. The solution was then poured into 100 mL of acetone, and the resulting precipitate was collected by filtration, washed with diethyl ether, and vacuum-dried (yield 750 mg). This isomerization reaction also occurs when **14** is dissolved in water.

Preparation of Related Ethylenediamine Complexes. The related "Pt(en)" analogues were prepared according to the methods described above. Products were identified by using ^{195}Pt and ^{13}C NMR. The aqua-chloro complexes [Pt(^{15}en)$(H_2O)_nCl_{2-n}]^{n+}$ and the aqua–Me_2SO complex [Pt(^{15}en)(H_2O)(*S*-Me_2SO)]$^+$ were prepared by adding 1 equiv of NaCl or Me_2SO, respectively, to an aqueous solution of [Pt(^{15}en)$(H_2O)_2](NO_3)_2$. Analogous "*cis*-Pt($^{15}NH_3)_2$" complexes were prepared in a similar fashion.

Results and Discussion

Protonation Reactions of the *cis*-[Pt(diamine)(*C2,O5*-Asc)] Chelates in Aqueous Solution. Since chelate formation through the C2 and O5 binding sites on the ascorbate ligand occurs with the loss of two protons, a study of the chelate protonation reaction should provide information on the accessibility of the monodentate complexes through a ring-opening pathway. The reactions between the relatively insoluble ascorbate chelates and aqueous solutions of noncoordinating acids, such as HNO_3, $HClO_4$, or $MeSO_3H$, were found to rapidly solubilize the chelates at low pH (<1.5). Using a variety of chemical and spectroscopic techniques, we have been able to characterize the products of these reactions.

While the initial intent of these studies was to prepare monodentate ascorbate complexes, NMR experiments show that the protonated ascorbate chelate must also be considered as a possible product in these reactions. A series of ^{195}Pt and ^{13}C NMR experiments were conducted with use of both ^{14}N- and ^{15}N-substituted (diamine)platinum ascorbate complexes, to examine the protonation process. ^{195}Pt NMR was used to monitor the titration of the ascorbate chelates with nitric acid. As shown in Figure 1, the ^{195}Pt resonance of [Pt(*S,S*-dach)(*C2,O5*-Asc)] shifts approximately 70 ppm upfield as a result of protonation, and the pK_a of the protonated complex was determined to be 2.0 from these data. The protonation reaction was found to be reversible, providing that the solution was not maintained at low pH (<2) for long periods of time, as under these conditions the complexes are unstable.

Table I. ^{195}Pt NMR Chemical Shifts (ppm) and ^{195}Pt–^{15}N Coupling Constants (Hz) for Relevant ^{15}N-Labeled (Diamine)platinum(II) Complexes

compd[a]	chem shift[b]	J	J'
[Pt(^{15}en)(*C2,O5*-Asc)] (**1**)	−2634	347[c]	253[d]
[Pt(^{15}en)(*C2,O5*-HAsc)]$^\bullet$ (**2**)	−2706	442[c]	244[d]
[Pt(^{15}en)(*C2*-HAsc)$(H_2O)]^+$ (**3**)	−2810	450[c]	222[d]
[Pt(^{15}en)$(H_2O)_2]^{2+}$ (**4**)	−1911	420	
[Pt(^{15}en)(*C2*-HAsc)Cl] (**13**)	−3105	404[e]	211[d]
[Pt(^{15}en)(*C2*-HAsc)(*S*-Me_2SO)]$^+$ (**15**)	−3660	296[f]	209[d]
[Pt(^{15}en)(*O3*-HAsc)(*S*-Me_2SO)]$^+$	−2929	376[c]	298[f]
[Pt(^{15}en)(H_2O)Cl]$^+$	−2122	403[c]	381[e]
[Pt(^{15}en)Cl_2]	−2390	358	
[Pt(^{15}en)(*S*-Me_2SO)$(H_2O)]^{2+}$	−3002	409[c]	293[f]
cis-[Pt($^{15}NH_3)_2(H_2O)_2]^{2+}$	−1593	390	
cis-[Pt($^{15}NH_3)_2(H_2O)$Cl]$^+$	−1841	369[c]	343[e]
cis-[Pt($^{15}NH_3)_2Cl_2$]	−2100	326	
cis-[Pt($^{15}NH_3)_2$(*S*-Me_2SO)$(H_2O)]^{2+}$	−2813	387[c]	250[f]

[a] Compounds were prepared in aqueous solution; all cations are nitrate salts. [b] Chemical shifts are measured relative to H_2PtCl_6 at 0 ppm. [c] Trans to oxygen. [d] Trans to carbon. [e] Trans to chlorine. [f] Trans to sulfur.

