90. Stereoselectivity in Reactions of Metal Complexes IX[1])

Stereoselective Formation of Cobalt(III) Complexes with New Linear Pentadentate Ligands

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Summary

The synthesis of cobalt(III) complexes with the new linear pentadentate ligands meso- and racemic 2,6-bis(3-carboxy-1,2-dimethyl-2-azapropyl)pyridine (**1a** and **1b**), respectively, and 2,6-bis[(3*S*)-3-carboxy-4-methyl-2-azapentyl]pyridine (**2**) are described. Only one of the different possible isomers is obtained from each ligand. The structure of the complexes has been assigned on the basis of their ^{1}H-NMR and CD spectra. The structure of the aqua-cobalt(III)-**1a** and the aqua-cobalt(III)-**1b** has been confirmed by X-ray analysis. Partial resolution of optical antipodes of the aqua-cobalt(III)-**1b** was achieved by column chromatography and a tentative assignment of their absolute configuration is made.

Introduction. – Multidentate ligands react frequently with metal ions by the formation of several geometrical isomers. By the introduction of special structural features in the framework of these ligands, certain of these isomers may be favored or even formed exclusively. Reactions with these ligands are then called stereospecific. When the selection occurs between diastereoisomers, the reaction is called diastereoselective. The knowledge of the factors leading to diastereoselectivity are of special interest in order to perform asymmetric reactions.

Between the great number of ligands reacting in a diastereoselective way, linear pentadentate ligands are not very frequent, but have the advantage of leaving only one coordination site free in an octahedral coordination sphere. Therefore, such ligands may be particularly appropriate for the study of the stereoselectivity of inner sphere electron transfer reactions. Some results in this field will be presented in a following paper.

Four geometrical isomers may be formed with a linear pentadentate ligand, three of them existing as optical antipodes [2].

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[1]) Part VIII, see [1].

[2]) Part of Ph. D. thesis of *Ph. P.*, Université de Neuchâtel.

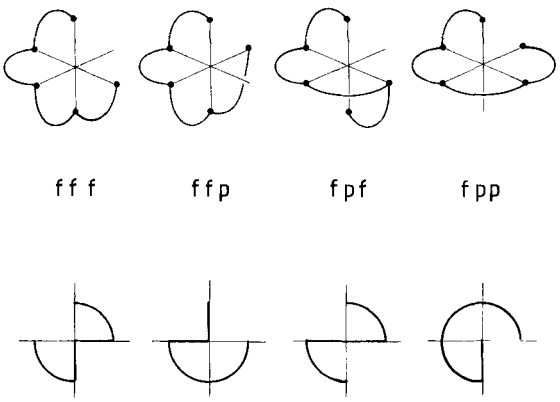


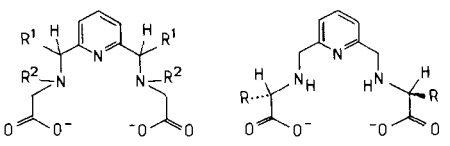
Fig. 1. *Geometrical isomers of octahedral complexes formed with linear pentadentate ligands*

The four isomers are characterized by the facial (f) or peripheric (p) arrangement of the three pairs of adjacent chelate rings and show a typical pattern, when the observer is looking towards the metal ion from the free coordination site *(Fig. 1)*.

For reasons presented in [3] we have choosen the (fpf) arrangement showing C_2-symmetry for the present study of stereoselective formation of inert octahedral cobalt(III) complexes.

To ensure the selection of the basic (fpf) geometry, a central pyridine unity substituted in the 2,6-positions is used. Such an arrangement must coordinate in a peripheric way for obvious steric reasons. On the other hand, the facial coordination of lateral chelate rings is strongly favored by the presence of a saturated N-atom as the coordinating atom connecting two five-membered chelate rings. It is well-known that a peripheric arrangement of such groups is strained and is only found in cases where the facial arrangement is not possible [4]. The chirality of the complex can now be fixed by the introduction of substituents into the ligand and by choosing a given chirality of the asymmetric C-atoms. These asymmetric centers should then fix the absolute configuration of the two tetrahedrally coordinated N-atoms. The substituents may be introduced either into the chelate rings formed by the pyridine unity and the tetrahedral N-atoms (type **I**) or into the chelate rings formed by the amino-carboxylate groups (type **II**).

