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Carbon-13 NMR Studies of Platinum(II) Complexes. 3. Investigation of the Configuration and Ligand Conformation of Complexes of the Cyclic α-Amino Acids Proline and Pipecolic Acid

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Received October 6, 1977

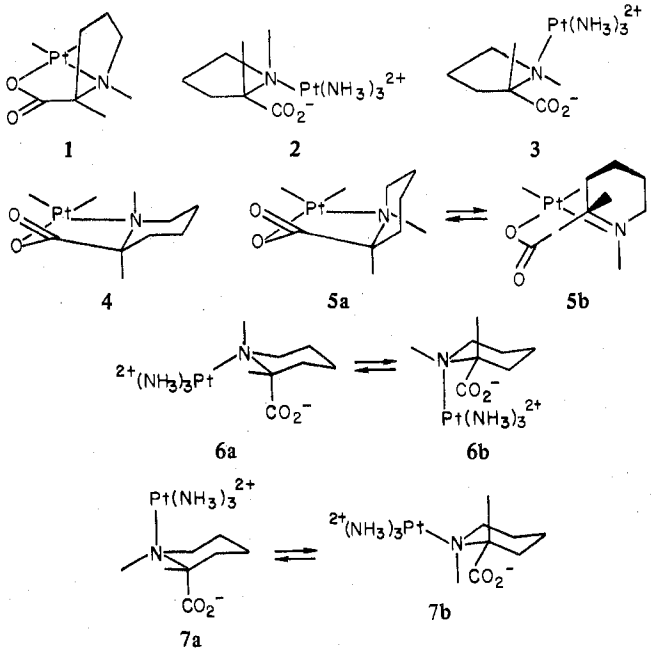
Carbon-13 NMR spectral data are reported for platinum(II) complexes of both chelated [Pt(amino acid)Cl_2]$^-$ and N-coordinated [Pt(amino acid)$(NH_3)_3$]$^+$ species, where amino acid is proline or pipecolic acid. Both types of complexes can exist in distinguishable isomer forms, cis- and trans-fused rings for the chelates and diastereomers, due to the presence of two asymmetric centers for the N-bound monodentate complexes. However, in all cases except [Pt(pip)Cl_2]$^-$, where a 2:1 ratio of cis to trans isomers is found, one isomer is strongly preferred. ^{13}C chemical shifts were used to make assignments of isomer structures. As in decalins, cis-fused rings exhibit ^{13}C chemical shifts more upfield than their trans-fused isomers. $^3J_{Pt-C}$ data support these assignments and permit assessment of preferred conformations of coordinated ligands. Isomer and conformer preferences can be reconciled by comparison with established distribution of rotamers in previously characterized platinum(II) complexes of *N*-methylalanine. A contrast of the steric forces involved in determining conformer preferences in the chelates and monodentate complexes is presented. Evidence for an envelope structure for the five-membered ring in the monodentate proline complex is given. Contrasts between the conformation and isomer preferences of these ligands in square-planar platinum(II) and octahedral cobalt(III) complexes are related to the influence of apical ligands in the latter.

Introduction

In an earlier paper in this series we reported carbon-13 NMR data for platinum(II) complexes of glycine and the *C*- and *N*-methylglycines.[2] Conclusions about the preferred conformations of five-membered glycinate chelate rings and corresponding N-coordinated unidentate species were drawn from ^{195}Pt–^{13}C coupling constants for ligand carbons and from comparison of proton[3] and carbon-13 NMR data for the series.

In this paper, we report a parallel ^{13}C NMR investigation of the stereochemistry of platinum(II) complexes of the cyclic amino acids proline (pro) and pipecolic acid (2-piperidine-carboxylic acid = pip). For these asymmetric ligands, as for *N*-methylalanine, coordination by Pt introduces a second chiral center at the coordinated nitrogen atom so that diastereomers are possible for both chelate and N-coordinated species. Ring closure to form glycinate-type chelate rings with the pro and pip ligands leads to chelates having fused rings in which ligand–ring constraints influence the chelate structures that are possible. For the proline chelate [Pt(pro)Cl_2]$^-$,[4] only a cis isomer, **1**, can be formed because of the constraint provided by the fused five-membered rings. On the other hand, both cis and trans isomers of the monodentate N-coordinated species [Pt(pro)$(NH_3)_3$]$^+$, **2** and **3**, are possible, in principle. For pipecolic acid complexes, both trans and cis isomers of [Pt(pip)Cl_2]$^-$, **4** and **5**, can be formed, with the cis configuration possessing two distinct conformers related by a ring-inversion equilibrium, **5a** ⇄ **5b**. The corresponding cis (*R*,*R* or *S*,*S*) and trans (*R*,*S* or *S*,*R*) isomers of [Pt(pip)$(NH_3)_3$]$^+$, **6a, b** and **7a, b**, are also possible.

Earlier workers[5,6] have used circular dichroism spectra to establish the stereochemistry of these three asymmetric ligands when they are chelated in octahedral complexes of the type [Co$(NH_3)_4$(aa)]$^{2+}$, where aa is an amino acid anion ligand. They concluded that stereospecific binding occurs for all three chiral ligands. For proline, the cis structure (like **1**) is favored. However, for pipecolic acid the trans form (as in **4**) prevails, while only the *R*,*S* chelate of *N*-methyl-L-alanine (with N–CH_3 and C–CH_3 trans) was observed. In view of the different steric constraints present in the octahedral complexes because of axial ligation, which are not present in square-planar complexes, significant differences in isomer distributions of Co(III) and Pt(II) complexes could be expected.



The characterization of isomers of the square-planar platinum(II) complexes of these asymmetric ligands by ^{13}C

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NMR spectroscopy offers considerable advantages over other approaches. First, proton NMR spectra are too complex to permit simple interpretation. Secondly, equilibrium compositions can be characterized without separating components. Finally, $^3J_{Pt-C}$ values can be used to relate isomer ratios and energy differences to specific conformational interactions in the coordinated ligands.

Experimental Section

Complexes of Proline. The proline complex *cis*-K[Pt(pro)Cl_2] was obtained by the same procedure used for substituted glycines,[3] namely, by slow addition of 5 mmol of KOH to a heated aqueous solution of 5 mmol of K_2PtCl_4 and 5 mmol of proline. The yellow solid precipitated on standing and was recrystallized from hot water to which a drop of 12 M HCl had been added to prevent chloride hydrolysis; yield 40%. Spectra could be obtained only for the more soluble species H[Pt(pro)Cl_2] and TMA[Pt(pro)Cl_2] obtained by cation-resin-exchanged treatment of K[Pt(pro)Cl_2] with resin in H^+ or TMA^+ (tetramethylammonium) form.

