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NMR Observation of Mixed Complex Formation and Stereochemical Non-Rigidity in Cobalt(II) Complexes

D. S. EVERHART* and R. F. EVILIA**

Department of Chemistry, University of New Orleans, Lakefront, New Orleans, La. 70122, U.S.A.

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Contact shift measurements of aqueous solutions containing a 1:1:1 mol ratio of Co(II): dien:asp (dien = $NH_2CH_2CH_2NHCH_2CH_2NH_2$, *Asp =* $NH_2CH(CH_2CO_2H)CO_2H$) *indicate that at pD's above 7.5 the predominant species (>97%) in aqueous solution is Co(dien)(Asp)*(D_2O). *This represents approximately a 4 Kcal* mol^{-1} *preference for the heterogenous complex. At lower pH's protonation of the dien results in loss of dien and production of a significant amount of Co(Asp)*$(D_2O)_3$ *and Co*$(Asp)_2^{-2}$. *The mixed ligand complex is stereochemically non-rigid at 34 °C with the asp portion undergoing rapid interconversion between isomers which differ in the carboxylate that is coordinated to the metal. At −14 °C, this interconversion is slow on the nmr time scale. At 100 °C, a bond rupture process becomes rapid which results in inversion of the dien nitrogens and stereochemical nonrigidity of the dien side.*

The complex Co(dien)$(D_2O)^{2+}$ *is found to exist in solution as approximately 67% meridonal and 33% facial form which are in rapid equilibrium with each other at 34 °C but slowly interconvert at −5 °C. This process is found to involve breakage of a cobalt nitrogen bond.*

Introduction

Whenever two different ligands are mixed with a metal ion it is possible to form mixed complexes. It is, of course, also possible to form a mixture of the two bis complexes or a mixture containing all three possibilities. If the complexes are non-labile, such as when cobalt(III) is utilized, it may be possible to separate the mixture into pure compounds chromatographically, but there is no guarantee that the measured distribution of complexes reflects the equilibrium rather than the kinetic stabilities. When labile complexes are considered, it is not possible to separate and isolate each component of the mixture for analysis. Since studies of non-labile complexes must be tempered by the realization that the data may reflect kinetic rather than thermodynamic preferences, it is desirable to study labile situations.

The factors which govern the formation of mixed complexes are not well knonw. One can imagine that ligand pairs which are capable of intramolecular hydrogen bonding may prefer to form mixed complexes; however, predicting *a priori* that a certain combination of ligands will lead to preferential formation of the heterogeneous product is, in general, not reasonable. Various attempts to determine the stereospecificity of mixed complex formation have been reported [1–9]. These studies have generally found small preferences for one stereoisomer over the others when tridentate ligands [1–4, 7, 8] are used, but essentially statistical distributions when bidentate ligands are used [5, 6]. For example Nagypal *et al.* [4] found calorimetrically that the formation constant for Cu(asp)(glu)$^{-2}$ (glu^{-2} = glutamate) was approximately .08 greater than the statistically expected value. McDonald and Phillips, in their classic work, found that Co(D hist)(L hist) was approximately 0.7 Kcal mol^{-1} more stable than either Co(D hist)$_2$ or Co(L hist)$_2$ [1]. Similarly Barnes and Pettit [8] found approximately 0.6 Kcal mol^{-1} greater stability for Ni(D hist)(L hist) complexes. Nancollas and I [5] and Yingst *et al.* [6], however, found essentially statistical mixtures of various bidentate complexes. Essentially complete formation of heterogeneous mixed ligand complexes of nickel(II) containing a rigid tridentate ligand has been reported [10].

In this paper a labile mixed ligand–metal mixture is reported which forms the heterogeneous mixed ligand complex almost exclusively (>97%) at high pH's and a mixture of complexes at low pH. These complexes are interesting because the formation of the mixed ligand complex can be demonstrated unequivocally and, since the complexes are labile, the mixed complex represents the thermodynamically favored product. Also, it appears that one of the

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*Present address, Department of Chemistry, University of North Carolina, Chapel Hill, NC 27514.