Scheme



type **I** type **II**

1 $R^1 = R^2 = CH_3$ **2** $R = CH(CH_3)_2$
1a (1*R*,1′*S*) = *meso*-form
1b (1*RS*,1′*RS*) = racemic form

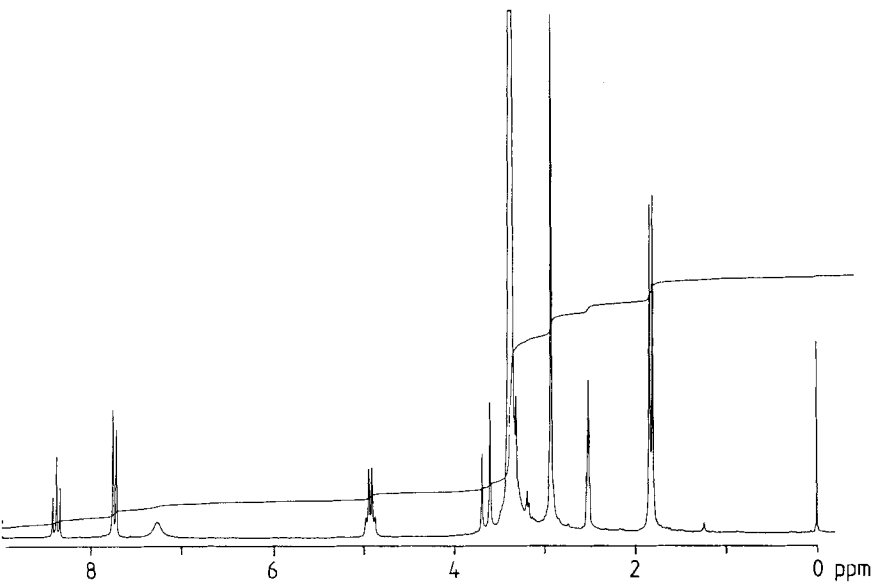


Fig. 2. *^{1}H-NMR Spectrum of aqua(2,6-bis[(1RS,1'RS)-3-carboxy-1,2-dimethyl-2-azapropyl]pyridine)cobalt(III) hexafluorophosphate* (racemic complex; 200 MHz, DMSO)

Results and Discussion. – The pentadentate ligand 2,6-bis[3-carboxy-1,2-dimethyl-2-azapropyl]-pyridine (**1**) exists in a *meso*- (**1a**) and in a racemic form (**1b**). Attempts to separate the two isomers of the free ligand failed. However, when the cationic aqua-cobalt(III) complex of the ligand mixture was crystallized as hexafluorophosphate (or as perchlorate), two clearly distinct crystalline forms were obtained; one consists of fine red needles and contains the racemic form of the ligand; the other is obtained as dark red plates and represents the complex containing the *meso*-form of the ligand. The two complexes were identified by their ^{1}H-NMR spectrum, represented in *Fig. 2* for the racemic and in *Fig. 3* for the *meso*-form.

As seen in these spectra, almost all the signals are doubled in the *meso*-form due to a different arrangement of the two halves of the ligand molecule in the complex, whereas the racemic form shows two identical halves, indicating perfect C_2-symmetry in the ligand arrangement.

The conclusions drawn from the ^{1}H-NMR spectra were finally confirmed by an X-ray structural analysis of the two solids; their molecular structure is shown in *Fig. 4* [5].