NMR experiments were conducted, with use of the ^{15}N-labeled complex [Pt(^{15}en)(*C2,O5*-Asc)], to determine the site of protonation. The ^{195}Pt–^{15}N coupling constant data obtained from these studies can be used to provide additional structural information on the products of the protonation reaction. Previous NMR studies of ^{15}N-labeled (diamine)platinum(II) complexes[2-10] have shown that the magnitude of $^1J(^{195}$Pt–^{15}N) is related to the donor properties of the ligands bound to platinum. In general, the X and Y ligands in complexes of the form *cis*-[Pt($^{15}NH_2R)_2$XY] produce both a cis and a trans influence on the magnitude of the ^{195}Pt–^{15}N coupling constants.[4] The trans influence typically dominates these relationships, with strong donors, such as sulfur or carbon-based ligands, giving smaller coupling constants ($^1J_{trans}$ = 200–300 Hz) than weak donors, such as water or oxygen-based ligands ($^1J_{trans}$ = 350–450 Hz). Furthermore, the ligand donor strength also influences the ^{195}Pt chemical shift in a predictable manner, with strong donors producing a more shielded environment.[3-5,11] These relationships were used, in conjunction with ^{13}C NMR studies, to characterize the products of the protonation reaction of the ^{15}N-labeled ascorbate chelate.

The ^{195}Pt NMR spectrum of [Pt(^{15}en)(*C2,O5*-Asc)] (**1**), obtained in water at pH 6, consists of a doublet of doublets centered at −2634 ppm (see Table I). As expected on the basis of the donor properties of the carbon- and oxygen-based ligands in **1**,[12] the coupling constant for the ^{15}N trans to the C2 carbon (253 Hz) is much smaller than that trans to the O5 oxygen (347 Hz).[2] When the ascorbate complex is titrated to pH <1 with HNO_3, the ^{195}Pt multiplet shifts 62 ppm upfield and the coupling constant trans to O5 increases by 95 Hz, while that trans to C2 decreases by 9 Hz. This effect is comparable to that found with the triammine complex [Pt($^{15}NH_3)_3$(OH)]$^+$, where the coupling constant trans to OH was observed to increase by 90 Hz upon protonation.[4] While these changes are consistent with protonation at O5, it is

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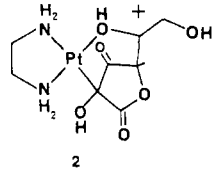
Table II. ^{13}C NMR Data (ppm) for [Pt(en)(*C2,O5*-Asc)] Complexes and Vitamin C

compd	chem shift[a] C1	C2	C3	C4	C5	C6	C1′, C2′ (en)
[Pt(en)(*C2,O5*-Asc)] (**1**)	197.8	71.3	178.4	81.9	84.8	64.4	47.4, 46.7
[Pt(en)(*C2,O5*-Asc)] + HNO_3	198.4	70.1	177.1	79.7	84.4	62.3	48.9, 46.6
ascorbic acid	175.9	120.6	158.1	78.9	71.7	64.8	
diff upon chelation	+21.9	−48.9	+20.3	+3.0	+13.1	−0.4	
diff upon protonation	+0.6	−1.2	−1.3	−2.2	−0.4	−2.1	+1.5, 0.1

[a] Chemical shifts are reported relative to CH_3OD (at 49.4 ppm) in D_2O.

difficult, on the basis of these data alone, to distinguish between the two possible products of the reaction: the protonated chelate (**2**) or the ring-opened complex (**3**). Since the oxygen donors



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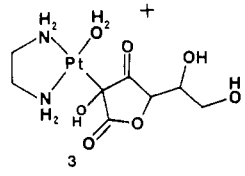

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in both forms of the protonated complex, ROH in **2** and H_2O in **3**, are weaker donors than the alkoxide ligand in the chelate, the coupling trans to O5 would be expected to increase in each case. As shown below, ^{13}C NMR can be used to distinguish between these two possibilities.

The ^{13}C chemical shifts of the carbon atoms in the unprotonated and protonated forms of the ascorbate chelate [Pt(en)(*C2,O5*-Asc)], as assigned by using DEPT[13] and HETCOR[14] techniques, are compared to those of vitamin C in Table II. When platinum binds to the C2 and O5 positions of the ascorbate ligand, the C2 resonance shifts upfield by 49 ppm while the C1, C3, and C5 resonances shift downfield by 22, 20, and 13 ppm, respectively. The large shift of the C5 carbon relative to that of C4 and C6, which move by less than 3 ppm upon coordination, is a characteristic feature of O5 binding in this class of compounds. When the ^{13}C spectrum of the protonated complex is compared to that of the C2,O5 chelate, each carbon resonance of the ascorbate ligand is found to shift by less than 2.3 ppm (see Table II). These data suggest that the protonated chelate (structure **2**) is the predominant species in solution at low pH. If the protonated complex were to adopt a ring-opened structure, the C5 resonance would be expected to undergo a significant shift (~13 ppm) upon detachment of the O5 hydroxyl group (as seen below with the ring-opened complexes, *cis*-[Pt(diamine)(*C2*-HAsc)X]$^{+/0}$, where X = Cl, *S*-Me_2SO). Since this resonance shifts by less than 1 ppm upon protonation, it is unlikely that the protonated complex adopts a ring-opened structure. Additional protonation studies of both *S,S*-dach– and *R,R*-dach–ascorbate complexes produced results similar to those found with the ethylenediamine complex; a complete listing of the ^{13}C NMR data is presented as supplementary material (Table S1).