**Person to whom correspondence should be directed.

TABLE I. Spectral Assignments

Complex	Peak Location[a]	Assignment
$Co(asp)(H_2O)_3$	37	$1\text{-}CH_2CO_2^-$
	45	$1\text{-}CH_2CO_2^-$
	161	$\text{-}CH\text{-}NH_2$
$Co(asp)_2^{2-}$	62	$1\text{-}CH_2CO_2^-$
	76	$1\text{-}CH_2CO_2^-$
	172	$CH\text{-}NH_2$
$Co(dien^{2+}(H_2O)_3$[b]	2	Assignments uncertain
	80	
	101	
	141	
	155	
	175	
Co(dien)(asp)[c]	41	asp
	45	asp
	57	dien
	63	dien
	104	dien
	108	dien
	131	dien
	136	dien
	149	asp
	162	dien
	170	dien

[a] ppm downfield of HOD at 34 °C unless stated otherwise. [b] −5 °C. [c] pD 7.8, 34 °C.

ligands binds in a bidentate fashion and undergoes rapid exchange of coordination site.

Experimental

All ligands were of highest available commercial purity and were used without further purification except for dien which was distilled from sodium and stored over molecular sieve. Stock 1.81 *M* Cobalt(II) nitrate in D_2O was standardized with potassium ferricyanide according to the standard method [11]. Complexes were made by adding, under nitrogen, 0.5 ml of stock cobalt(II) solution and 0.9 mmol of dien to 0.5 ml of a solution made by dissolving 0.9 mmol of the amino acid in enough sodium deuteroxide to neutralize the carboxylates. The water was removed by rotary evaporation and subsequent redissolution in 0.5 ml of deuterium oxide. The pH was then measured on a Corning 110 pH meter equipped with a Sargent Welch S-30070-10 combination microelectrode. Sodium deuteroxide or deuterium chloride was used to adjust the pD (assuming pD = pH + .4) [12] to the desired value. Because these complexes rapidly react with oxygen, it is important that oxygen be carefully excluded during these procedures. Exposure to oxygen results in the production of an intensely colored brown compound. All samples which were exposed were discarded.

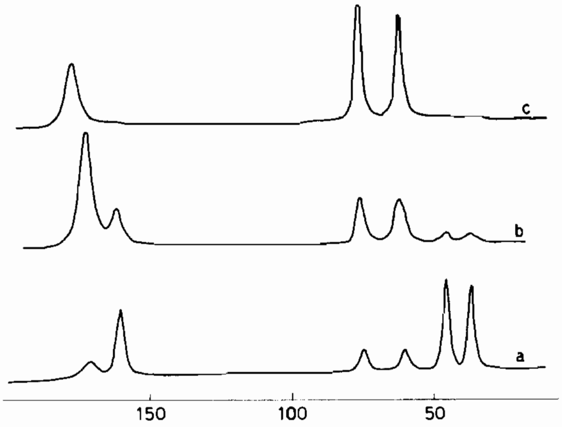

Figure 1. 34 °C paramagnetic nmr spectra of 1:2 molar ratio of Co(II):Asp at pD's of a) 5.1, b) 6.8, c) 7.3. Scale is ppm from HOD.

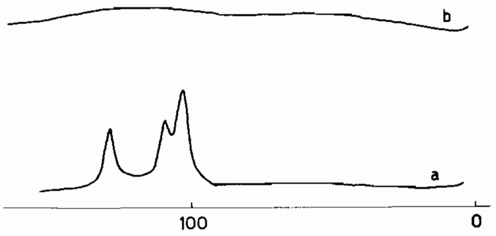

Figure 2. 34 °C paramagnetic nmr spectra of 1:1 molar ratio of Co(II):dien at pD of a) 7.0, b) 9. Scale is ppm from HOD.

The methylene protons of aspartic acid were exchanged for deuterium by adjusting the pD of a 0.9 *M* solution of aspartic acid to 13.8 and refluxing overnight. Deuteration was followed by the decrease in intensity of the methylene multiplet. Approximately 75% deuteration was accomplished this way. No change in the specific rotation of the acid occurred from this process. A side reaction producing an insoluble product of uncertain structure occurs if the pD is made much higher than 13.8.

