50. Stereoselectivity in Reactions of Metal Complexes. V[1]).

Synthesis of Mixed-Ligand Cobalt(III) Complexes with (S)-Aspartic-N-monoacetic Acid and Different Amino-acids

by **Gérard Colomb** and **Klaus Bernauer**

Laboratoire de Chimie inorganique et analytique de l'Université de Neuchâtel, Avenue de Bellevaux 51, CH-2002 Neuchâtel

(24. IX. 76)

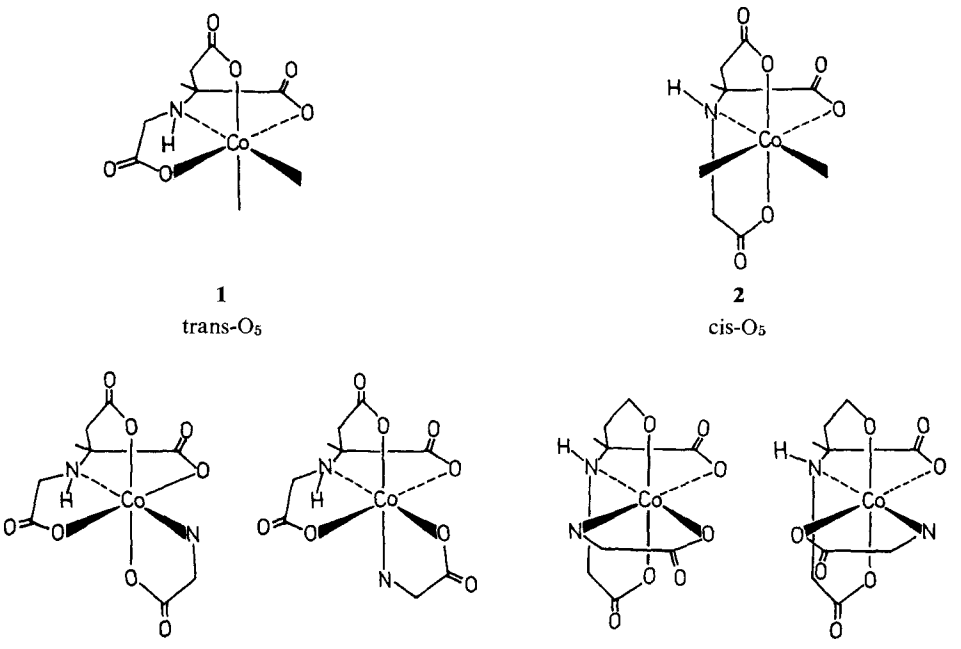
Summary

The synthesis of mixed-ligand cobalt(III) complexes with (*S*)-aspartic-N-monoacetic acid ((*S*)-AMA) and different amino-acids Na[Co((*S*)-AMA)(AA)] (AA = gly, (*R*)- and (*S*)-ala, val, phe, ser and leu) leads to a mixture of *cis*-N- and *trans*-N-isomers. These isomers are formed stereospecifically. VIS., CD.- and NMR.-spectra are reported and a proposal is given for the absolute configuration of all the compounds isolated.

Quadridentate branched ligands of the type aminopolycarboxylate have been studied from the point of view of the formation of labile complexes in solution. Stereoselectivity in the formation of mixed-ligand complexes with amino-acids has been reported [2] [3]. The corresponding inert complexes have not been described until recently [4].

In this work, we report some results concerning mixed-ligand cobalt(III) complexes containing (*S*)-aspartic-N-monoacetic acid, as a quadridentate ligand of known absolute configuration, and an amino acid as auxiliary chelating agent. Depending on the relative position of the carboxylate groups forming the five-membered chelate rings (O_5), the quadridentate ligand can adopt two different geometries in the coordination octahedron of the Co^{3+} ion (Fig. 1, structures 1 and 2), each of which determines the absolute configuration of the coordinated nitrogen atom, *S*(N)-*trans*-O_5 and *R*(N)-*cis*-O_5. The diastereomeric structures *R*(N)-*trans*-O_5 and *S*(N)-*cis*-O_5 can be disregarded, due to angular strain at the nitrogen atom site. With glycine as the secondary ligand, the number of possible isomers increases to four (Fig. 1, **3** to **6**) and with an amino acid containing an asymmetric carbon atom, eight isomers are finally possible, *i.e.* four pairs of diastereoisomers corresponding to the forms **3** to **6**.

[1]) Part IV: see [1].



1
trans-O_5

2
cis-O_5

3
trans-N, trans-O_5

4
cis-N, trans-O_5

5
cis-N, cis-O_5

6
trans-N, cis-O_5

Figure 1

Experimental part

1. Syntheses. – 1.1. (S)-*Aspartic*-N-*monoacetic acid* ((S)-*AMA*). Prepared according to [2], and recrystallized twice from water. Mol.-wt.: Calc.: 191.1; Found: 191 (acidimetric titration). $[\alpha]_{365}^{25} = +28°$ ($c = 0.22$ in H_2O).