The ammine complex [Pt(pro)$(NH_3)_3$]$^+$ was obtained by treating 1 mmol of K[Pt(pro)Cl_2] with 5 mL of 10 M NH_3 and warming on a hot plate for 10–15 min. On evaporation to 1–2 mL and on chilliing in an ice bath, a white precipitate of [Pt(pro)$(NH_3)_3$]Cl appeared. This was separated by centrifuging and was redissolved in about 1 mL of D_2O to yield a saturated solution (about 0.5 M) of [Pt(pro)$(NH_3)_3$]$^+$. The ^{13}C NMR spectrum of the mid-pH solution was recorded, after which a drop of 1 M KOH was added to allow equilibration of potential cis and trans isomers, and the spectrum was recorded again. Finally, an excess of concentrated H_2SO_4 (0.5 mL = 2 mmol) was added to ensure protonation of carboxyl oxygen, and the ^{13}C NMR spectrum of the protonated species [Pt(proH)$(NH_3)_3$]$^{2+}$ was recorded.

Complexes of Pipecolic Acid. *trans*-K[Pt(pip)Cl_2] was obtained as a sparingly soluble (~0.05 M in H_2O at room temperature) yellow solid by the same reaction used for the other amino acids;[2,3] yield 1.5 g, 36%. After attempts to convert the potassium salt to the H^+ form were complicated by the appearance of a slowly forming yellow precipitate and an extra set of peaks in the NMR spectrum, the tetramethylammonium (TMA) salt was prepared by passing a slurry of the solid over cation-exchange resin in the TMA^+ form. The NMR spectrum showed that only a single species was present in the solution of the TMA^+ salt.

cis-K[Pt(pip)Cl_2] was obtained from 1.1 g of the less soluble trans isomer by raising the pH of a saturated aqueous solution of the trans isomer to 10 with 1 M KOH for 10 min to permit equilibration.[7] After the pH was returned to about 4 by addition of HCl, the solution was concentrated to 5 mL by evaporation and chilled in ice to precipitate considerable *trans*-K[Pt(pip)Cl_2]. Addition of 20 mL of 95% ethanol precipitated more *trans*-K[Pt(pip)Cl_2] and probably some *cis*-K[Pt(pip)Cl_2]. However, evaporation of the remaining ethanol–water solution yielded 280 mg of a solid whose ^{13}C NMR spectrum (in 1.5 mL of D_2O) differed sharply from that of the less soluble trans species and corresponded to the major species observed in an equilibrated mixture consisting initially of only *trans*-TMA[Pt(pip)Cl_2].

A solution of *trans*-[Pt(pipH)Cl_3]$^-$, in which three chlorides occupy coordination sites of Pt and the amino acid is N-coordinated and protonated at the carboxyl position, was obtained by treating 200 mg of *trans*-K[Pt(pip)Cl_2] with 1 mL of 4 M DCl (5 mL of 12 M HCl and 10 mL of D_2O) and warming gently until the yellow solid dissolved. The spectrum corresponded exactly to the spectrum of an unexpected species that was present in significant amounts in solutions of *trans*-H[Pt(pip)Cl_2]. (See Results for further elaboration on this point.)

[Pt(pip)$(NH_3)_3$]Cl was obtained from *trans*-K[Pt(pip)Cl_2] by the same NH_3 treatment used for all the other amino acids. As with the substituted glycines,[2] the very soluble white compound was not isolated, but spectra of the reconstituted reaction mixture were recorded.

Recording Spectra. Spectra were recorded with a Bruker WH-90 FT NMR spectrometer operating in the pulse mode. From 5000 to 40 000 fid's (at 16K) were accumulated before being transformed and recorded.

Results

A typical carbon-13 NMR spectrum, that of the more soluble cis isomer of K[Pt(pip)Cl_2], is shown in Figure 1. The spectrum consists of five equal-intensity peaks which are assigned to the five ring carbons as designated in Figure 1. Each of the peaks is flanked by the doublet of [^{195}Pt(pip)Cl_2]$^-$. The spacing between doublet components is J_{Pt-C}. For the C-4 carbon, the satellites are not clearly resolved, but their presence is manifested in a somewhat broadened peak. The much weaker signal for the C=O carbon at 182.19 ppm is not shown on this trace. Platinum satellites of carbonyl carbons were too weak (because of signal saturation) to determine J_{Pt-C} reliably.

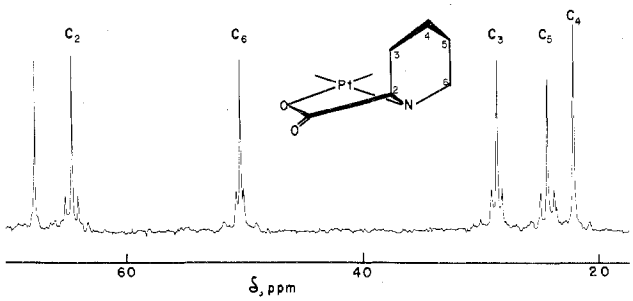


Figure 1. Proton-decoupled ^{13}C NMR spectrum of the more soluble (cis) isomer of K[Pt(pip)Cl_2] in D_2O (~0.5 M). Carbonyl carbon resonance at 182.19 ppm is not shown. The reference was 1,4-dioxane.

Table I. Carbon-13 Chemical Shifts and Platinum-195–Carbon-13 Coupling Constants of Proline Complexes of Pt(II)[a]

Species	Chemical shifts and coupling constants				
	C=O	C-2	C-3	C-4	C-5
cis-[Pt(pro)Cl_2]$^-$	192.24	65.57	30.70	25.61	55.29
	(38)	(17)	(19)	(24)	(13)
[Pt(pro)$(NH_3)_3$]$^+$	178.23	68.37	30.03	24.81	53.08
	(NO)[b]	(5)	(37)	(41)	(5)
[Pt(proH)$(NH_3)_3$]$^{2+}$	174.92	65.90	29.35	24.52	53.32
	(NO)	(5)	(37)	(42)	(5)

[a] Chemical shifts are in ppm relative to Me_4Si; coupling constants, in Hz, are in parentheses. [b] NO indicates platinum satellites not observed because of diminished intensity of carbonyl resonances due to saturation.