All nmr spectra was recorded on a Perkin Elmer–Hitachi R20B spectrometer equipped with a Hewlett Packard 230B power amplifier as previously described [13]. Variable temperature spectra were obtained by use of the R202VT variable temperature unit of the spectrometer calibrated against ethyleneglycol for high temperatures and methyl alcohol for low temperatures.

Results

The effect of pH on the spectra behavior of Co-$(dien)^{2+}$ and 2:1 asp: Co mixtures are shown in

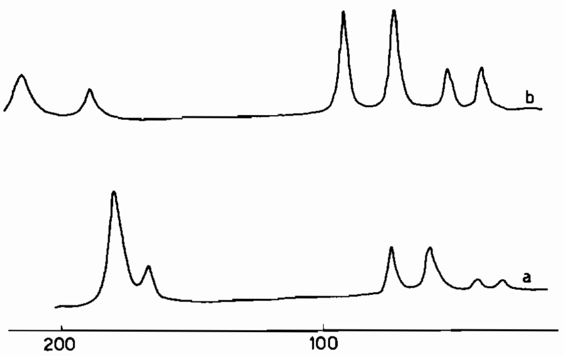

Figure 3. Paramagnetic nmr spectra of a) 1:2 molar ratio of Co(II):Asp at pD 6.8, 34 °C, b) 1:1.5 molar ratio of Co(II): Asp at pD 7.0, −10 °C. Scale is ppm from HOD.

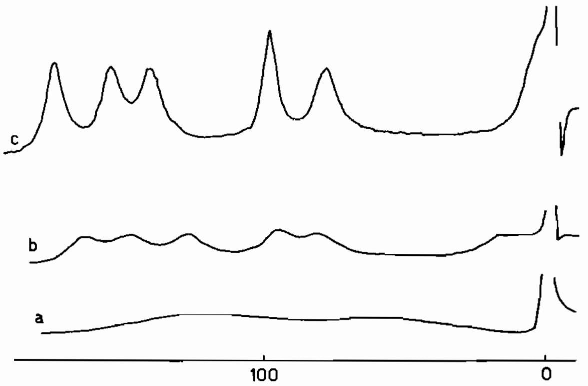

Figure 4. Paramagnetic nmr spectra of $Co(dien)(D_2O)_3^{2+}$ at pD 9; a) 34 °C, b) 10 °C, c) −5 °C. Scale is ppm from HOD.

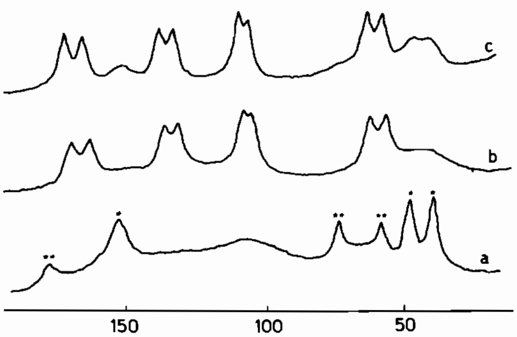

Figure 5. Paramagnetic nmr spectra of 1:1:1 Co:dien:asp mixture at 34 °C. a) pD = 6.0, b) pD = 7.5, c) pD = 7.8. Scale is ppm from HOD. *Indicates $Co(asp)(D_2O)$ peaks. **Indicates $Co(asp)_2^{-2}$ peaks.

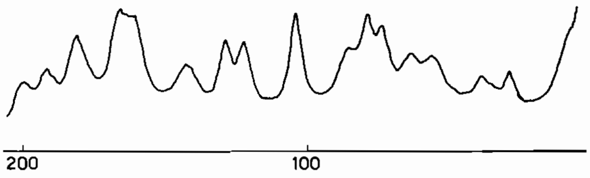

Figure 6. Paramagnetic nmr spectrum of 1:1:1 co:dien:azo at pD ~9, −14 °C. Scale is ppm from HOD.