The ascorbate chelates are unstable when they are treated with aqueous nitric acid at low pH (<2). Under these conditions, the products of the acid hydrolysis reactions were identified as free ascorbic acid and the corresponding *cis*-[Pt(diamine)$(H_2O)_2]^{2+}$ complex, by using ^{195}Pt and ^{13}C NMR spectroscopy. While the [Pt(diamine)(*C2,O5*-Asc)] chelates (en and *R,R*- and *S,S*-dach) are fairly insoluble in water (≤18 mg/mL) at neutral pH, the protonated chelates are soluble to the extent of 100 mg/mL of solution at pH <1. At these concentrations, ^{195}Pt NMR was found to be a convenient method for monitoring the kinetics of the hydrolysis reaction. Good-quality spectra were obtained by using relatively short acquisition times (5–10 min) when compared to the half-lives of the protonated species ($t_{1/2}$ > 100 min).

The ^{195}Pt spectrum of an aqueous solution of [Pt(^{15}en)(*C2,O5*-Asc)], taken 2 h after acidification with HNO_3, is shown in Figure 2. At this point, approximately 50% of the protonated

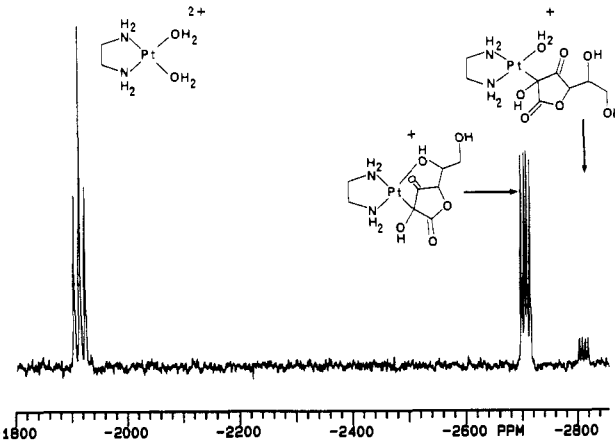

Figure 2. ^{195}Pt spectrum of the reaction between [Pt(^{15}en)(*C2,O5*-Asc)] (**1**; 55 mg in 3 mL of H_2O) and HNO_3 (pH 0.4), taken at 2 h. The three species seen in the spectrum are [Pt(^{15}en)$(H_2O)_2]^{2+}$ (**4**) at −1911 ppm, [Pt(^{15}en)(*C2,O5*-HAsc)]$^+$ (**2**) at −2706 ppm, and [Pt(^{15}en)(*C2*-HAsc)$(H_2O)]^+$ (**3**) at −2810 ppm.

chelate **2** (−2706 ppm) has converted to the diaqua complex $[Pt(^{15}en)(H_2O)_2]^{2+}$ (**4**, −1911 ppm). In addition to these two major sets of resonances in the ^{195}Pt spectrum, a small doublet of doublets can also be seen at −2810 ppm. This species has been identified as the ring-opened form of the protonated chelate, [Pt(^{15}en)(*C2*-HAsc)$(H_2O)]^+$ (**3**), on the basis of the ^{195}Pt chemical shift and coupling constant data (see Table I) and by comparison to the related chloro–ascorbate analogue [Pt(^{15}en)(*C2*-HAsc)Cl] (**13**, see below).

Examination of the ^{195}Pt–^{15}N coupling constant data obtained on the protonated chelate **2** and the ring-opened complex **3** show that the ascorbate ligand becomes a better donor as a result of the ring-opening reaction (^1J decreases from 244 to 222 Hz, trans to C2). This effect can be explained by examining the structural data obtained from X-ray crystallographic studies of [Pt(*cis*-dach)(*C2,O5*-Asc)] (**5**)[1] and [Pt(*S,S*-dach)(*C2,O5*-Asc)] (**6**).[3] The crystallographic studies show that the geometry at the C2 carbon of the ascorbate ligand in **5** and **6** is distorted as a result of geometric constraints imposed by the C2,O5 chelate ring. Under idealized conditions, as found in the structure of the related carbon-bound acac complex K[Pt(*C2*-acac)(*O2,O4*-acac)Cl][15] (acac = acetylacetonate), the geometry at the C2 carbon should approach that expected of sp^3 hybridization, with bond angles of 109°. The distortion in the C2 geometry for the chelates **5** and **6** can be seen by examining the angle made between the Pt–C2 bond and the plane of the ascorbate ring. This angle is reduced from the expected value of 109° to an average value of 96° in **5** and **6**. This change in geometry, which can be viewed as a tipping of the Pt–C2 vector (by 13°) toward the O5 hydroxyl group, apparently results from the steric requirements of the oversized bite distance in the ascorbate ligand (C2–O5 = 3.14 Å and C2–Pt–O5 = 98.4° in **5**). As a result of the tipping of the Pt–C2 vector away from the direction of maximum Pt–C2 bond overlap, the ^{195}Pt–^{15}N coupling constant is expected to increase relative to that found with a monodentate ascorbate-C^2 complex. These structural changes can be used to account for the 22-Hz