From these results it follows that in all the cases of complexes with this type of ligand, the basic geometry is the same, independent of the steric influences of the substituents. Any isomer showing the two carboxylate groups in *cis*-position (fpp structure; *cf. Fig. 1*) can be excluded. In the complex formed by the *meso*-ligand, the two lateral chelate rings are therefore not differentiated by their relative geometrical arrangement with respect to the rest of the molecule, but only by the relative position of the substituents on the two central chelate rings. In one of these the two neighbouring methyl groups are in an almost eclipsed conformation, whereas in the complex

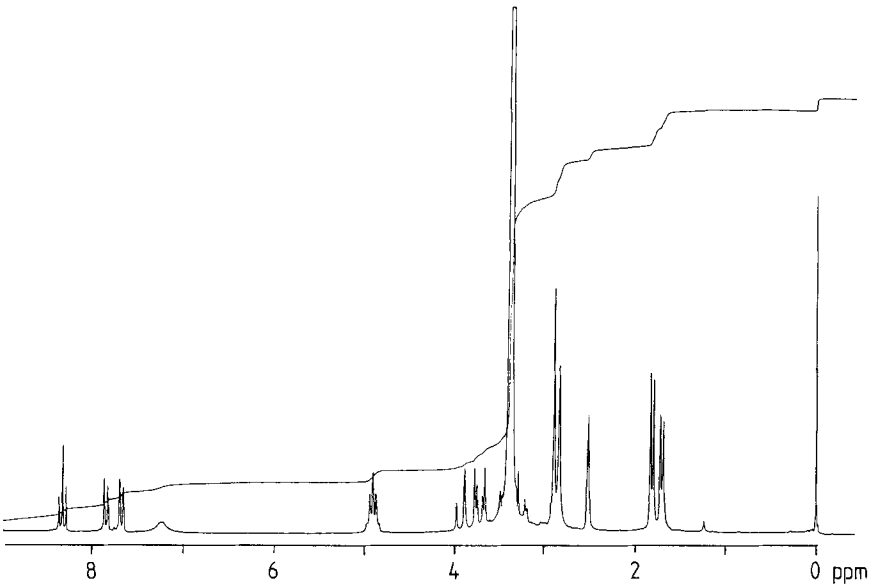


Fig. 3. *^{1}H-NMR Spectrum of the aqua(2,6-bis[(1R,1'S)-3-carboxy-1,2-dimethyl-2-azapropyl]pyridine)cobalt(III) hexafluorophosphate* (*meso*-complex; 200 MHz, DMSO)

with the racemic ligand both chelate rings have their substituents in the most stable staggered arrangement. The complex will therefore assume a configuration of predictable chirality, when the chirality of the asymmetric C-atoms is given.

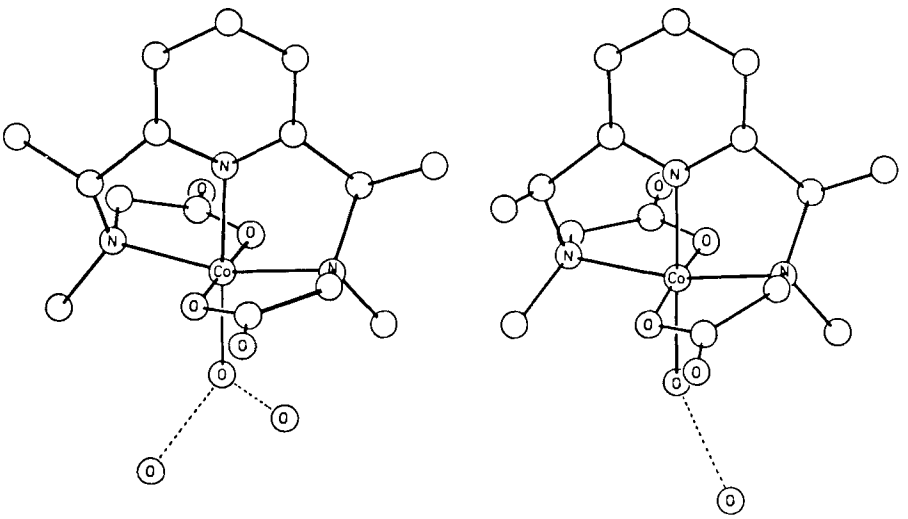


Fig. 4. *Molecular structures of the aqua(2,6-bis[(1RS,1'RS)-3-carboxy-1,2-dimethyl-2-azapropyl]pyridine)-cobalt(III) hexafluorophosphate* (**1b**, racemic complex) *and of the aqua(2,6-bis[(1R,1'S)-3-carboxy-1,2-dimethyl-2-azapropyl]pyridine)cobalt(III) hexafluorophosphate* (**1a**, *meso*-complex)