Table II. Carbon-13 Chemical Shifts and Platinum-195–Carbon-13 Spin Coupling Constants of Pipecolic Acid Complexes of Pt(II)[a]

Species	Chemical shifts and coupling constants					
	C=O	C-2	C-3	C-4	C-5	C-6
trans-[Pt(pip)Cl_2]$^-$	186.83	67.56	29.21	24.09	26.18	53.63
	(NO)[b]	(25)	(41)	(5)	(48)	(5)
cis-[Pt(pip)Cl_2]$^-$	182.19	64.57	28.70	22.23	24.46	50.36
	(NO)	(25)	(20)	(3)	(26)	(15)
trans-[Pt(pipH)Cl_3]$^-$	174.84	64.81	30.75	23.25	26.72	54.16
	(NO)	(15)	(36)	(4)	(37)	(24)
trans-[Pt(pip)-$(NH_3)_3$]$^+$	179.63	68.80	31.41	23.43	26.31	52.99
	(NO)	(16)	(35)	(4)	(37)	(18)
trans-[Pt(pipH)-$(NH_3)_3$]$^{2+}$	175.82	65.63	30.89	23.06	25.87	53.32
	(NO)	(16)	(33)	(5)	(37)	(18)

[a] Chemical shifts are in ppm relative to Me_4Si; coupling constants, in Hz, are in parentheses. [b] NO indicates platinum satellites not observed because of diminished intensity of carbonyl resonances due to saturation.

Chemical shifts and coupling constants are summarized in Tables I and II. Chemical shifts were measured with respect to internal dioxane and were converted to the Me_4Si scale by assigning a shift of 67.73 ppm to dioxane. The more positive shifts were more downfield. Shifts are reported to 0.01 ppm and are reproducible from sample to sample to within 0.1 ppm. Coupling constants are reported to the nearest Hz.

Table I lists the data for both chelated and N-coordinated proline species. An inspection of molecular models reveals that only the cis chelate species is possible without introducing unreasonable strain. Similarly, the ^{13}C spectrum for the

Scheme I

$$[Pt(N\sim O)Cl_2]^- + H_2O \rightleftarrows [Pt(N\sim O)(H_2O)Cl] + Cl^-$$
$$\uparrow\downarrow H^+, Cl^- \qquad\qquad \uparrow\downarrow H^+$$
$$[Pt(N\sim OH)Cl_3]^- + H_2O \rightleftarrows [Pt(N\sim OH)(H_2O)Cl_2] + Cl^-$$

N-coordinated species $[Pt(pro)(NH_3)_3]^+$ shows only one set of resonances. Since it is unlikely that both the cis and trans isomers of this species **2** and **3** would have identical chemical shifts for all five carbons, one isomer must be preferred by a factor of about 10 or more.

The spectral parameters for pipecolic acid complexes are summarized in Table II. Data for the trans isomer were obtained from spectra of samples of the TMA^+ salt derived from the less soluble $K[Pt(pip)Cl_2]$ under conditions which inhibit racemization (pH <5). For the more soluble cis isomer, the data listed are for the potassium salt of the purified compound. ^{13}C NMR spectral data did not show any dependence on the type of cation used to solubilize some of these species.

The assignment of structures to the two isomers of $[Pt(pip)Cl_2]^-$ is based on both coupling constant and chemical shift data. For the less soluble isomer, $^3J_{Pt-C}$ = 41 and 48 Hz for C-3 and C-5; for the more soluble isomer, $^3J_{Pt-C}$ = 20 and 26 Hz for C-3 and C-5. For the trans isomer (**4**), which is conformationally locked, C-3 and C-5 are oriented trans to Pt and would be expected to be strongly coupled to Pt.[2,8,9] For the cis isomer, two distinct conformations are possible (**5a** and **5b**) with ring inversion interconverting them. In only one of the two (**5a**) are C-3 and C-5 oriented trans to Pt; in the other conformer (**5b**) the Pt–N–C–C dihedral angles to C-3 and C-5 are now ~120° and should give rise to a much lower $^3J_{Pt-C}$. Therefore, the less soluble isomer must be the trans isomer while the more soluble isomer must be the cis isomer with both **5a** and **5b** forms present in nearly equal abundance.

Further support for this assignment is provided by the relative chemical shifts of cis and trans isomers. If the structure assignment based on coupling constants is accepted, the chemical shifts of all carbons of the cis isomer lie upfield from those of the trans isomer. The situation is clearly analogous to the cis–trans decalins for which all carbons of the cis isomer lie upfield from corresponding carbons of the trans isomer.[10] This correlation must certainly be made with some caution[11] but does seem to hold true for the majority of ^{13}C resonances of substituted decalins[10] and decahydroquinolines,[12,13] and this trend must reflect the structural differences between cis-fused and trans-fused rings, especially the added γ-gauche interactions present in the cis-fused conformer.

The ^{13}C spectral and solution behavior of the *trans*-H-$[Pt(pip)Cl_2]$ species is unusual in the series of amino acid chelates studied.[2] A solution of this chelate in D_2O gives a ^{13}C spectrum with six stronger resonances assignable to the piperidine carbons of the parent chelate and six less intense resonances (approximately one third the intensity of the above) ascribable to a second piperidine species, monodentate N-bound $[Pt(pipH)Cl_3]^-$. Also both the C-2 and C-6 resonances of the trans chelate appear as a sharp doublet of nearly equal intensity, with a separation of 3 Hz between lines and a set of platinum satellites of equal J_{Pt-C} surrounding each line of the doublet. A yellow solid also deposits from this solution shortly after preparation.

These observations can best be interpreted in terms of the hydrolysis equilibria which are involved in the aqueous solution chemistry of these chloro complexes as depicted in Scheme I, where N∼O denotes chelated pip and N∼OH denotes carboxyl protonated pip. Significant hydrolysis of the parent piperidine chelate (**4**), *trans*-$[Pt(N\sim O)Cl_2]^-$, to *trans*-$[Pt(N\sim O)Cl(H_2O)]$ would be expected to occur if the chelate were dissolved in chloride-free water.[14] These two chelated species would probably have very similar proton and carbon NMR spectra and their presence in almost equal amounts in the equilibrated aqueous solution is manifested as the doubling of the C-2 and C-6 resonances in the predominant spectrum of the chelate. Addition of a little excess chloride to the solution reduces these "doublets" to a single signal.