Figures 1 and 2. Figures 3 and 4 show the effect of temperature on the spectra of $Co(dien)^{2+}(D_2O)_3$, $Co(asp)(D_2O)_3$ and $Co(asp)_2^{2-}$. Because of insufficient solubility spectra were not obtained for $Co(dien)_2^{2+}$. In Figure 5 the spectra of 1:1:1 (cobalt:dien:asp) mixtures are reported as functions of pD. The effect of temperature on a mixture containing a 1:1:1 mol ratio of these species at constant pD is shown in Figure 6. Spectral assignments are tabulated in Table I.

Discussion

Figures 1 through 4 show spectra of cobalt(II) complexes containing only one of the ligands. The lack of resonances at the shift positions observed for the homogeneous complexes, the appearance of peaks at new positions in the high pD solutions of 1:1:1 mol ratios and the differences in pD and temperature dependences are the principle evidence for the preferential formation of the heterogeneous complex under these conditions. The aspartic acid pD dependence is easily explained on the basis of a solution whose composition is a mixture of $Co(asp)(D_2O)_3$ and $Co(asp)_2^{2-}$ with the relative amounts of each of the species dependent on the pD of the solution. The pD dependence observed for the formation of the aspartic acid complexes indicates some protonation of the aspartic acid ad pD's below 7. Examination of solutions containing 1:1 mol ratios and methylene deuterated aspartic acid confirm the spectral assignments given in Table I. Since aspartic acid, by virtue of its geometry, can only coordinate facially, the structure of the 1:1 and 1:2 Co:asp complexes is clear. The only question which needs to be answered concerning the structure of the asp complexes in solution is whether or not all three potential ligand coordinating sites are actually coordinated to the cobalt. This question can be answered by consideration of the effect coordination of the second carboxylate ($-CH_2CO_2^-$) will have on the appearance of the spectrum. Namely, if the carboxylate does not coordinate the methylene protons should appear as a single average resonance because of rapid rotation about single bonds. That the carboxylate is coordinated at least part of the time is demonstrated by the appearance of separate resonances for each proton in the asp; the non-equivalence of the methylene protons being due to coordination. A similar argument has been used to show ethereal and alcoholic oxygen bonding in a variety of cobalt(II) complexes [14]. Thus, the data in Figure 1 show that, over the pH range studied, all three coordinating groups of the asp are coordinated in both Co(asp)-

$(D_2O)_3$ and $Co(asp)_2^{-2}$ for a significant fraction of the time. Obviously, since there is a pD dependence, there must be some fraction of time when one of the carboxylates is uncoordinated. Unfortunately, it is not possible to determine from these data the fraction of time that the asp is tridentate. It is clear from the slight resonance shifts with pD, that the amount of tridentate coordination increases at higher pD values; above pD 7.5 the spectra are essentially pD independent.

Dien is a more complex ligand than asp because it can coordinate in both facial and meridonal geometries when all three amine groups are utilized for bonding. Since facial ⇌ meridonal isomerization can be fast on the nmr time scale [10], rapid interconversion of these two forms is possible leading to observation of an average spectrum. Since $Co(dien)_2^{2+}$ did not have adequate solubility for these studies, only $Co(dien)(D_2O)_3^{2+}$ was examined. The spectral temperature dependence shown in Figure 4 illustrates the consequences of facial ⇌ meridonal isomerization. At low temperature (–5 °C) the interconversion is slow enough that the spectra of the individual isomers are observed. In assigning the low temperature spectrum is it assumed, as previously reported for nickel(II) complexes, that the meridonal isomer does not undergo rapid $\delta \rightleftarrows \lambda$ conversion while the facial isomer does [10]. This assumes that the Co–N bond life time is long (on the nmr time scale) at –5 °C. This assumption leads to the prediction that the meridonal isomer spectrum should contain four non-equivalent proton signals and the spectrum of the facial isomer should consist of two non-equivalent proton signals. The low temperature spectrum of $Co(dien)(D_2O)_3^{2+}$ shown in Figure 4 has the six peaks required for slow facial ⇌ meridonal interconversion. Unfortunately, all six peaks are of roughly the same area (±10%) when measured with a planimeter. In view of the difficulty in obtaining reliable integrals with measurements of this type [14], it does not seem reasonable to make spectral assignments on the basis of the slight area differences observed. Thus the spectral assignment is uncertain. However, since each meridonal peak corresponds to two protons while each facial peak corresponds to four protons, one can say that there must be approximately twice as much of the meridonal form as there is the facial form. Thus, the percentages of facial and meridonal isomers calculated at –5 °C are approximately 33% and 67% respectively. Unfortunately, it is not possible to compute a theoretical room temperature spectrum from these data because the spectral assignments are uncertain, the percentage of each isomer is expected to be a function of temperature and cobalt(II) complexes often don't follow the Curie Law [15]. Thus, we are unable to determine the percentage of meridonal and facial forms in rapid equilibrium at room temperature. It is probably reasonable to assume, however, that it is not greatly different from the percentages reported above. The mechanism for facial ⇌ meridonal interconversion appears to involve bond breakage. This is shown by the pD dependence of the rate of interconversion. At low pD the rate of interconversion is much faster than at high pD, indicating the protonation of the ligand aids the process (see Figure 2).