$C_6H_9O_6N$ (191.1) Calc. C 37.66 H 4.74 N 7.32% Found C 37.65 H 4.84 N 7.35%

1.2. *Sodium* (S)-*aspartato*-N-*monoacetato-glycinatocobaltate(III)* (*Na*[*Co*((S)-*AMA*)gly] · 2 H_2O). A mixture of 5 mmol of freshly prepared $Na_3[Co(CO_3)_3] \cdot 3H_2O$, 5 mmol of (*S*)-AMA, 5 mmol of glycine and 0.25 g active charcoal is placed in 100 ml of water and heated with stirring at 55° for 3 h. After cooling, the charcoal is filtered off and one half of the filtrate is poured into an anion-exchanger column (Dowex 1-X4, 200–400 mesh, Cl^- form; h = 25 cm, ⌀ = 2 cm). Cationic and uncharged species are washed out with water. Three main bands appear upon elution with 0.1 M $CaCl_2$: E-1 (red), E-2 (violet, clearly separated from E-1) and E-3 (violet again). The proportional amounts contained in each band are determined spectrophotometrically. Further purification is obtained by passing each of the three fractions through a column of Sephadex G 10 (h = 125 cm, ⌀ = 4 cm)[2]). Each band is then passed separately through a cation exchanger column (Dowex 50-X8, 200–400 mesh, H^+ form) to eliminate the remaining Ca^{2+}. The eluate is evaporated to dryness and the free acid H[Co((*S*)-AMA)gly] · H_2O is dried in a vacuum dessiccator over KOH. Absorption spectra were measured before and after evaporation and showed no decomposition of the products. The free acids are converted to the sodium salts on a cation exchanger (Dowex 50-X8, 200–400 mesh, Na^+ form). Weighed samples (*ca.* 25 mg) of the sodium salts are dissolved in 10 ml deionized-distilled

[2]) No new products could be detected, but this fairly rapid (2–4 h) purification step eliminates a great part of the calcium chloride and allows essentially complete separation of the E-1 and E-2 components, the interconversion of which shall be discussed in a subsequent paper [5].

water and passed through a small cation exchanger column (Dowex 50-X8, 200–400 mesh, H^+ form). The column is washed to neutrality with water and the eluate is titrated with NaOH to pH = 6, allowing the determination of the equivalent weight. These titrated solutions were used for the measurements of absorption spectra, CD. spectra and optical rotation. On the basis of the obtained results, the three fractions are identified as the following products:

E-1: Na-*trans*-*N*-[Co((*S*)-AMA)gly] · $2H_2O$ (Na[Co($C_6H_6N_2O_6$)($C_2H_4NO_2$)] · $2H_2O$):
Mol.-wt.: Calc. 380.1, Found 370
Calc. C 25.26 H 3.66 N 7.37% Found C 24.09 H 3.35 N 7.49%

E-2: Na-*cis*-*N*-[Co((*S*)-AMA)gly] · $2H_2O$ (Na[Co($C_6H_6N_2O_6$)($C_2H_4NO_2$)] · $2H_2O$);
Mol.-wt.: Calc. 380.1, Found 370
Calc. C 25.26 H 3.66 N 7.37% Found C 24.09 H 3.56 N 7.61%

E-3: Na_3[Co((*S*)-AMA)$_2$] · $4H_2O$ (Na_3[Co($C_6H_6N_2O_6$)$_2$] · $4H_2O$):
Mol.-wt.: Calc. 576.2, Found 576
Calc. C 25.01 H 3.50 N 4.86% Found C 24.90 H 3.53 N 5.31%

Total yield of the three complexes: 52% relative to $Na_3[Co(CO_3)_3]$.

Relative yields: E-1 36%, E-2 50%, E-3 13%.

1.3. *Sodium* (S)-*aspartato*-N-*acetato-aminoacidatocobaltate(III)* (*Na*[*Co*((S)-*AMA*)(*AA*)] · *n* H_2O) (*AA* = (R)- *and* (S)-*alanine, valine, serine, leucine and phenylalanine*[3]). These compounds are prepared according to the procedure given in section 1.2. The obtained products are characterized by their absorption spectra, their molecular weight and their chiroptical properties. The nature of the substance contained in the third band, E-3, is independant of the amino acid introduced at the start.

The ratios of the yields in E-1 (*cis*-N) and E-1 (*trans*-N) are given in Table 1. The ratios depend on the experimental procedure and do not reflect a thermodynamic stereoselectivity, as will be shown in a subsequent paper [5].