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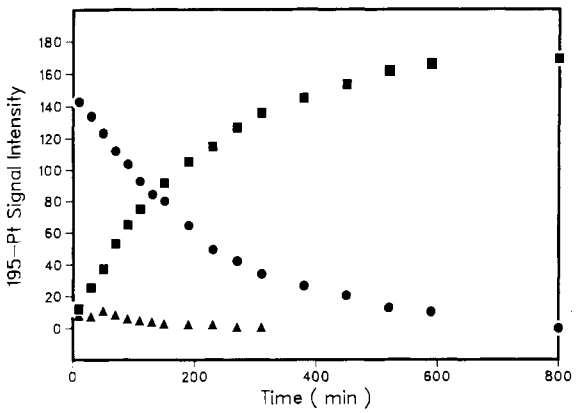

Figure 3. Plot of ^{195}Pt signal intensity versus time for the reaction between [Pt(*S*,*S*-dach)(*C2*,*O5*-Asc)] (**6**; 200 mg in 3 mL of H_2O) and HNO_3 at pH 1.0, showing the profiles of the three species that form during the reaction: (●) [Pt(*S*,*S*-dach)(*C2*,*O5*-HAsc)]$^+$ (**7**); (▲) [Pt(*S*,*S*-dach)(*C2*-HAsc)(H_2O)]$^+$ (**8**); (■) [Pt(*S*,*S*-dach)(H_2O)$_2$]$^{2+}$ (**9**). The observed first-order rate constant k_{obsd}, under these conditions, was determined to be 7.7 (1) × 10^{-5} s^{-1} from the least-squares fit of ln (^{195}Pt signal intensity) vs time for the disappearance of [Pt(*S*,*S*-dach)(*C2*,*O5*-HAsc)]$^+$.

difference that is observed in comparing the coupling constants trans to C2 in **2** and **3**.

The time course of the acid hydrolysis reaction was monitored by ^{195}Pt NMR. Kinetic data were derived from the ^{195}Pt signal intensity vs time profiles for the three species observed during the reaction. A representative plot of the intensity profiles for the reaction of [Pt(*S*,*S*-dach)(*C2*,*O5*-Asc)] (**6**) with HNO_3 is shown in Figure 3. In the initial stage of reaction, the predominant species in solution is the protonated chelate [Pt(*S*,*S*-dach)(*C2*,*O5*-HAsc)]$^+$ (**7**). The ^{195}Pt resonance associated with this complex is found to decrease as a function of time in a fashion that yields first-order disappearance kinetics. Linear plots of ln (^{195}Pt signal intensity) vs time, over a period of 4 half-lives, were used to obtain the first-order rate constant (k_{obsd} = 7.7 (1) × 10^{-5} s^{-1}; see Figure 3) for the hydrolysis reaction. Using the measured pH of the solution and the calculated pK_a of the protonated chelate (2.0), it was possible to estimate the amount of unprotonated chelate present during the initial stage of reaction (t < 5 min). Assuming that proton exchange at O5 is rapid relative to the rate of hydrolysis at pH 0.4, the expression for K_a in eq 1 sets the ratio

$$\underset{\mathbf{7}}{[Pt(S,S\text{-dach})(C2,O5\text{-HAsc})]^+} + H_2O \rightleftharpoons \underset{\mathbf{6}}{[Pt(S,S\text{-dach})(C2,O5\text{-Asc})]} + H_3O^+ \quad (1)$$

of **7**:**6** at 16:1. This ratio could not be measured independently since only one ^{195}Pt signal was observed for both species even at low temperatures (to 2 °C).

When the hydrolysis reaction is followed as a function of time, the signals for the ring-opened complex [Pt(*S*,*S*-dach)(*C2*-HAsc)(H_2O)]$^+$ (**8**) and the hydrolyzed product [Pt(*S*,*S*-dach)(H_2O)$_2$]$^{2+}$ (**9**) appear in successive ^{195}Pt spectra. While the concentration of the ring-opened complex **8** reaches a maximum (at t = 50 min) and then decreases as the reaction continues, the signal from the diaqua complex **9** increases with time and becomes the only detectable resonance at the end of the reaction (see Figure 3). This behavior can be explained by the reaction sequence

$$\underset{\mathbf{7}}{[Pt(S,S\text{-dach})(C2,O5\text{-HAsc})]^+} + H_2O \rightarrow \underset{\mathbf{8}}{[Pt(S,S\text{-dach})(C2\text{-HAsc})(H_2O)]^+} \quad (2)$$

$$\underset{\mathbf{8}}{[Pt(S,S\text{-dach})(C2\text{-HAsc})(H_2O)]^+} + H_3O^+ \rightarrow \underset{\mathbf{9}}{[Pt(S,S\text{-dach})(H_2O)_2]^{2+}} + H_2Asc \quad (3)$$

Equation 2 represents the ring-opening reaction, in which water displaces the O5 hydroxyl group of the coordinated ascorbate ligand. Since the concentration of **8** remains low throughout the reaction, it appears that both ring-opening and ascorbate-dissociation steps proceed at similar rates. While the rate of reaction increases with decreasing pH, it proved difficult to use ^{195}Pt NMR to perform a quantitative analysis of the rate dependence on [H^+], as the chelates have low solubility at pH >1.5. While it was not possible to perform a complete kinetic analysis by using this technique, preliminary studies suggest that UV–vis spectroscopy could be employed to further study the kinetics of this reaction.