For the purpose of future studies, we were mainly interested by the complex containing the racemic ligand and the first problem which arose, was the separation of the complex into its optical antipodes. This separation could be achieved by elution chromatography of the complex using potassium antimonyltartrate as the optically active eluent, and by precipitation of the racemic perchlorate from the partially enriched fractions. *Fig. 5* shows the CD spectra of the solutions of fractions of the highest optical activity obtained. When these CD spectra are compared with the corresponding spectrum of the aqua-(2,6-bis[(3*S*)-3-carboxy-4-methyl-2-azapentyl]pyridine)cobalt(III) the absolute configuration *Λ*-aqua-(2,6-bis[(1*S*,1′*S*)-3-carboxy-1,2-dimethyl-2-azapropyl]pyridine)cobalt(III) may tentatively be attributed to the complex showing a negative CD band at 530 nm (curve *a*, *Fig. 5*).

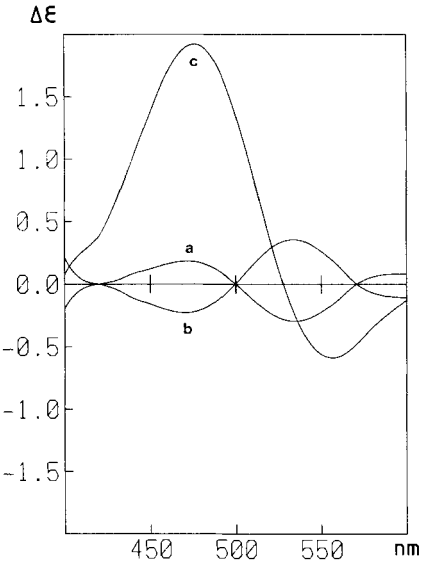


Fig. 5. *CD spectra of:* a) *Λ-aqua(2,6-bis[(1S,1′S)-3-carboxy-1,2-dimethyl-2-azapropyl]pyridine)cobalt(III) perchlorate,* b) *Λ-aqua(2,6-bis[(1R,1′R)-3-carboxy-1,2-dimethyl-2-azapropyl]pyridine)cobalt(III) perchlorate,* c) *Λ-aqua(2,6-bis[(3S)-3-carboxy-4-methyl-2-azapentyl]pyridine)cobalt(III) hexafluorophosphate.* Tentative attribution of the absolute configuration as discussed in the text.

As an example of ligands of type **II** we prepared the 2,6-bis[(3*S*)-3-carboxy-4-methyl-2-azapentyl]pyridine (**2**). The advantage of this type of ligand lies in the fact that only one isomer is obtained when an optically active amino acid is used as starting material. The cobalt(III) complex prepared from this ligand may exist in two diastereoisiomeric forms. They are shown in *Fig. 6* for the ligand with the (*S*,*S*)-configuration.

A tentative assignment of the absolute configuration of the compound obtained may be based on ^{1}H-NMR spectra. It is known that in cobalt(III) complexes of ethylenediamine diacetic acid, $[Co^{III}(EDDA)(en)]^+$, the methylene group in the amino-acid moiety shows different chemical shifts for the H_a (*exo*) and H_b (*endo*) proton (the signal for H_a appears at lower field than that for H_b due to the magnetic anisotropy of

