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Appendix. Note on the Ligand Field Arising from Coordination of an Unsymmetrical, Planar, Conjugated Bidentate Moiety

The $\pi\perp$ perturbation from an unsymmetrical, planar, conjugated bidentate moiety LL′ can be treated analogously to that of a symmetrical one by using the methods of the present paper. If the plane of the ligand is chosen to be the *ZX* plane, then again the $\pi\perp$ orbitals of the bidentate overlap only with the d orbitals (yz) and (xy). However, because of the loss of the 2-fold axis of the bidentate moiety, a phase-based classification of the ligand $\pi\perp$ orbitals into ψ and χ no longer coincides with different symmetry species. In other words, both ψ and χ orbitals are $A''(C_{1h})$, where C_{1h} is the point group defined by the central ion and the planar unsymmetrical bidentate ligand. Therefore, (yz) and (xy) will in general no longer be eigenfunctions in an AOM sense, and the matrix of $\hat{A}(\pi\perp)$ will contain a nonvanishing, nondiagonal element so that its form will be

$$\begin{array}{cc} \hat{A}(\pi\perp) & \begin{matrix} (yz) & (xy) \end{matrix} \\ \begin{matrix} (yz) \\ (xy) \end{matrix} & \begin{bmatrix} e_{\psi LL'} & e_{\psi\chi LL'} \\ e_{\psi\chi LL'} & e_{\chi LL'} \end{bmatrix} \end{array} \tag{67}$$

where $e_{\psi LL'}$, $e_{\chi LL'}$, and $e_{\psi\chi LL'}$ are independent, radial parameters to be found empirically.

We have already mentioned that the numerical values of the independent parameters $e_{\psi LL}$ and $e_{\chi LL}$, required in the case of a symmetrical bidentate moiety, will not be easy to obtain from spectral and magnetic data. This, of course, will be even more true when yet another parameter has to be extracted from experiment.

We want to further comment on the three independent parameters in the energy matrix (67). The sum of the squares of the elements of a matrix is invariant to a unitary transformation. Therefore, this sum is for the matrix (67) independent of the way in which LL′ is placed within the *ZX* plane. However, this is not true for the individual parameter values. There will certainly be a placement of LL′ for which the nondiagonal element $e_{\psi\chi LL'}$ will be zero, but this placement is not determined by symmetry and therefore will remain unknown until a full parametrical analysis of experimental results has been made on the basis of an arbitrarily chosen placement. Therefore, there will always remain three independent empirical parameters even if one of them may be chosen as an angle[1] instead of an energy parameter.

Our conclusion is that there is little hope that an AOM treatment of an unsymmetrical conjugated bidentate will be useful. Therefore, regarding this type of ligands, the implications of the CDV work[1,2] and especially that regarding parametrization of their perturbation by only two parameters, should be reexamined carefully.

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Steric Constraints inside the Metal-Coordination Sphere As Revealed by Diastereotopic Splitting of Methylene Protons

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A solution NMR study performed on [$PtCl_2$(ethambutol)] [ethambutol = *N,N′*-bis(1-hydroxy-2-butyl)ethylenediamine] has shown that the nitrogen substituents [$-CH(CH_2OH)(CH_2CH_3)$] conform themselves so as to direct the least bulky side (the tertiary hydrogen atom) toward the cis chlorine ligand, and this appears to be the most compelling steric requirement. As a consequence, the hydroxymethyl and ethyl radicals (R) are directed one inward and the other outward with respect to the chelating moiety. The radical directed toward the chelate ring deeply interacts with it, and as a consequence, the methylene protons of this radical exhibit, in the NMR spectrum, a diastereotopic splitting the average value of which is 0.45 ppm in the case of hydroxymethyl and 0.80 ppm in the case of ethyl.