Table III. ^{195}Pt NMR Chemical Shift Data (ppm) for Relevant (Diamine)platinum(II) Complexes

compd	chem shift[a]
[Pt(*S*,*S*-dach)(*C2*,*O5*-Asc)] (**6**)	−2610[b]
[Pt(*S*,*S*-dach)(*C2*,*O5*-HAsc)](NO_3) (**7**)	−2682[b]
[Pt(*S*,*S*-dach)(*C2*-HAsc)(H_2O)](NO_3) (**8**)	−2770[b]
[Pt(*S*,*S*-dach)(H_2O)$_2$](NO_3)$_2$ (**9**)	−1870[b]
[Pt(*S*,*S*-dach)(*C2*-HAsc)(*O3*-HAsc)] (**18**)	−2630[b]
[Pt(*R*,*R*-dach)(*C2*,*O5*-Asc)] (**10**)	−2639[b]
	−2579[c]
	−2548[d]
	−2555[e]
[Pt(*R*,*R*-dach)(*C2*,*O5*-HAsc)]($MeSO_3$) (**11**)	−2690[c]
	−2689[e]
[Pt(*R*,*R*-dach)(*C2*-HAsc)Cl] (**12**)	−3040[c]
	−3030[e]
[Pt(*R*,*R*-dach)(*C2*-HAsc)(*S*-Me_2SO)]($MeSO_3$) (**14**)	−3638[d]
[Pt(*R*,*R*-dach)(*C2*-HAsc)(*O3*-HAsc)] (**16**)	−2644[b]
[Pt(*R*,*R*-dach)(*O3*-HAsc)(*S*-Me_2SO)]($MeSO_3$) (**17**)	−2894[d]
	−2888[e]
[Pt(*R*,*R*-dach)Cl_2]	−2280[d]
[Pt(*R*,*R*-dach)(*S*-Me_2SO)Cl]Cl	−3254[d]
[Pt(*R*,*R*-dach)(*S*-Me_2SO)(H_2O)](NO_3)$_2$	−2906[b]

[a] Chemical shifts are reported relative to H_2PtCl_6 at 0 ppm. [b] In H_2O. [c] In DMF-d_7. [d] In Me_2SO-d_6. [e] In MeOH-d_4.

Protonation Reactions of the *cis*-[Pt(diamine)(*C2*,*O5*-Asc)] Chelates in Nonaqueous Solvents. A number of reactions were carried out in nonaqueous solvents in an attempt to isolate and characterize a ring-opened ascorbate complex. When the protonation reaction of **10** was conducted with use of methanesulfonic acid in a dry alcohol (MeOH or EtOH), the protonated chelate **11** was obtained as the major product of the reaction and was isolated as a white precipitate (eq 4). The ^{195}Pt and ^{13}C spectra

$$\underset{\mathbf{10}}{[Pt(R,R\text{-dach})(C2,O5\text{-Asc})]} + MeSO_3H \rightarrow \underset{\mathbf{11}}{[Pt(R,R\text{-dach})(C2,O5\text{-HAsc})](MeSO_3)} \quad (4)$$

of **11** (obtained in MeOH-d_4) are nearly identical with those obtained when the chelate **10** is protonated with HNO_3 in water or methanol. As expected from the studies described above, when the protonated chelate is redissolved in water, it decomposes to [Pt(*R*,*R*-dach)(H_2O)$_2$]$^{2+}$ and ascorbic acid, in a pH-dependent fashion. Attempts to prepare the ring-opened chloro–ascorbate complex [Pt(*R*,*R*-dach)(*C2*-HAsc)Cl] (**12**), from the reaction of **11** with LiCl in methanol, also proved unsuccessful. While **12** was observed as an intermediate by ^{195}Pt NMR, this reaction rapidly produced [Pt(*R*,*R*-dach)Cl_2] and ascorbic acid as final products.