Apparently, the cobalt(II)–nitrogen bond is rather labile even in the absence of significant deuterium ion concentration since, at 100 °C, the spectral pattern of all the complexes (except $Co(asp)(H_2O)_3$ and $Co(asp)_2^{2-}$) collapse indicating an averaging mechanism involving bond rupture (*i.e.* the nitrogens are inverted).

If one now examines the spectra shown in Figure 5 obtained from a 1:1:1 (Co:dien:asp) molar mixture at various pD's preferential formation of the mixed complex Co(dien)(asp) at high pH is readily apparent from the absence of peaks attributable at $Co(asp)(D_2O)_3$ or $Co(asp)_2^{-2}$ or $Co(dien)(D_2O)_3^{2+}$ and the appearance of a new set of peaks for the heterogeneous complex. For example, at pD 6.0 one can clearly see peaks assignable to the homogeneous ligand complexes $Co(asp)(D_2O)_3$, $Co(asp)_2^{2-}$ and $Co(dien)(D_2O)_3^{2+}$. As the pH is increased, however, the peaks of the homogeneous complexes decrease and new peaks, assignable to the heterogeneous product, appear. At a pD of 7.5 there is no longer any sign of the homogeneous complexes, the solution contains essentially only the mixed ligand complexes. It is possible to estimate the upper limit of homogeneous product which might exist but not be detected from the data shown. The signal to noise ratio is approximately 30:1. If one assumes that a signal equal to the noise level would be observable, there can not be more than 3% of the homogeneous product. Thus, the mixed complex is formed virtually exclusively (⩾97%). From these data one calculates that the mixed complex is more stable than a mixture of the bis complexes (above pD 7.5) by at least 4 Kcal mol^{-1}! Further increases in pD make only slight changes in the spectrum.

In view of the fact that the fraction of heterogeneous complex formed is a function of pD, the simple disproportionation reaction shown below is not an adequate description of the pD dependent processes as it does not involve deuterium ion:

$$2Co(AA)(dien) \rightleftharpoons Co(AA)_2^{2-} + Co(dien)_2^{2+}$$

The explanation is obvious, however, upon examination of Figure 5. In this figure it is seen that addition of deuterium ion results in the loss of the dien resonances from the mixed complex and appearance of peaks assignable to $Co(asp)(D_2O)_3$ and $Co(asp)_2^{-2}$ (*i.e.* the dien is removed by protonation and the resulting $Co(asp)(D_2O)_3$ complex equilibrates to form a mixture of $Co(asp)(D_2O)_3$, $Co(asp)_2^{2-}$ and $Co(D_2O)_6^{2+}$). This indicates that significant protonation of the amine occurs at a pD value of 6 for an apparent pK_b of approximately 8. Since pK_b of uncoordinated dien is approximately 4 [16], these data show that formation of the complex results in only about a four order of magnitude decrease in the basicity of the dien. This slight decrease in basicity suggests a weak cobalt–dien bond in spite of the large formation constant [16].