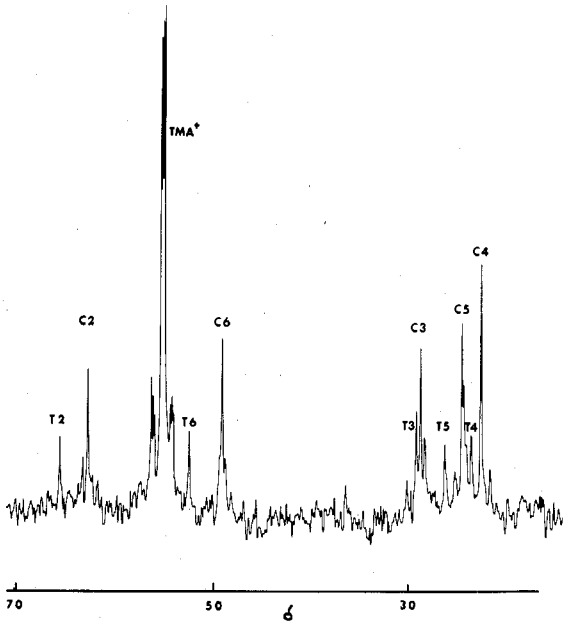


Figure 2. Proton-decoupled ^{13}C NMR spectrum of equilibrium mixtures of *cis*- and *trans*-TMA$[Pt(pip)Cl_2]$ (~0.3 M total concentration).

With acid (counterion) and chloride ion (from the above hydrolysis) available in solution, some of the remaining $[Pt(N\sim O)Cl_2]^-$ or $[Pt(N\sim O)Cl(H_2O)]$ can be converted to the corresponding ring-opened, monodentate N-bound species $[Pt(N\sim OH)Cl_3]^-$ or $[Pt(N\sim OH)Cl_2(H_2O)]$. The remaining weaker six resonances in the ^{13}C spectrum are attributed to the species $[Pt(N\sim OH)Cl_3]^-$, which was prepared independently. The insoluble precipitate which deposits may be due to the neutral species $[Pt(N\sim OH)Cl_2(H_2O)]$ or perhaps $H[Pt(N\sim OH)Cl_3]$. It is noteworthy that ring opening appears to occur quite readily for *trans*-$[Pt(pip)Cl_2]^-$ (**4**) but is not significant for *cis*-$[Pt(pip)Cl_2]^-$ (**5a, b**) or *cis*-$[Pt(pro)Cl_2]^-$ (**1**) under similar conditions.

Like $[Pt(pro)(NH_3)_3]^+$, $[Pt(pip)(NH_3)_3]^+$ consists of only one important N-coordinated species (trans/cis ≈ 8) whose spectral parameters are listed in Table II. Values are given both for the high-pH form in which the CO_2^- group is not protonated and for the low-pH form, obtained from the former by addition of excess D_2SO_4. The chief argument favoring the assignment of the trans configuration to this species is the close correspondence between chemical shifts and coupling constants of *trans*-$[Pt(pipH)Cl_3]^-$ (like **7**) and $[Pt(pipH)(NH_3)_3]^+$. Both have a protonated carboxyl group. The former must have the trans configuration since it was derived from *trans*-$[Pt(pip)Cl_2]^-$ (**4**) at low pH, conditions which do not permit racemization at the quaternary nitrogen.[7]

The results of a cis–trans equilibration study of $[Pt(pip)Cl_2]^-$ are illustrated in Figure 2. The spectrum is that of an equilibrium mixture of cis and trans isomers obtained from *trans*-TMA$[Pt(pip)Cl_2]$ by briefly raising the pH to ~10 to permit room-temperature equilibration. The process was repeated to ensure that equilibrium had been reached. The ratio of cis to trans isomers obtained from peak-height measurements for carbons 2, 3, and 6 is 2.2 ± 0.2. Using a

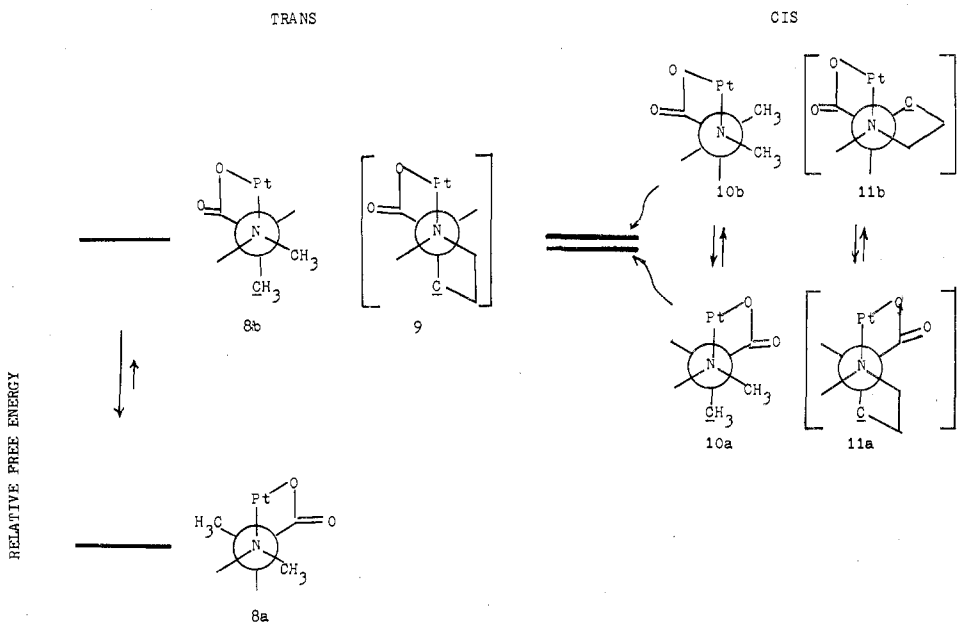


Figure 3. Relative energies of conformers of *cis*- annd *trans*-$[Pt(pip)Cl_2]^-$ and corresponding isomers of $[Pt(N\text{-}Me(ala))Cl_2]^-$. **8** = *trans*-*S,R*-$[Pt(N\text{-}Me(ala))Cl_2]^-$ ($^3J_{Pt-C}$ = 11 Hz); **10** = *cis*-*R,R*-$[Pt(N\text{-}Me(ala))Cl_2]^-$ ($^3J_{Pt-C}$ = 31 Hz); **9** = *trans*-$[Pt(pip)Cl_2]^-$ ($^3J_{Pt-C}$ = 41 Hz); **11** = *cis*-$[Pt(pip)Cl_2]^-$ ($^3J_{Pt-C}$ = 20 Hz). ^3J data given here are for coupling of platinum with corresponding carbons.