When protonation was conducted in aprotic solvents, genuine ring-opened complexes were obtained as isolable products. The chloro–ascorbate complex [Pt(*R*,*R*-dach)(*C2*-HAsc)Cl] (**12**) was prepared by treating **10** with $MeSO_3H$–LiCl in dry DMF (eq 5).

$$\underset{\mathbf{10}}{[Pt(R,R\text{-dach})(C2,O5\text{-Asc})]} + MeSO_3H + LiCl \rightarrow \underset{\mathbf{12}}{[Pt(R,R\text{-dach})(C2\text{-HAsc})Cl]} \quad (5)$$

The ring-opened complex **12**, which was isolated by precipitation with acetone, was characterized by ^{195}Pt and ^{13}C NMR. In this reaction, methanesulfonic acid produces the protonated chelate **11** (−2690 ppm), which rapidly converts to the ring-opened complex **12** (−3040 ppm) upon addition of LiCl. The position of the ^{195}Pt resonance in **12** is similar to that found for the ^{15}en analog [Pt(^{15}en)(*C2*-HAsc)Cl] (**13**: −3105 ppm, Table I), which is seen

Table IV. Selected ^{13}C NMR Data (ppm) for Platinum Ascorbate Chelates and Ring-Opened Complexes

compd	^{13}C chem shifts					
	C1	C2	C3	C4	C5	C6
[Pt(*R*,*R*-dach)(*C2*,*O5*-Asc)] (**10**)[a]	198.5	69.3	175.6	80.6	85.8	64.8
[Pt(*R*,*R*-dach)(*C2*,*O5*-Asc)] (**10**)[b]	199.4	69.9	176.9	82.0	86.6	66.4
[Pt(*R*,*R*-dach)(*C2*,*O5*-HAsc)]$^+$ (**11**)[b]	198.7	67.8	174.6	78.2	84.2	62.5
[Pt(*R*,*R*-dach)(*C2*-HAsc)(*O3*-HAsc)] (**16**)[c]						
C2 bound	201.1	69.1	181.4	80.8	69.8	61.9
O3 bound	176.5	114.2	169.5	78.4	69.8	62.7
[Pt(*R*,*R*-dach)(*C2*-HAsc)Cl] (**12**)[b]	201.3	65.8	178.8	83.8	73.1	63.4
[Pt(*R*,*R*-dach)(*C2*-HAsc)(*S*-Me_2SO)]$^+$ (**14**)[a]	206.3	63.8	177.7	82.0	69.4	62.0
[Pt(*R*,*R*-dach)(*O3*-HAsc)(*S*-Me_2SO)]$^+$ (**17**)[c]	176.0	115.4	168.6	77.8	69.8	62.8
diff upon ring opening						
Cl–ascorbate (**12**–**10**)[b]	+1.9	−4.1	+1.9	+1.8	−13.5	−3.0
Me_2SO–ascorbate (**14**–**10**)[a]	−7.8	−5.5	+2.1	+1.4	−16.4	−2.8

[a] In Me_2SO-d_6. [b] In DMF-d_7. [c] In D_2O.

as a transient species during aqueous reactions of the chelate **1** with HCl. Comparison of the ^{195}Pt–^{15}N coupling constants for the chloro–ascorbate complex to those of the hydrolysis products of [Pt(^{15}en)Cl_2][2] and *cis*-[Pt($^{15}NH_3$)$_2Cl_2$][7,8] provides useful information on the donor properties of the ligands in the ring-opened complexes.

Recently, Appleton et al.[4] examined the relationship between chloride substitution and the resulting change in cis and trans coupling constants in the series of diammine complexes *cis*-[Pt($^{15}NH_3$)$_2$(H_2O)$_n$$Cl_{2-n}$]$^{n+}$, where n = 0, 1, 2 (see Table I). These data show that, when H_2O is replaced with Cl^-, the ^{195}Pt–^{15}N coupling constants cis and trans to Cl decrease by 21 and 47 Hz, respectively. In the case of the analogous ^{15}en complexes (Table I), the chloride ligand produces a cis and trans influence of similar magnitude (−17 and −39 Hz, respectively). Chloride substitution, as one goes from [Pt(^{15}en)(*C2*-HAsc)(H_2O)]$^+$ (**3**) to [Pt(^{15}en)(*C2*-HAsc)Cl] (**13**), reduces the cis (−11 Hz) and trans (−46 Hz) oriented coupling constants in a similar fashion. The predictable nature of ligand substitution effects in this series of complexes is also displayed in the chemical shift data. Replacing H_2O with Cl^- produces a relatively constant (250 ± 40 ppm) upfield shift of the ^{195}Pt resonance.

A second series of ring-opened complexes of the form *cis*-[Pt(diamine)(*C2*-HAsc)(*S*-Me_2SO)]$^+$ was obtained when the protonation reaction was conducted in Me_2SO. The ^{195}Pt NMR data for these compounds show that Me_2SO coordination causes the ^{195}Pt resonance to shift upfield by roughly 1000 ppm. As indicated by the data obtained on a series of related Me_2SO complexes (Tables I and III), an upfield shift of this magnitude is characteristic of S-bound Me_2SO.[10,16] The excellent donor ability of the Me_2SO ligand is clearly reflected in the coupling constant data obtained on related ^{15}N-labeled complexes.[10] The trans influence of the Me_2SO ligand, as judged by the ^{195}Pt–^{15}N coupling constants in the *cis*-[Pt(diamine)(*S*-Me_2SO)(H_2O)]$^{2+}$ compounds ($^{15}NH_3$ and ^{15}en), is among the highest seen for Pt(II)–amine complexes; replacing H_2O with *S*-Me_2SO reduces the trans-oriented coupling constant by ~130 Hz.[4,10] A comparable effect is seen in the ring-opened Me_2SO complex [Pt(^{15}en)(*C2*-HAsc)(*S*-Me_2SO)]$^+$ (**15**), where ^1J decreases by 154 Hz. The strength of the Pt–*S*-Me_2SO interaction is also reflected in studies of substitution reactions of Pt(II) complexes, which show that S-bonded Me_2SO ligands produce a large kinetic trans effect.[16–19] The ascorbate-C^2 ligand has an even stronger trans effect than Me_2SO, as judged by the coupling constant data (*C2*-HAsc vs H_2O reduces ^1J by 198 Hz). The large trans effect of the carbon-bound ascorbate ligand was found to lead to ammonia release at the site trans to C2 in the reaction between *cis*-[Pt($^{15}NH_3$)$_2$(H_2O)$_2$](NO_3)$_2$ and sodium ascorbate[2] and was predicted on the basis of bond energy calculations preformed on *cis*-[Pt(NH_3)$_2$(*C2*,*O5*-Asc)].[12]