Introduction

The stereochemistry of complexes with chelate ligands has been widely investigated in the past. As far as the chelate ring of ethylenediamines is concerned, it has been found that this is markedly puckered in an essentially strain-free structure.[1] In solution, by internal rotation, the skew conformation of the N–C–C–N chain can change to another skew form, which is a reflection of the original; as a result of this process axial bonds are transformed into equatorial bonds and vice versa so that, on the average, the chelate ring is coplanar with the coordination plane and the substituents on the chelating moiety are equally displaced above and below this plane.

Another feature of the complexes with N-substituted ethylenediamines is that, in the solid state, the N substituents are rotated in such a way as to direct the least bulky side toward the cis metal ligand, and this appears to be the most compelling steric requirement.[2] The present investigation has shown that the same situation occurs also in solution and it brings about very peculiar and noticeable features.

Results and Discussion

Ethambutol is a symmetrically substituted ethylenediamine [*N,N′*-bis(1-hydroxy-2-butyl)ethylenediamine] and can be synthesized in three isomeric forms having absolute configurations *R,R*, *S,S*, and *R,S* at the asymmetric carbons. It has a tuberculostatic activity and has been in clinical use since the mid-1960s.[3]

Optically pure isomers of the diamine were prepared by the method of ref 3, and by reaction with [$PtCl_2(DMSO)_2$], in methanol, the complexes [$PtCl_2$(ethambutol)] were obtained in

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Table I. Analytical Data and Properties of *N,N'*-Bis(1-hydroxy-2-butyl)ethylenediamine (Ethambutol) and Corresponding Platinum Complexes

compound	isomer[a]	formula	% yield[b]	anal. % found (% calcd) C	H	Cl	N	α_D,[c] deg
ethambutol·2HCl	*R,R*	$C_{10}H_{26}N_2O_2Cl_2$	48	(43.3)	(9.4)	(25.6)	(10.1)	−6.8
				43.2	9.5	25.7	9.9	
	S,S		45	43.5	9.7	25.5	10.1	+6.8
	R,S		25	43.1	9.5	25.5	10.0	
[PtCl$_2$((*R,R*)-ethambutol)]	**1**	$C_{10}H_{24}N_2O_2Cl_2Pt$	80	(25.5)	(5.1)	(15.1)	(6.0)	−8.4
				25.0	5.1	15.0	5.6	
[PtCl$_2$((*S,S*)-ethambutol)]	**4**		80	25.1	5.1	14.8	5.7	+8.4
[PtCl$_2$((*R,S*)-ethambutol)]	**7,8**		30	25.6	5.1	14.9	5.6	
	9		40	25.4	5.0	14.6	5.5	

[a] Complex isomers are indicated with reference to Chart I. [b] Yields are based on the total possible species. [c] Specific optical rotations are for solutions 10% in water in the case of ethambutol·2HCl and for solutions 0.5% in DMSO in the case of [PtCl$_2$(ethambutol)]. All measurements were performed at 20 °C.

Table II. Proton Chemical Shifts (δ, Downfield from SiMe$_4$)[a] of Free and Complexed *N,N'*-Bis(1-hydroxy-2-butyl)ethylenediamine (Ethambutol)[b]

compound	solvent	chem shift −CH$_3$	−CH$_2$Me	−CH$_2$−N	−CH	−CH$_2$−O	−OH	−NH
(*R,R*)- and (*S,S*)-ethambutol·2HCl	D$_2$O	0.90 (7)	1.66	3.44	3.21	3.76		
(*R,S*)-ethambutol·2HCl	D$_2$O	0.88 (7)	1.65	3.43	3.20	3.75		
1, 4	DMSO-d_6	0.87 (7) {3}	1.72 {2}	2.50 {2}	3.05 {1}	3.62 {2}	4.78 (5) {1}	6.08 [65] {1}
		0.94 (7) {3}	1.61 {1}	2.71 {2}	3.20 {1}	3.81 {1}	4.93 (5) {1}	6.27 [65] {1}
			2.34 {1}			4.28 {1}		
7, 8	DMSO-d_6	0.86 (7) {3}	1.50 {1}	2.24 {2}	3.22 {2}	3.52 {2}	4.76 (5) {1}	5.88 [65] {1}
			1.76 {1}					
		0.92 (7) {3}	1.44 {1}	2.58 {2}		3.89 {1}	4.92 (5) {1}	6.18 [70] {1}
			2.38 {1}			4.34 {1}		
9	DMSO-d_6	0.92 (7) {6}	1.60 {2}	2.57 {4}	3.14 {2}	3.64 {4}	4.80 (5) {2}	6.06 [65] {2}
			2.26 {2}					