Table 1. *Relative yields in* cis-*N- and* trans-*N*-[*Co*((S)-*AMA*)(*AA*)]$^-$ *for different amino-acids*

AA	Ratio *cis*-N/*trans*-N		AA
gly	1.37		gly
(*R*)-val	1.22	0.97	(*S*)-val
(*R*)-ala	1.47	0.98	(*S*)-ala
(*R*)-phe	2.47	2.51	(*S*)-phe
(*R*)-leu	1.31	0.92	(*S*)-leu
(*R*)-ser	1.29	1.32	(*S*)-ser

2. Measurements. – The absorption spectra were measured with a UNICAM SP 800 spectrophotometer and the CD. spectra with a JASCO J 20 spectropolarimeter. Rotation measurements were obtained with a *Perkin-Elmer* 141 polarimeter. All the products used were of analytical grade.

Results and discussion

The results obtained show that only two of the four possible isomers (structures **3** through **6**) are formed in detectable amounts, one *cis*-N and one *trans*-N. As an example, the CD. and VIS. spectra of the two isomers of the mixed-ligand complexes with glycine and of the two isomers of the complexes with each antipode of leucine

[3] Complexes with phenylalanine have been prepared without active charcoal.

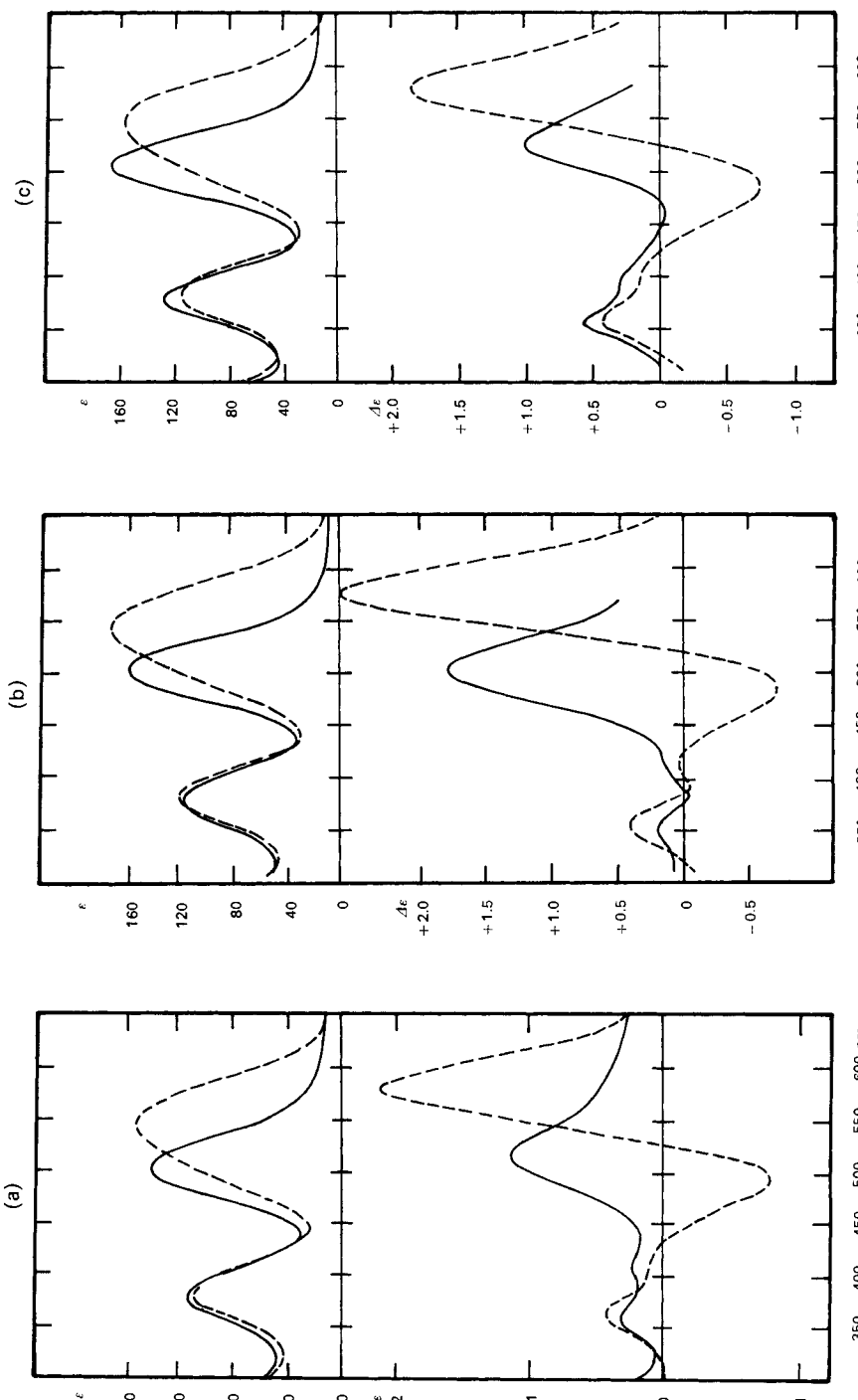


Fig. 2. *VIS. and CD. spectra of Na-trans-N-[Co((S)-AMA)(AA)] (——) and Na-cis-N-[Co((S)-AMA)(AA)] (– – – –).* a) AA = gly, b) AA = (*R*)-leucine, c) AA = (*S*)-leucine