The spectrum of the mixed ligand complex is interesting. One observes that the eight dien protons are magnetically non-equivalent, while the three asp protons give rise to 3 broadened signals. This indicates that the aspartic acid portion of the complex is stereochemically non-rigid while the dien portion is not. The stereochemical non-rigidity can be easily explained as arising from rapid rotation of the asp fragment about the face of the coordination octahedron while the dien remains essentially stationary or by the presence of an uncoordinated arm of asp (*i.e.* one cobalt coordination site occupied by water). The presence of an uncoordinated ligand arm has been shown to lead to non-rigidity in other areas [13, 17]. In view of the previous cases involving uncoordinated ligand arms and studies of the interaction of oxygen with the mixed complexes [18] the latter explanation for the non-rigidity seems most reasonable. This interpretation is confirmed by the low temperature spectrum shown in Figure 6. At low temperature the aspartic acid portion of the spectrum changes drastically while the dien portion of the spectrum is essentially unaffected. At −14 °C the asp portion of the spectrum, which was 3 broad peaks at 34 °C, appears as nine moderately well resolved peaks while the eight peaks observed for dien at 34 °C remain virtually unchanged.

When the interchange is slow, one can see spectra from four different types of aspartic acid coordination: aspartic acid nitrogen *cis* to both terminal dien nitrogens, aspartic acid nitrogen *trans* to one terminal dien nitrogen, $CHCO_2^-$ coordinated, $CH_2CO_2^-$ coordinated. Analysis of the number of peaks expected from each of these isomers predicts that 10 aspartic acid peaks should exist at low temperature. These 10 aspartic acid peaks add to the 8 dien peaks for a predicted total of 18 peaks for the low temperature spectrum. In Figure 6, 17 peaks are seen (one is a shoulder on the water peak). The missing peak is most certainly not observed because of overlap with one of the other resonances.

It should not be inferred that $\delta \rightleftarrows \lambda$ conversion of the dien portion is necessarily slow (although it may be in this mixed complex). Because of the asymmetric nature of the asp ligand, rapid $\delta \rightleftarrows \lambda$ conversion of the dien portion will not result in complete averaging of the resonance positions.

Increasing the temperature leads to, of course, an increase in the rate of asp isomer interchange, but also to an increase in the rate of interconversion of dien protons. In fact, at 100 °C, the dien portion of the spectrum consists of two poorly resolved peaks (one due to NH_2–CH_2 and one due to CH_2–NH–CH_2) indicating rapid averaging of all the dien proton resonances. One can imagine three types of processes being responsible for the averaging of the dien resonances: rapid $\delta \rightleftarrows \lambda$ conversion, rapid rotation around the face of the octahedron or rapid removal and recoordination of dien. The former explanation seems reasonable (if the inherent differences referred to above are small) as it results in averaging of axial and equatorial differences while the second process does not and the third process requires rapid rupture of three cobalt–nitrogen bonds. The question which naturally arises though, is: why should $\delta \rightleftarrows \lambda$ conversion of dien be slow at 34 °C in these complexes? While it is tempting to invoIk some sort of intramolecular hydrogen bonding, such a picture is inconsistent with the observed rapid interconversion of the aspartic acid side of the molecule unless the hydrogen bonding involves the coordinated water and the dien N–H's. If such were the case, however, slow $\delta \rightleftarrows \lambda$ conversion should be observed in Co(dien)-$(D_2O)_3^{2+}$, but is not. It is possible that the observed magnetic non-equivalences arise from a conformational preference rather than slow conformational interchange, but this explanation suffers from two problems: first, it is not clear why there should be a conformational preference of this magnitude (~17 Kcal mol^{-1} at 34 °C) and, second, it is not reasonable that this conformational preference would completely disappear at higher temperatures. The complete averaging observed at high temperature requires complete removal of any energy difference between the conformations and rapid exchange of protons between the possible environments. These requirements seem most consistent with a nitrogen inversion process. Although we cannot state with certainty that the high temperature process is nitrogen inversion (which requires Co–N bond rupture), rapid rupture of cobalt–nitrogen bonds at 100 °C has been observed previously [14, 17], and appears to be operative in the facial meridonal isomerization. Thus, it seems that the dien protons spectral differences are averaged by a bond rupture mechanism which leads to rapid nitrogen inversion.

This mixed ligand complex represents an interesting case of unexpected stability for a mixed ligand complex. It is not obvious why the heterogeneous complex should be so much more stable, but it can be clearly shown that it is.

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