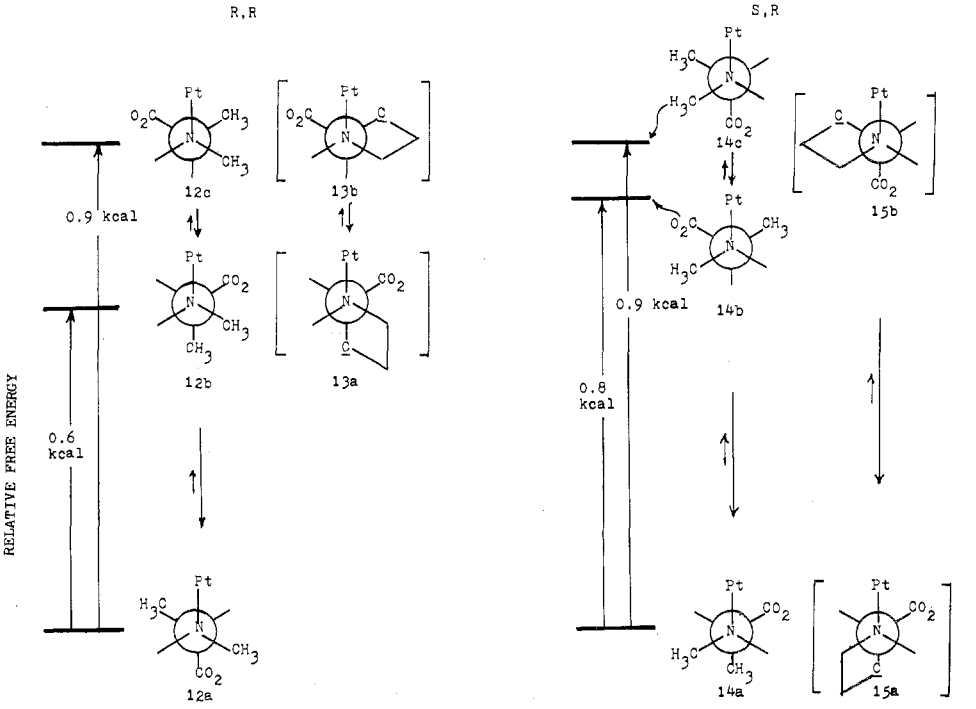


Figure 4. Relative energies of conformers of $[Pt(pip)(NH_3)_3]^+$ and corresponding isomers of $[(Pt(N\text{-}Me(ala))(NH_3)_3]^+$. **12** = *R,R*-$[Pt(N\text{-}Me(ala))(NH_3)_3]^+$ ($^3J_{Pt-C}$ = 23 Hz); **13** = *cis*-$[Pt(pip)(NH_3)_3]^+$ (isomer not observed); **14** = *S,R*-$[Pt(N\text{-}Me(ala))(NH_3)_3]^+$ ($^3J_{Pt-C}$ = 35 Hz); **15** = *trans*-$[Pt(pip)(NH_3)_3]^+$ ($^3J_{Pt-C}$ = 35 Hz). ^3J data given here are for coupling of platinum with corresponding carbons.

Table III. Equilibrium Isomer Ratios of Platinum(II) Complexes of *N*-Methylalanine[a] and Pipecolic Acid

Complex	Ratio (trans:cis)	$^3J_{Pt-C}$, Hz	
		Trans	Cis
$[Pt(N\text{-}Me(ala))Cl_2]^-$	8 ± 2	11	31
$[Pt(pip)Cl_2]^-$	0.45 ± 0.05	41	20
$[Pt(N\text{-}Me(ala))(NH_3)_3]^+$	1.0 ± 0.1[b]	35	23
$[Pt(pip)(NH_3)_3]^+$	8	35	

[a] See ref 2 and 3. [b] *S,R*:*R,R* for this case, where *S,R* and *R,R* of monodentate N-bound complexes are derived without inversion at the nitrogen asymmetric center from *trans*- and *cis*-*N*-Me(ala) chelates, respectively.

similar procedure, we had earlier[2] determined the *S,R* to *R,R* isomer ratio for the $[Pt(N\text{-}Me(ala))(NH_3)_3]^+$ complex to be 1.0 ± 0.1. These data are summarized in Table III.

Discussion

Conformational Effects in *N*-Methylalanine and Pipecolic Acid Complexes. A comparison of the cis/trans equilibrium isomer ratios and NMR parameters of chelated and N-coordinated species of pipecolic acid and *N*-methylalanine provides considerable insight into the stereochemical influence of the six-membered piperidine ring. Pertinent equilibrium and coupling constant data are summarized in Table III and

related conformational structures are given in Figures 3 and 4. For the chelates, the trans isomer (**8a, b**) of *N*-methylalanine is strongly preferred over the cis isomer (**10a, b**), while the cis isomer of pipecolic acid (**11a, b**) is preferred over the trans isomer (**9**) by a 2/1 ratio. By contrast, for the N-coordinated species, *S,R* and *R,R* isomers of *N*-methylalanine (**14a–c** and **12a–c**) are present in approximately equal concentrations, while the trans (*S,R* or *R,S*) isomer (**15a, b**) of pipecolic acid is strongly preferred over the cis (*R,R* or *S,S*) isomer (**12a, b**).

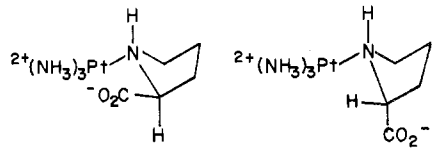
Taken together, the equilibrium ratios and coupling constants of the two extreme conformations of cis and trans isomers suggest the relative free energies of [Pt(*N*-Me(ala))Cl_2]$^-$ as shown[2] in Figure 3. The values for $^3J_{Pt-C}$ for C–CH_3 carbons for each isomer provide the basis for the estimate of conformational energies. The relative energies of corresponding species of [Pt(pip)Cl_2]$^-$ shown in Figure 3 were then estimated by assuming that insertion of CH_2–CH_2 between gauche N–CH_3 and C–CH_3 carbons will have the same effect in each conformer. Thus, the lower energy of *trans*-[Pt(*N*-Me(ala))Cl_2]$^-$ (relative to the cis isomer) can be accounted for by the availability of a low-energy conformation (**8a**) in which C–CH_3 and N–CH_3 groups adopt pseudoaxial orientations to avoid each other. In the corresponding [Pt(pip)Cl_2]$^-$ chelates, the conformer analogous to **8a** is not possible due to the constraints of the piperidine ring. As a result, the single conformer of the trans isomer (**9**) and the two conformers of the cis isomer (**11a, b**) have nearly equal energies so that the cis form is favored by a 2:1 ratio. Comparison of $^3J_{Pt-C}$ for the two isomers supports this model. The coupling between Pt and the vicinal carbons in conformation **11b** is expected to be small ($^3J_{trans} \cos^2 60° \approx 10$ Hz) because of the gauche orientation of coupling nuclei, while the coupling in the other conformer, **11a**, should approach that seen for the trans conformer (**9**) because both maintain a trans arrangement of Pt and C nuclei. A $^3J_{Pt-C}$ of 25 Hz ($^1/_2$(10 + 41)) should be observed if the two cis conformations are equally probable. However, since the observed $^3J_{Pt-C}$ is 20 Hz, there appears to be a small preference for conformation **11b** which has the vicinal carbons gauche to the platinum atom.