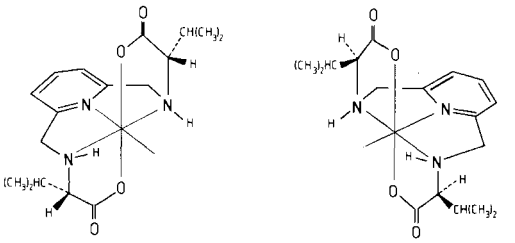


Fig. 6. *Possible diastereoisomeric forms of (2,6-bis[(3S)-3-carboxy-4-methyl-2-azapentyl]pyridine)cobalt(III) complex*

the C–N bond [6]). When one of the two types of protons is replaced by a substituent, the signal of the corresponding proton disappears, whereas the other remains almost unchanged. By this method *Cooke et al.* [6] attributed the absolute configuration of the $[Co^{III}(EDDP)(en)]^+$-isomers by comparison of their ^{1}H-NMR spectra with that of the $[Co^{III}(EDDA)(en)]^+$-complex. The partial spectrum (*1* of *Fig. 7*) shows the H_a-proton (3.6 ppm) and H_b-proton (3.3. ppm) of our aqua-cobalt(III)-**1b** complex; the spectrum (*2* of *Fig. 7*) corresponding to the aqua-cobalt(III)-**2** complex, exhibits only an H_b (3.2 ppm) proton signal indicating that the isopropyl group has replaced the H_a-proton. Therefore the cobalt(III)-**2** complex should have the *Λ-exo*-configuration when the ligand is obtained from the (*S*)-amino acid.

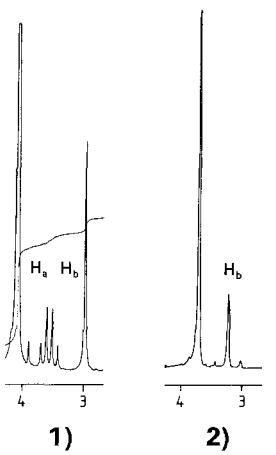


Fig. 7. *Partial ^{1}H-NMR spectra of:* 1) *aqua-cobalt(III)-***1b** *complex* (DMSO, 200 MHz) *after addition of D_2SO_4 in order to shift the water signal,* 2) *aqua-cobalt(III)-***2** *complex* (DMSO, 200 MHz)

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Experimental Part

1. *General.* Optical rotations were measured on a *Perkin-Elmer 241* polarimeter, UV and VIS spectra were measured on a *Uvikon 820* spectrophotometer and CD measurements were obtained from a *Jasco J-500* spectropolarimeter. ^{1}H-NMR spectra were recorded on a *Bruker WP200* at 200 MHz and on a *Hitachi Perkin-Elmer R24B* at 60 MHz.

2. *Syntheses.* – 2.1. *2,6-bis[1-(N-methylamino)ethyl)]pyridine* [7]. 2,6-Bis(acetyl)pyridine (25 g, 0.15 mol) [8] was added to 750 ml of an ethanolic solution of 33% CH_3NH_2. The mixture was hydrogenated for 10 h at r.t. and 4 atm. in the presence of Pt/C (10%) as catalyst. The solution was filtered on *Celite* and EtOH and excess CH_3NH_2 were evaporated under vacuum. The residual yellowish oil was distilled at 0.15 mm/Hg and the main fraction (b.p. 78–79°) collected. Yield: 18 g (60%). ^{1}H-NMR (200 MHz; $CDCl_3$): 1.7 (*d*, *J* = 7.5, 6H); 2.6 (*s*, 2H); 4.1 (*q*, *J* = 7.5, 2H); 7.5 (*d*, *J* = 7.5, 2H); 8.0 (*t*, *J* = 7.5, 1H).

The product, which constitues a mixture of the *meso*- and racemic form was used for synthesis without further purification.