[a] Values of *J*(H−H) (in parentheses) and *J*(Pt−H) (in brackets) in Hz are given when assignable. Integral values are given in braces. [b] Complex isomers are indicated with reference to Chart I.

good yield. Since upon coordination to platinum the two nitrogen atoms also become stable chiral centers,[2,4] even when one starts with an optically pure isomer of the diamine several isomeric complexes can be formed [**1**–**3**, **4**–**6**, and **7**–**10** starting from (*R,R*)-, (*S,S*)-, and (*R,S*)-ethambutol respectively; Chart I].

We sought the conditions for the obtainment of pure isomeric species, and by digestion of the mixture of isomers obtained in the formation reaction (at 80 °C, under stirring and in contact with the mother liquor), complete conversion into one isomer was observed in the case of (*R,R*)- and (*S,S*)-ethambutol. In the case of (*R,S*)-ethambutol, after digestion at 80 °C, the solid was still a mixture of isomers and by fractional crystallization from water or from DMF/MeOH two species were isolated.

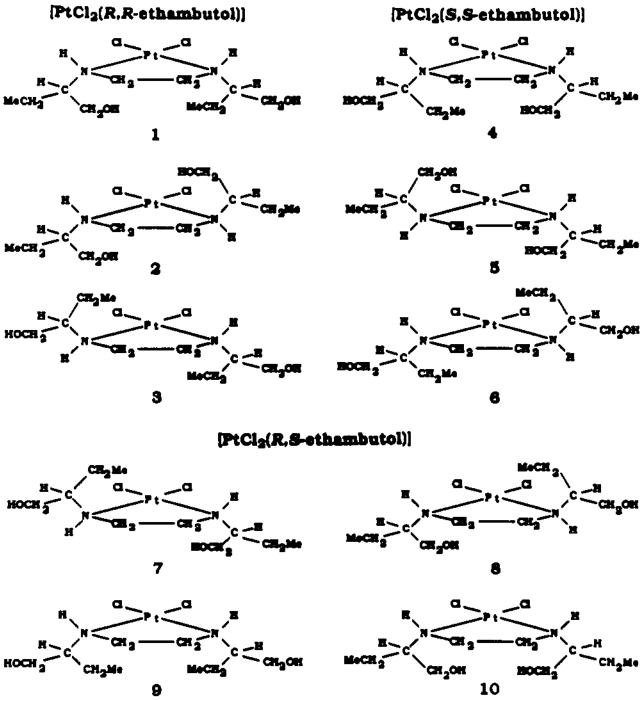
All compounds had similar elemental analyses (Table I) but different structures which could be inequivocally established on the basis of the ^{1}H NMR data (Table II).

The pure complex isomers isolated with either (*R,R*)- or (*S,S*)-ethambutol had identical NMR spectra. They showed two signals for each type of protons indicating that each half of the ligand molecule was in a different magnetic environment. This is in accord with only one of the three structures allowed for each of them [**1** for (*R,R*)-ethambutol and **4** for (*S,S*)-ethambutol, respectively] since the other two possible structures have a C_2 symmetry through which the halves of the ligand molecule are equivalent.

An unexpected feature of the spectra was that the methylene protons of one hydroxymethyl and one ethyl radical gave two multiplets each. The separation between the two multiplets was 0.46 and 0.74 ppm, respectively. On the contrary, a single narrow multiplet was present for the methylene protons of each remaining hydroxymethyl and ethyl radical.