The ^{13}C NMR data obtained on the chloro (**12** and **13**) and Me_2SO (**14** and **15**) substituted ascorbate complexes also indicate that these species adopt a ring-opened structure. As shown by the NMR data presented in Table IV, the main difference seen in comparing the chloro- and Me_2SO–ascorbates **12** and **14** to the C2,O5 chelate **10** is a shift in the position of the C5 resonance. This carbon moves upfield an average of 15 ppm upon detachment of the O5 hydroxyl group. The ^{13}C resonances for the monodentate ascorbate ligands in **12**–**15** are similar to those found for the C2-bound ascorbate ligand in the bis(ascorbate) complex [Pt(*R*,*R*-dach)(*C2*-HAsc)(*O3*-HAsc)] (**16**), which was previously isolated from the reaction that was used to make [Pt(*R*,*R*-dach)(*C2*,*O5*-Asc)].[1,2] The bis(ascorbate) complex **16** is a ring-opened species that contains an ascorbate-C^2 ligand bound to platinum through the opposite (*si*) face of the ascorbate ring.[2]

The chloro- and Me_2SO–ascorbate complexes **12**–**15**, which contain ascorbate bound through the *re* face, are unstable in water. In dilute aqueous solution, the chloro–ascorbate complex **12** rapidly converts to the C2,O5 chelate **10** (eq 6), as judged by HPLC and

$$\underset{\mathbf{12}}{[Pt(R,R\text{-dach})(C2\text{-HAsc})Cl]} \xrightarrow{H_2O} \underset{\mathbf{10}}{[Pt(R,R\text{-dach})(C2,O5\text{-Asc})]} + HCl \quad (6)$$

$$\underset{\mathbf{14}}{[Pt(R,R\text{-dach})(C2\text{-HAsc})(S\text{-}Me_2SO)]^+} \xrightarrow{H_2O} \underset{\mathbf{17}}{[Pt(R,R\text{-dach})(O3\text{-HAsc})(S\text{-}Me_2SO)]^+} \quad (7)$$

^{195}Pt NMR studies. When the Me_2SO–ascorbate complex **14** is dissolved in water, the C2-bound ascorbate ligand rapidly isomerizes to the ascorbate-O^3 complex **17** (eq 7, Tables III and IV). The dissociation of the ascorbate-C^2 ligand may result from the strong cis effect of the S-bound Me_2SO ligand. This observation is consistent with previous studies that show S-bound Me_2SO ligands produce a large cis effect in square-planar substitution reactions of platinum(II) complexes.[16–19]

A number of other attempts were made to prepare ring-opened complexes from the ascorbate chelates, with use of a variety of acids and solvents, and in each case the resulting ring-opened complexes were unstable in aqueous solution. When the ascorbate ligand is bound to Pt through the *re* face at the C2 carbon, chelate formation is clearly favored. The affinity for this mode of binding has been noted in the reactions of *cis*-[Pt(diamine)(H_2O)$_2$]$^{2+}$ complexes with sodium ascorbate, where a diastereofacial selectivity for substitution at the *re* face of ascorbic acid was observed.[2]

Conclusion

The reaction of *cis*-[Pt(diamine)(*C2*,*O5*-Asc)] complexes with noncoordinating acids, in solvents with weak donor properties, yields the O5-protonated chelate *cis*-[Pt(diamine)(*C2*,*O5*-HAsc)]$^+$. The protonated chelates formed from these reactions decompose in water to give *cis*-[Pt(diamine)(H_2O)$_2$]$^{2+}$ and ascorbic acid. The

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protonated complexes have greater stability in alcohols and aprotic solvents such as DMF. These complexes react with good donors such as Cl^- and Me_2SO in aprotic solvents to give ring-opened complexes of the form *cis*-[Pt(diamine)(*C2*-HAsc)L]$^{+/0}$. The ring-opened chloro–ascorbate complex rapidly converts to the C2,O5 chelate in water. The ascorbate-C^2 ligand in the analogous S-bound Me_2SO complex was found to rearrange in aqueous solution to the oxygen-bound complex *cis*-[Pt(diamine)(*O3*-HAsc)(*S*-Me_2SO)]$^+$. The low pH (<1.5) required to produce a ring-opened complex in aqueous solution precludes the formation of stable complexes as the Pt–C bond hydrolyzes under these conditions.