At a glance it is not entirely obvious why the rotameric forms of [Pt(pip)Cl_2]$^-$, trans (**9**) and cis (**11a, b**), should be nearly equal in energy when the cis conformers seem to generate a larger number of unfavorable butane gauche-type interactions. A similar dilemma appears to exist in understanding the preference of the diaxial conformer (**8a**) of *trans*-[Pt(*N*-Me(ala))Cl_2]$^-$ over the diequatorial form (**8b**). However, an inspection of molecular models suggests that the gauche interaction of *N*-methyl groups with the chelated carboxyl group and *C*-methyl groups with the Cl–Pt–Cl moiety in the glycinate-type chelates is not as pronounced as the gauche interaction of N–CH_3 with free CO_2^- and C–CH_3 with $Pt(NH_3)_3^{2+}$ shown to be significant in determining rotameric preferences in monodentate N-bound glycinate–platinum(II) complexes of the type [$Pt(NH_3)_3$(gly)]$^+$ studied earlier.[2] This difference appears to arise partly because of a distortion from the idealized rotameric structures (shown in Figure 3) brought about by formation of the glycinate chelate ring. X-ray structural studies[15] show that the Pt–N–C_α–C=O dihedral angle is between 0 and 30°,[16] not the 60° angle in the idealized structure. Also, in the chelates the carboxyl and platinum moieties have a relatively fixed nonrotating position which tends to direct these groups away from N–CH_3 and C–CH_3 substituents. The rotationally locked Cl–Pt–Cl moiety is probably less bulky than the freely rotating $Pt(NH_3)_3^{2+}$ group present in the monodentate complexes. Thus, the (N–CH_3)–(C–CH_3) interactions appear to be the dominant force governing the conformational preferences in these glycinate-type chelates. Structures like **8a**, where interacting methyl groups are well separated, are favored relative to a rotamer like **8b**, where methyl groups are gauche to one another. If the strain energy introduced in each rotamer of [Pt(pip)Cl_2]$^-$, **9**, **11a**, and **11b**, due to glycinate chelate ring formation is of similar magnitude and if the interaction of C–CH_2 and N–CH_2 substituents with the chelate ring groups (CO_2 and ClPtCl) are not very important, these rotamers (**9**, **11a, 11b**) then might be expected to have nearly equal energies, and equal populations, as is observed experimentally.

Similar reasoning can be utilized to explain the strong preference for the trans isomer (**15a**) of N-coordinated [Pt(pip)$(NH_3)_3$]$^+$, as shown in Figure 4. The relative energies of the six rotamers of *S,R*- and *R,R*-[Pt(*N*-Me(ala))$(NH_3)_3$]$^+$ shown in Figure 4 are based on an analysis of the observed values of $^3J_{Pt-H}$, $^3J_{Pt-C}$, and $^3J_{H-H}$.[2] Note particularly that each isomer has available one low-energy rotamer (**12a** and **14a**) which minimizes unfavorable steric interactions between bulky substituents. The nearly equal population of *S,R* and *R,R* isomers of N-bound *N*-Me(ala) requires essentially equal energies for these two low-energy rotamers. The four conformations of *cis*- and *trans*-[Pt(pip)$(NH_3)_3$]$^+$, **13a, b** and **15a,b**, that can be obtained from the corresponding rotamers of *S,R*- and *R,R*-[Pt(*N*-Me(ala))$(NH_3)_3$]$^+$ by connecting gauche methyl carbons via an ethylene bridge are depicted in square brackets in Figure 4. Again we have assumed that connecting gauche C–CH_3 and N–CH_3 carbons to form the piperidine ring has the same effect in each conformer, so that the relative energies of [Pt(pip)$(NH_3)_3$]$^+$ species should be the same as the relative energies of corresponding [Pt(*N*-Me(ala))$(NH_3)_3$]$^+$ rotamers. In this case, the predicted effect of forming the piperidine ring is to lead to one conformer of [Pt(pip)$(NH_3)_3$]$^+$, **15a**, being substantially lower in energy than the other three possible conformers, **13a**, **13b**, and **15b**. As a result, the trans conformer **15a** should predominate and the observed $^3J_{Pt-C}$ value for that isomer should be relatively large, in agreement with the experiment (35 Hz). Parallel reasoning in Figures 3 and 4 thus reconciles the predominance of the cis form of the chelate [Pt(pip)Cl_2]$^-$ and the trans form of the monodentate N-bound species [Pt(pip)$(NH_3)_3$]$^+$.

Although the qualitative features of the model agree with experimental data, if the energy differences between [Pt(pip)$(NH_3)_3$]$^+$ conformers are identical with the energy differences between corresponding [Pt(*N*-Me(ala))$(NH_3)_3$]$^+$ rotamers, the trans:cis ratio should be approximately 2. The failure to observe any detectable amount of cis isomer requires an even greater energy difference between cis and trans species than is implied in Figure 4. This suggests that the trans:cis ratio is greater than 8, which would correspond to an energy difference between cis and trans isomers of [Pt(pip)$(NH_3)_3$]$^+$ of at least 1.3 kcal/mol rather than 0.8 kcal/mol inferred from the corresponding *N*-methylalanine rotamers. It is noteworthy that the low-energy conformer of the trans isomer of [Pt(pip)$(NH_3)_3$]$^+$ is the one which has both CO_2^- and $Pt(NH_3)_3^{2+}$ groups equatorial, maximizing the possible hydrogen bonding or charge attraction of these substituents which was also seen in our earlier studies of substituted glycine complexes.[2]

The related proline complex, [Pt(pro)$(NH_3)_3$]$^+$, can also be envisioned as adopting cis or trans orientations (**2** or **3**) on the five-membered aliphatic ring. However, evidence for only one isomer is found and the relatively large vicinal platinum–carbon coupling constants, to C-3 (37 Hz) and C-4 (41 Hz), require a nearly trans orientation of the $Pt(NH_3)_3^{2+}$ moiety with respect to these carbon atoms. Either of the particular envelope conformations of the five-membered proline ring depicted in **16a** and **16b** provides the necessary trans orientation of Pt with C-3 and C-4. From the data in Table I it is not possible to determine with certainty which of these



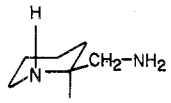
16a 16b

conformers, trans (**16a**) or cis (**16b**), is the predominant form of $[Pt(pro)(NH_3)_3]^+$ in solution. Inspection of models reveals a closer proximity of the charged ring substituents in the axial–equatorial cis conformation (**16b**) than the trans conformer (**16a**). By comparison with earlier rotamer preferences in similar N-bound amino acid complexes,[2] the cis isomer, which appears to allow closer interaction of CO_2^- and $Pt(NH_3)_3^{2+}$, may be the form present. Interestingly, protonation of the carboxyl has virtually no effect on the coupling constants and, presumably, on the ring conformation of monodentate, N-bound proline or pipecolic acid complexes.