With reference to Chart I, if we assume that the 1-hydroxy-2-butyl groups are forced to direct the less hindering tertiary hydrogen atom toward the cis chlorine ligands (so to reduce the steric interactions inside the coordination sphere of platinum),

Chart I. Schematic Drawing of the Different Stereoisomers of [PtCl$_2$(ethambutol)]



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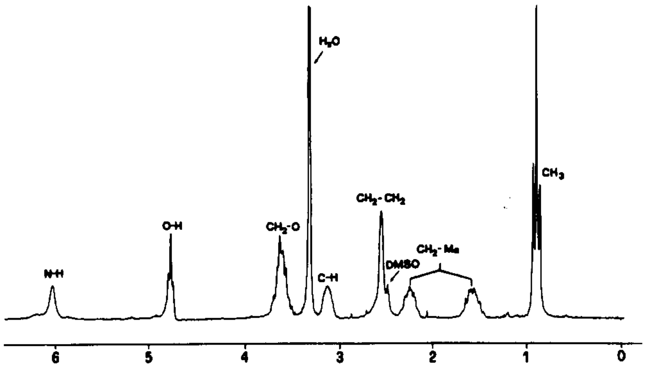

Figure 1. ^{1}H NMR spectrum of a solution of **9** in DMSO-d_6 showing the diasterotopic splitting of the $-CH_2Me$ methylene protons.

the other two radicals attached to the tertiary carbon atom (hydroxymethyl and ethyl) will be directed one inward and the other outward with respect to the chelating moiety. The former will interact strongly with the $N-CH_2-CH_2-N$ chain,[5] and this could be the cause of a remarkable diastereotopic inequivalence of the CH_2 protons.[6] Structures **1** and **4** have indeed one hydroxymethyl and one ethyl radical directed toward the en bridge, and according to the above hypothesis, only these will experience a great diasterotopic splitting of the methylene protons.

One of the two isomers isolated for $[PtCl_2((R,S)\text{-ethambutol})]$ exhibited, in the NMR spectrum, two signals for each type of protons, which is again an indication that the halves of the ligand molecule are in different magnetic environments. This is the case for species **7** and **8**, which, being enantiomorphic, have identical NMR spectra. As observed in compounds **1** and **4**, also in this case the NMR spectrum showed a remarkable inequivalence of the methylene protons (0.44 ppm) for only one of the two hydroxymethyl radicals; similarly, the diastereotopic inequivalence of the methylene protons was great (0.92 ppm) for one ethyl radical and small (0.24 ppm) for the other. Indeed in structures **7** and **8**, only one hydroxymethyl and one ethyl radical are directed toward the en chain and hence will exhibit enhanced diastereotopic inequivalence of the methylene protons. The small inequivalence of the methylene protons observed in this case also for the ethyl radical directed outward with respect to the chelate ring can be due to the different configuration of the diamine ligand, which is trans in **7** and **8** but cis in **1** and **4**.[7]

The latter isomer isolated for $[PtCl_2((R,S)\text{-ethambutol})]$ exhibited one signal for each type of protons in accord with the halves of the ligand molecule being in equivalent magnetic environments. This is the case for isomers **9** and **10**, both of which have a C_s symmetry. However, two multiplets separated by 0.65 ppm were observed for the methylene protons of the ethyl radicals while a single, rather narrow, multiplet was observed for the methylene protons of the hydroxymethyl radicals (Figure 1). This is in accord with structure **9** in which only the two ethyl groups are brought about the en bridge and therefore will exhibit enhanced diastereotopic inequivalence of the methylene protons.

In conclusion, the observation, made in the solid state, that in platinum complexes with N-substituted ethylenediamines the *N*-substituents ($-CR^1R^2R^3$) conform themselves as to direct the least bulky R toward the cis metal–ligand moiety applies also in solution. This causes the other two groups to be directed one inward and the other outward with respect to the metallacycle; the former though deeply interacts with it and, in the case under investigation, exhibits enhanced diastereotopic inequivalence of the methylene protons. This phenomenon is general and is observed if the ligand has either the cis (as in **1**, **4**, and **9**) or the trans conformation (as in **7** and **8**).