2.2. *2,6-Bis(3-carboxy-1,2-dimethyl-2-azapropyl)pyridine.* A concentrated aq. solution of 10.28 g (0.11 mol) of chloroacetic acid was added slowly to a solution of 10 g (0.05 mol) of 2,6-bis[1-(*N*-methylamino)ethyl]pyridine in 100 ml of H_2O. The temperature of the mixture was raised to 50° and the pH of the solution maintaned at 9.5 by addition of 4M NaOH. When no further change of pH was observed the solution was diluted with H_2O to about 500 ml and introduced into a cation exchange column (*Dowex-50X8*; column length 30 cm; bed volume 400 ml; form H^+). The resin was washed with H_2O to neutrality and the product was eluted with 0.1M NaOH. The effluent solution was fractionated and the fractions were analyzed by acidimetric titration. The disubstituted product was contained in the nearly neutral fractions showing a buffer region around pH = 9. These fractions were evaporated under vacuum; 5 g (33% yield) of an oily product were obtained. All tentatives to crystallize the product failed and it was therefore used in its crude form for the synthesis of cobalt(III) complexes. ^{1}H-NMR (60 MHz; D_2O): 1.9 (*d*, *J* = 7.5, 6H); 3.1 (*s*, 6H); 3.9 (*s*, 4H); 4.7–5.2 (*m* unresolved, 2H); 7.3 (*d*, *J* = 7.5, 2H); 8.0–8.2 (*m* unresolved, 1H).

2.3. *2,6-Bis[(3S)-3-carboxy-4-methyl-2-azapentyl]pyridine.* 2,6-Bis(bromomethyl)pyridine (5.5 g, 0.02 mol) [9] were dissolved in 100 ml of EtOH and mixed with 100 ml of an aq. solution containing 4.9 g (0.04 mol) of (*S*)-valine. The pH of the mixture was fixed at 10 by addition of 2M NaOH. Further NaOH was added to maintain the pH at the initial value. When no more comsumption of NaOH occured, the mixture was neutralized with HCl and introduced into a cation exchange column. Washing and elution were performed as indicated in *1.2*. The fractions showing negative optical rotation in neutral solution were collected and evaporated under vacuum. The product solidified on the addition of Et_2O; yield 4.5 g (63%). The ligand was used without further purification for the synthesis of the corresponding aqua-cobalt(III) complex.

2.4. *Aqua[2,6-bis(3-carboxy-1,2-dimethyl-2-azapropyl)pyridine]cobalt(III) hexafluorophosphate.* To 300 ml of an aq. solution containing 11.2 g (0.036 mol) of 2,6-bis(3-carboxy-1,2-dimethyl-2-azapropyl)pyridine, prepared as indicated in *1.2*, 14 g (0.04 mol) of freshly prepared $Na_3[Co(CO)_3]\cdot 3\ H_2O$ and 2 g of active charcoal were added. The temperature of the mixture was maintained during 3 h at 50° and the pH of the solution was kept at 6.5 by addition of AcOH. The solution was filtered on *Celite* and the filtrate was poured into a cation exchange column *SPC-25 Sephadex* (Na^+). The column was washed with H_2O and the complex eluted with 1% NaCl. From the concentrated effluent solution, NaCl was eliminated by elution on *Sephadex G-10*. The salt-free solution was evaporated to dryness and the complex dissolved in the minimum amount of 10% NH_4PF_6. By slow evaporation of the solution, two types of crystals were formed. The complex containing the racemic ligand crystallized as fine red needles, whereas the complex containing the *meso*-ligand formes large dark red plates. The two crystalline forms were separated manually and both complexes were purified by recrystallization from 10% NH_4PF_6. The purity of the compounds were checked by ^{1}H-NMR measurements (*cf. Fig. 2* and *3*). Anal. calc. for rac-$[Co(C_{15}H_{21}N_3O_4)]PF6\cdot 2H_2O$ (565) (acidimetric titration: $pK_a = 8.3$; M = 569 g/mol): Co 10.40, C 31.87, H 4.81, N 7.43; found: Co 10.80, C 31.84, H 4.35, N 7.40.

2.5. *Chloro(2,6-bis(3-carboxy-1,2-dimethyl-2-azapropyl)pyridine)cobalt(III).* Racemic aqua(2,6-bis(3-carboxy-1,2-dimethyl-2-azapropyl)pyridine)cobalt(III) hexafluorophosphate (0.6 g) was dissolved in 50 ml of 37% HCl. The acid was slowly evaporated in an oil bath at 120° and the residue dissolved in EtOH. The solution of the chloro complex was again evaporated under vacuum to dryness. After dissolution in the minimum volume of hot EtOH, the complex crystallized on standing in the refrigerator. Violet crystals, yield 0.2 g (47%). Anal. calc. for $[Co(C_{15}H_{21}N_3O_4)Cl]$ (401): C 44.80, H 5.27, N 10.46; found: C 44.50, H 5.37, N 10.11.