Comparison of Stereochemistry of Square-Planar and Octahedral Complexes. A comparison of the isomer ratios of square-planar Pt(II) chelates of *N*-methylalanine, proline, and pipecolic acid with those of similar Co(III) chelates emphasizes the importance of apical ligands in determining the isomer preference of six-coordinate octahedral cobalt(III) chelates.[5,6] For Δ-$[Co(en)_2(N\text{-Me-L-ala})]^{2+}$, the two methyl groups are exclusively trans, like those of the preferred isomer of $[Pt(Me(ala))Cl_2]^-$. However, x-ray evidence[18] shows a diequatorial disposition of the methyl substituents in this case, not the preferred diaxial arrangement as in **8a**. For proline chelates, only cis coordination is possible for octahedral Co(III) or square-planar Pt(II) complexes. By contrast, only the trans form of pipecolic acid is found[6] in Λ-$[Co(en)_2(\text{D-pip})]^{2+}$. An x-ray structure of this species is also available.[19] The asymmetric $Co(en)_2$ moiety apparently forces complete preference for that pipecolic acid configuration (trans, **9**) which is the less important one in square-planar $[Pt(pip)Cl_2]^-$ which lacks an apical ligand. In addition, trans coordinated D-pipecolic acid ensures essentially complete preference for Λ-$[Co(en)_2(\text{D-pip})]^{2+}$ over the Δ isomer.

Two-Bond Germinal Pt–C Coupling and Ring Strain. Coupling constants between ^{195}Pt and ^{13}C for carbons which are connected to the Pt-coordinated nitrogen generally fall in the range 13–25 Hz. These *J* values are typical of those found for corresponding germinal carbons of platinum(II) complexes of the methylglycines.[2] For the platinum chelates of proline and pipecolic acid, $^{2,3}J_{Pt\text{-}N\text{-}C}$ values[20] (25, 25, and 17 Hz) for the α-carbon (C-2) suggest substantial deviation from planarity in the glycinate ring, with a corresponding reduction in the three-bond contribution via the Pt–O–C–C path as compared to the more planar glycine chelate ring ($^{2,3}J_{Pt\text{-}N\text{-}C}$ = 46 Hz).[2] Similarly, $^2J_{Pt\text{-}N\text{-}C}$ for C-5 of $[Pt(pro)Cl_2]^-$ (13 Hz) and C-6 of *cis*-$[Pt(pip)Cl_2]^-$ (15 Hz) are comparable to N–CH_3 values for *N*-methylglycines. However, $^2J_{Pt\text{-}N\text{-}C}$ for C-6 of *trans*-$[Pt(pip)Cl_2]^-$ is 5 Hz, the smallest $^2J_{Pt\text{-}C}$ we have observed in our studies of platinum(II) complexes of amino acids[2] and aliphatic diamines.[8] Equally small values for $^2J_{Pt\text{-}N\text{-}C}$ are found for both two-bond couplings to C-2 and C-5 of N-coordinated proline. In both cases, the effect might well be related to the Pt–N–C bond angle. For geminal proton–proton coupling, bond angle enlargements are predicted to reduce the magnitude of $^2J_{H\text{-}H}$.[21] For $[Pt(pip)Cl_2]^-$, closing the chelate ring could easily require some increase in the Pt–N–C(6) angle. Similarly, in $[Pt(pro)(NH_3)_3]^+$, the envelope structure (**16b**) might produce a similar increase in the Pt–N–C angle to C-2 (and to C-5). Both the ring opening propensity and the unusually small coupling to C-6 of *trans*-$[Pt(pip)Cl_2]^-$ could have their origins in the strain introduced to form the chelate ring.

^{13}C NMR Data and Configuration of Other Piperidine-Containing Chelates. We earlier reported ^{13}C NMR data for a 2-(aminomethyl)piperidine (pipen), **17**, complex of Pt(II),



17

$[Pt(bpy)(pipen)]^{2+}$, where bpy = 2,2′-bipyridine.[8] On the basis of relatively large couplings to C-3 and C-5, we assigned a trans structure, analogous to **5a**, to the single species which was isolated from the reaction of pipen with $Pt(bpy)Cl_2$. Comparison of NMR parameters of $[Pt(bpy)(pipen)]^{2+}$ with those of *cis*- and *trans*-$[Pt(pip)Cl_2]^-$ suggests that this assignment may be incorrect. These data are summarized in Table IV. The significantly smaller couplings to C-3 and C-5 for the pipen complex (41 and 30 Hz), compared to *trans*-$[Pt(pip)Cl_2]^-$ (48 and 41 Hz), suggest that the single isomer that was isolated may actually be the cis isomer.

Contributions from conformations analogous to **5b** (with an ethylenediamine instead of a glycinate chelate ring), in which $^3J_{Pt\text{-}C}$ is gauche to C-3 and C-5, would be expected to lead to smaller couplings for these carbons. Comparison of chemical shifts for the piperidine-ring carbons of the three chelates also supports assignments of a cis configuration to $[Pt(bpy)(pipen)]^{2+}$. The piperidine shifts of $[Pt(bpy)(pipen)]^{2+}$, like those of *cis*-$[Pt(pip)Cl_2]^-$, are all upfield from those of corresponding carbons of *trans*-$[Pt(pip)Cl_2]^-$. From these considerations, it appears that this pipen complex should be assigned a cis configuration and that a **5a**-type conformer is more important than the **5b**-type conformer which would lead to even smaller coupling to C-3 and C-5.

Chemical Shifts. A comparison of the chemical shifts of corresponding carbons of analogous monodentate N-bound proline and pipecolic acid complexes shows striking similarities. This is particularly true of the N-coordinated species for which C=O, C-2 (the α-carbon), and C-3 are within 1.5 ppm for both protonated and deprotonated forms. Similarly, shifts of the C-5 carbon of proline complexes are virtually identical with shifts of corresponding C-6 carbons of pipecolic acid complexes. For the α-C, C-2, the observed shifts of deprotonated species, 68.37 and 68.80 ppm, are slightly greater than the value calculated from shift parameters derived from methylglycines which take into account only α- and β-substitution;[2] i.e., $\delta = \delta_0 + \delta(C\text{–}CH_3) + \delta(N\text{–}CH_3) = 50.67 + 6.82 + 9.00 = 66.49$ ppm.