These results are promising for a better understanding of the stereochemistry and sterical constraints inside the coordination sphere of metal complexes with chelate ligands, and in the particular case of platinum complexes with diamines, they can have some relevance to the biochemistry of these molecules.

Materials and Methods

Commercial reagent grade chemicals were used without further purification.

N,N'-Bis(1-hydroxy-2-butyl)ethylenediamine (ethambutol is the generic name reserved by the Lederle Laboratories Division of the American Cyanamid Co.) has been prepared by starting from 2-amino-1-butanol and 1,2-dichloroethane.[3] It is obtainable in one meso (*S,R*) and two enantiomorphic forms (*R,R* and *S,S*).

If one starts with (*R*)- and (*S*)-2-amino-1-butanol, the corresponding enantiomorphic forms of ethambutol (*R,R* and *S,S*) are obtained as pure optical isomers. In a typical experiment, 1,2-dichloroethane (3.0 g, 0.03 mol) and an excess of (*S*)-2-amino-butanol (from commercial *rac*-2-aminobutanol by the tartrate resolution procedure of Radke et al.)[8] (10 g, 0.11 mol) were heated to 100 °C for 1 h. The solution was then cooled to room temperature, neutralized with alcoholic HCl, and concentrated under vacuum. The residue was crystallized from ethanol to give a 50% yield of pure (*S,S*)-*N,N'*-bis(1-hydroxy-2-butyl)ethylenediamine, (*S,S*)-ethambutol.

The (*R,S*)-N,N'-bis(1-hydroxy-2-butyl)ethylenediamine, (*R,S*)-ethambutol, was obtained by heating to 100 °C for 1 h a solution of *rac*-2-aminobutanol in excess 1,2-dichloroethane. The separation of the meso isomer from the two enantiomeric forms was accomplished by fractional crystallization from ethanol in which the meso dihydrochloride is less soluble.

$[PtCl_2(DMSO)_2]$ was prepared by the method of Kukushkin et al.[9] and used as starting material for the preparation of the ionic species $[PtCl(DMSO)(\text{ethambutol})]Cl$ according to the method of Romeo et al.[10] Thermal decomposition of the ionic species in the presence of chloride ion afforded the desired neutral complex $[PtCl_2(\text{ethambutol})]$.[2]

In a typical experiment, 1 mmol of $[PtCl_2(DMSO)_2]$ suspended in methanol (40 mL) was treated with 1 mmol of free amine in the same solvent (20 mL) and stirred until a clear solution was formed. After being cooled to 5 °C and filtered, the solution was concentrated under vacuum and the residue treated with an aqueous solution of lithium chloride to separate a yellow solid, which was a mixture of isomers (**1–3**, starting from (*R,R*)-ethambutol; **4–6** starting from (*S,S*)-ethambutol; and **7–10** starting from (*R,S*)-ethambutol; Chart I). If the solid and the mother liquor are heated to 80 °C for 5 h and then cooled to room temperature, the precipitate that is left is observed to be a pure single isomer in the case of (*R,R*)- and (*S,S*)-ethambutol (isomers **1** and **4** of Chart I, respectively) but still a mixture of isomers in the case of (*R,S*)-ethambutol. In the latter case, it has been possible to isolate pure single isomers by fractional crystallization from water or DMF/MeOH. One isomer (**9** in Chart I), being less soluble, precipitates preferentially from the solution; a second compound (corresponding to a racemic mixture of **7** and **8** in Chart I) can be recovered from the mother liquor by evaporation of the solvent under vacuum. Elemental analyses and NMR data are given in Tables I and II, respectively.

Physical Measurements. IR spectra in the range 4000–400 cm^{-1} were recorded as KBr pellets; spectra in the range 400–200 cm^{-1} were recorded as polythene pellets on Perkin-Elmer 283 and FT 1600 spectrophotometers. ^{1}H NMR spectra were obtained with Varian XL 200 and Bruker AM 250 spectrometers. Polarimetric determinations were performed with a Perkin-Elmer 241 MC instrument.

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