2.6. *Aqua(2,6-bis[(3S)-3-carboxy-4-methyl-2-azapentyl]pyridine)cobalt(III) hexafluorophosphate.* The complex was prepared as indicated under *1.4* from 2,6-bis[(3*S*)-3-carboxy-4-methyl-2-azapentyl]pyridine. The product was characterized by ^{1}H-NMR, CD and visible spectra. ^{1}H-NMR (200 MHz; DMSO): 1.1 (*d*, *J* = 7.5, 6H); 1.2 (*d*, *J* = 7.5, 6H); 2.3 (*m* unresolved, 2H); 3.2 (*d*, *J* = 7.5, 2H); 4.4 and 5.1 (*AB*-system, *J* = 15, 2 2H); 6.2 (br. *s*, 2H); 7.5 (*s*, 2H); 7.7 (*d*, *J* = 7.5, 2H); 8.2 (*t*, *J* = 7.5, 1H). D_2O-addition leads to the disappearance of the signals at 7.5 and 6.2 ppm.

3. *Partial Resolution of the Racemic Aqua[2,6-bis(3-carboxy-1,2-dimethyl-2-azapropyl)pyridine]cobalt(III) Complex.* An aq. solution containing 1 g of the racemic complex was introduced into a *SP-C25 Sephadex* cation exchange column (Na^+, length 150 cm, diameter 3.5 cm). The fixed complex was eluted with 0.15M potassium (+)-antimonyltartrate. The eluted band was divided in two equal parts which were introduced separately into a cation exchange column (*Dowex-50*, Na^+). The column was washed with H_2O and the complex eluted with 2% NaCl. The concentrate effluent solution was freed from excess salt by passing through a *Sephadex G-10* column. The optical enrichment of the two fractions was controlled by the determination of the specific rotation. Values of $[\alpha]_{436} \approx 200°$ were obtained (calculated for the hexafluorophosphate, M = 565 g/mol).

Further enrichment could be achieved in the following way: the salt-free solution containing the enriched complex was evaporated to dryness under vacuum and the residue was dissolved in a small amount of 10% $NaClO_4$. In a first step almost racemic product crystallized, whereas the optically active compound remained in solution. When the specific rotation of the solution exceeded values of about $[\alpha]_{436} = 500°$ the optically active complex crystallized preferentially. This product was then recrystallized from 10% $NaClO_4$ solution as long as the optical activity of the crystallized solid and the mother solution were different. By this procedure, products showing specific rotations of $[\alpha]_{436} = +1050°$ and $-1010°$ ($c = 0.2$; H_2O; r.t.) were obtained.

REFERENCES

[1] *R. Deschenaux & K. Bernauer,* Helv. Chim. Acta *67,* 373 (1984).
[2] *M. Brorson, T. Damhus & C.E. Schäffer,* Inorg. Chem. *22,* 1569 (1983).
[3] *K. Bernauer, R. Deschenaux & T. Taura,* Helv. Chim. Acta *66,* 2049 (1983).
[4] *K. Bernauer,* Topics Curr. Chem. *65,* 1–35 (1976).
[5] *H. Stoeckli, L. Brehm, Ph. Pousaz, K. Bernauer & H.-B. Bürgi,* Helv. Chim. Acta, to be published.
[6] *L.N. Schoenberg, D.W. Cooke & C.F. Liu,* Inorg. Chem. *7,* 2386 (1977).
[7] *K. Bernauer & C. Soerensen,* Helv. Chim. Acta, to be published.
[8] *R. Lukes,* Collect. Czech. Chem. Commun. *24,* 36 (1959).
[9] *T. Baker,* J. Chem. Soc. *1958,* 3594.