The effect of carboxylate protonation, which produces an upfield shift of 2.5–4 ppm for the carboxyl and C-2 carbons, in both compounds is typical of protonation shifts of carboxylic acids.[22]

For the chelated complexes $[Pt(pip)Cl_2]^-$ and $[Pt(pro)Cl_2]^-$, a comparison of the carbons near the coordination site shows substantial differences. We have already noted the upfield shift of all carbons of *cis*-$[Pt(pip)Cl_2]^-$ relative to the trans isomer as evidence for the spectral assignments. The large difference in shifts for carbons near the coordination site of cis isomers of the two amino acids is also noteworthy. In each case proline chemical shifts are more downfield: C=O, 10 ppm; C-2, 1 ppm; C-5 (pro) vs. C-6 (pip), 5 ppm. A study of molecular models reveals that the cis-fused rings in the proline chelate are oriented in a way to minimize steric proximity of substituents of the two fused rings, while in the piperidine chelate cis isomer, **5a**, shown to be predominant earlier, the carboxyl group is seen to be an axial substituent on the chair piperidine ring and hence engage in gauche interactions with C-4 and C-6 methylene groups. It is not unreasonable to expect a significant upfield shift of the ^{13}C resonances of methylene groups and the carboxyl carbons by analogy with the upfield-shift effect of axial methyl groups on cyclohexane-ring carbons three bonds removed.[23] Thus,

Table IV. A Comparison of the Carbon-13 Chemical Shifts[a] and J_{Pt-C}[b] Values for Platinum(II) Chelates of Piperidine-Type Bidentate Ligands

Piperidine carbon	*trans*-$[Pt(pip)Cl_2]^-$	*cis*-$[Pt(pip)Cl_2]^-$	$[Pt(bpy)(pipen)]^{2+}$ [c]
C-2	67.562 (25)[b]	64.57 (25)	63.64 (10)
C-3	29.21 (41)	28.70 (20)	26.54 (41)[d]
C-4	24.09 (5)	22.23 (<3)	18.88 (<3)
C-5	26.18 (48)	24.46 (26)	24.44 (30)[d]
C-6	53.63 (5)	50.36 (15)	48.64 (25)

[a] In ppm vs. Me_4Si. [b] In Hz, found in parentheses behind chemical shifts. [c] Data taken from ref 8; bpy = 2,2'-bipyridine. [d] This assignment may be reversed.

the appearance of these proline resonances more downfield from the similar resonances of the piperidine chelate are a manifestation of the differences in geometry imposed by the aliphatic rings in these two fused-ring compounds. For the C=O carbon, the proline shift (192.24 ppm) is close to that expected on the basis of shift parameters for methylglycines;[2] i.e., $\delta = \delta_0 + \delta(C\text{–}CH_3) + \delta(N\text{–}CH_3) = 190.28 + 1.32 - 1.65 = 190.01$ ppm plus a small contribution from C-4.

Acknowledgment. The authors acknowledge the National Institutes of Health, the National Science Foundation, and the Research Corp. (L.E.E.), which provided financial support, and the University of Arizona and Professor Michael Barfield, who provided spectrometer time and laboratory facilities for completion of the work.

Registry No. *cis*-K[Pt(pro)Cl_2], 51139-35-6; [Pt(pro)$(NH_3)_3$]Cl, 66140-49-6; *trans*-K[Pt(pip)Cl_2], 66085-34-5; *cis*-K[Pt(pip)Cl_2], 66182-96-5; [Pt(pip)$(NH_3)_3$]Cl, 66085-35-6; $[Pt(proH)(NH_3)_3]^{2+}$, 66140-50-9; *trans*-$[Pt(pipH)Cl_3]^-$, 66085-36-7; *trans*-$[Pt(pipH)(NH_3)_3]^{2+}$, 66085-37-8.

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EPR Studies of Axial Ligation of a Low-Spin Cobalt(II) Macrocyclic Schiff Base Complex

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Received November 10, 1977

EPR studies demonstrate that 1:1 adducts of cobalt(II) 5,7,12,14-tetramethyldibenzo[*b*,*i*][1,4,8,11]tetraazacyclotetradecahexaene with ligands containing phosphorus, nitrogen, sulfur, and oxygen donor atoms all have a $(d_{xz}d_{yz}d_{x^2-y^2})^6d_{z^2}^1$ ground-state configuration and similar spin-density distributions. The primary difference between the adducts is the energy separation between the ground state and the $(d_{xz}d_{x^2-y^2}d_{z^2})^6d_{yz}^1$ state which decreases as the strength of the axial bond decreases, until in very weakly coordinating solvents such as neat toluene it is not possible to definitely say which is the ground state. All of the EPR spectra have rhombic symmetry which is due to a difference in the energies of the d_{yz}^1 and d_{xz}^1 states. This difference becomes larger as the strength of the axial bond increases. The EPR results are compared with results for analogous cobalt(II) porphyrin complexes. Solvent effects also occur and cause an orientation- and m_I-dependent broadening of the EPR lines in a manner consistent with the ground-state assignment.

The use of EPR in studying the electronic structure of low-spin Co(II) compounds is well documented.[1-14] In particular this technique has been extensively applied to cobalt(II) porphyrins and related four-coordinate complexes. Since these compounds generally undergo axial ligation to form five- and six-coordinate structures which are also EPR active, the yield of electronic structural information obtained from EPR studies can be high. For example from the EPR parameters it is possible to determine the electronic configuration of the ground state as well as calculate the spin density which resides on the central Co(II) ion. Although this type of analysis has been performed for cobalt(II) porphyrin complexes, the dependence of these variables on the structural parameters associated with the macrocyclic framework itself such as ring size, its charge, and degree of unsaturation has not been studied. Macrocyclic Schiff bases and their analogues exist in a diversity of structural types[15] and as such are useful vehicles for a systematic investigation of this kind of molecular–electronic structural relationship.

The Schiff base formed from *o*-phenylenediamine and acetylacetone, I, has a number of structural features in common with the porphyrins.[16,17] It is a highly conjugated although not aromatic (24π) tetraaza macrocyclic ligand. Analogous to the porphyrins, in the presence of transition-metal ions it readily deprotonates to give the dianionic form of the ligand. Its metallo derivatives are intensely colored and

0020-1669/78/1317-1717$01.00/0