Acknowledgment. We thank Arthur V. Miller for experimental assistance with many aspects of this work.

Registry No. **1**, 108007-37-0; **2**, 115160-60-6; **3**, 115160-62-8; **4**, 107984-67-8; **6**, 106160-56-9; **7**, 115224-85-6; **8**, 115185-33-6; **9**, 94042-09-8; **10**, 91897-69-7; **11**, 115185-31-4; **12**, 115185-29-0; **13**, 115185-59-6; **14**, 115203-85-5; **15**, 115185-55-2; **16**, 115185-34-7; **17**-($MeSO_3$), 115226-54-5; **17**(NO_3), 115226-55-6; **22**, 115224-86-7; [Pt(*R*,*R*-dach)Cl_2], 61848-66-6; [Pt(^{15}en)(H_2O)Cl](NO_3), 115160-65-1; [Pt(^{15}en)Cl_2], 115160-63-9; [Pt(^{15}en)(H_2O)(*S*-Me_2SO)](NO_3)$_2$, 115185-61-0; *cis*-[Pt($^{15}NH_3$)$_2$(H_2O)$_2$](NO_3)$_2$, 78022-63-6; *cis*-[Pt($^{15}NH_3$)$_2$(H_2O)Cl](NO_3), 78039-63-1; *cis*-[Pt($^{15}NH_3$)$_2$$Cl_2$], 78017-69-3; *cis*-[Pt($^{15}NH_3$)$_2$(*S*-Me_2SO)(H_2O)](NO_3)$_2$, 115204-01-8; [Pt(*R*,*R*-dach)(*S*-Me_2SO)Cl]Cl, 115185-56-3; [Pt(*R*,*R*-dach)(*S*-Me_2SO)(H_2O)](NO_3)$_2$, 115185-58-5; ^{195}Pt, 14191-88-9.

Supplementary Material Available: A listing of ^{13}C NMR data for the complexes relevant to this study (1 page). Ordering information is given on any current masthead page.

Contribution from the Department of Chemistry, University of Florence, Florence, Italy

Synthesis, Redox Behavior, Magnetic Properties, and Crystal Structure of a Nickel(II)–Semiquinone Adduct with an Unusually Strong Ferromagnetic Coupling

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Received March 28, 1988

Ni(CTH)$^{2+}$ (CTH = *dl*-5,7,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane) forms with the anion of 3,5-di-*tert*-butylsemiquinone, DTBSQ, stable complexes of formula [Ni(CTH)DTBSQ]Y (Y = ClO_4, $B(C_6H_5)_4$, PF_6). The formulation as a nickel(II)–semiquinone complex is confirmed by redox behavior and structural, spectral, and magnetic properties. The last show that the coupling between nickel(II), $S = 1$, and semiquinonate, $S = {}^1/_2$, is exceptionally strong in such a way that no evidence of population of the excited doublet state is observed at room temperature. The electronic structure of the complex is also studied through single-crystal EPR spectra. [Ni(CTH)DTBSQ]PF_6 crystallizes in the monoclinic system, space group $P2_1/n$. The lattice constants are a = 11.896 (4) Å, b = 32.98 (5) Å, c = 9.697 (9) Å, and β = 101.01 (8) with $Z = 4$. Least-squares refinement converged to a conventional R value of 0.0836. The asymmetric unit comprises a Ni(CTH)DTBSQ$^+$ cation and the PF_6^- anion.

Introduction

The search for conditions under which separate paramagnetic centers can interact strongly to yield the highest spin multiplicity state as the ground state has been actively undertaken. Interesting results have been obtained for aromatic hydrocarbons,[1,2] charge-transfer complexes,[3] and metal ion pairs,[4-6] as well as for systems containing coupled transition-metal ions and stable organic radicals.[7-13] The exchange interactions responsible for the parallel alignment of the spins are rather different. When the magnetic orbitals are orthogonal to each other, with fairly large overlap density at some common atom,[14] the exchange mechanism is called either direct or superexchange. A second type of interaction, which in the physical literature is called double exchange,[15] is observed in mixed-valence species.[16] In the case of organic radicals ferromagnetic coupling can be obtained either by Heitler–London exchange between positive spin density on a radical and negative spin density on another or by admixing of a virtual low excited state with the ground state for a chain of alternating radical-cation donors and radical-anion acceptors.[17,18]

The interactions between metal ions and stable organic radicals acting as a ligand are particularly simple to interpret. In this case in fact the magnetic orbitals of the two interacting centers are well-defined and, if they are kept orthogonal to each other, strong ferromagnetic coupling may be achieved. The magnetic interactions between metal and ligand spins in metalloporphyrin π cation radicals have been easily justified on the basis of these considerations.[11]

Among the organic radical ligands there has been a growing interest in nitroxides[7,8,10,19-23] and semiquinones.[24-31] The latter

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