Table 2. *Molar rotations and characteristics of the absorption spectra and CD. spectra of the complexes Na[Co((S)-AMA)(AA)] · n H_2O*

Complex (L = (*S*)-AMA)	Φ^{20}_{578}	Visible spectra $\tilde{\nu}_{max}$ cm^{-1}	ε_{max} M^{-1} cm^{-1}	Circular dichroism $\tilde{\nu}_{max}$ cm^{-1}	$\Delta\varepsilon_{max}$ M^{-1} cm^{-1}
Na-*trans*-N-[CoL(gly)] · 2H_2O	+1056	19840	143	19370	+1.15
Na-*cis*-N-[CoL(gly)] · 2H_2O	−2081	18310	155	17180	+2.09
				20200	−0.80
Na-*trans*-N-[CoL((*R*)-val)] · 3H_2O	+1069	19800	157	19720	+1.73
Na-*cis*-N-[CoL((*R*)-val)] · 2H_2O	−1468	18310	171	17180	+2.71
				20400	−0.53
Na-*trans*-N-[CoL((*S*)-val)] · 2H_2O	+1216	19800	159	18940	+0.90
Na-*cis*-N-[CoL((*S*)-val)]	−2294	18310	152	17150	+1.66
				20400	−0.70
Na-*trans*-N-[CoL((*R*)-ala)] · 2H_2O	+1395	19760	143	19700	+1.48
Na-*cis*-N-[CoL((*R*)-ala)] · 3.5H_2O	−1954	18350	169	17300	+2.43
				20400	−0.76
Na-*trans*-N-[CoL((*S*)-ala)]	+1042	19760	142	19050	+1.30
Na-*cis*-N-[CoL((*S*)-ala)] · 2H_2O	−2294	18310	162	17240	+1.97
				20400	−0.85
Na-*trans*-N-[CoL((*R*)-phe)] · H_2O	+ 647	19800	148	19700	+1.14
Na-*cis*-N-[CoL((*R*)-phe)] · 2H_2O	−1220	18400	154	17250	+2.12
				20530	−0.46
Na-*trans*-N-[CoL((*S*)-phe)] · 2H_2O	+ 10	19760	155	18520	+0.64
Na-*cis*-N-[CoL((*S*)-phe)] · 2H_2O	−1579	18320	161	17250	+1.81
				20620	−0.63
Na-*trans*-N-[CoL((*R*)-leu)] · 1.5H_2O	+1544	19760	160	19800	+1.77
Na-*cis*-N-[CoL((*R*)-leu)] · 2H_2O	−1754	18310	172	17300	+2.58
				20620	−0.70
Na-*trans*-N-[CoL((*S*)-leu)] · 2H_2O	+ 978	19800	164	19050	+0.98
Na-*cis*-N-[CoL((*S*)-leu)] · 1.5H_2O	−2315	18310	156	17300	+1.85
				20530	−0.74
Na-*trans*-N-[CoL((*R*)-ser)] · 2H_2O	+1599	19800	160	19700	+1.80
Na-*cis*-N-[CoL((*R*)-ser)] · H_2O	−1958	18400	166	17250	+2.56
				20160	−0.77
Na-*trans*-N-[CoL((*S*)-ser)] · 2H_2O	+ 859	19800	158	18870	+0.91
Na-*cis*-N-[CoL((*S*)-ser)] · H_2O	−2130	18400	159	17120	+1.73
				20530	−0.60

are represented in Fig. 2. Table 2 summarizes the results obtained with all the compounds isolated.

The visible spectra of the compounds in the E-1 fractions show the lowest energy absorption maximum between 19700 and 19900 cm^{-1}, whereas the corresponding absorption band is situated at 18300–18400 cm^{-1} in the spectra of the complexes from E-2 fractions. According to *Hidaka et al.* [6–8], these bands can be attributed to *trans*-N-[CoN_2O_4]- and *cis*-N-[CoN_2O_4]-chromophores, respectively.

The CD. spectra of the *trans*-N compounds show a positive maximum between 18500 and 19800 cm^{-1}, the CD. spectra of *cis*-N-isomers in turn show a positive

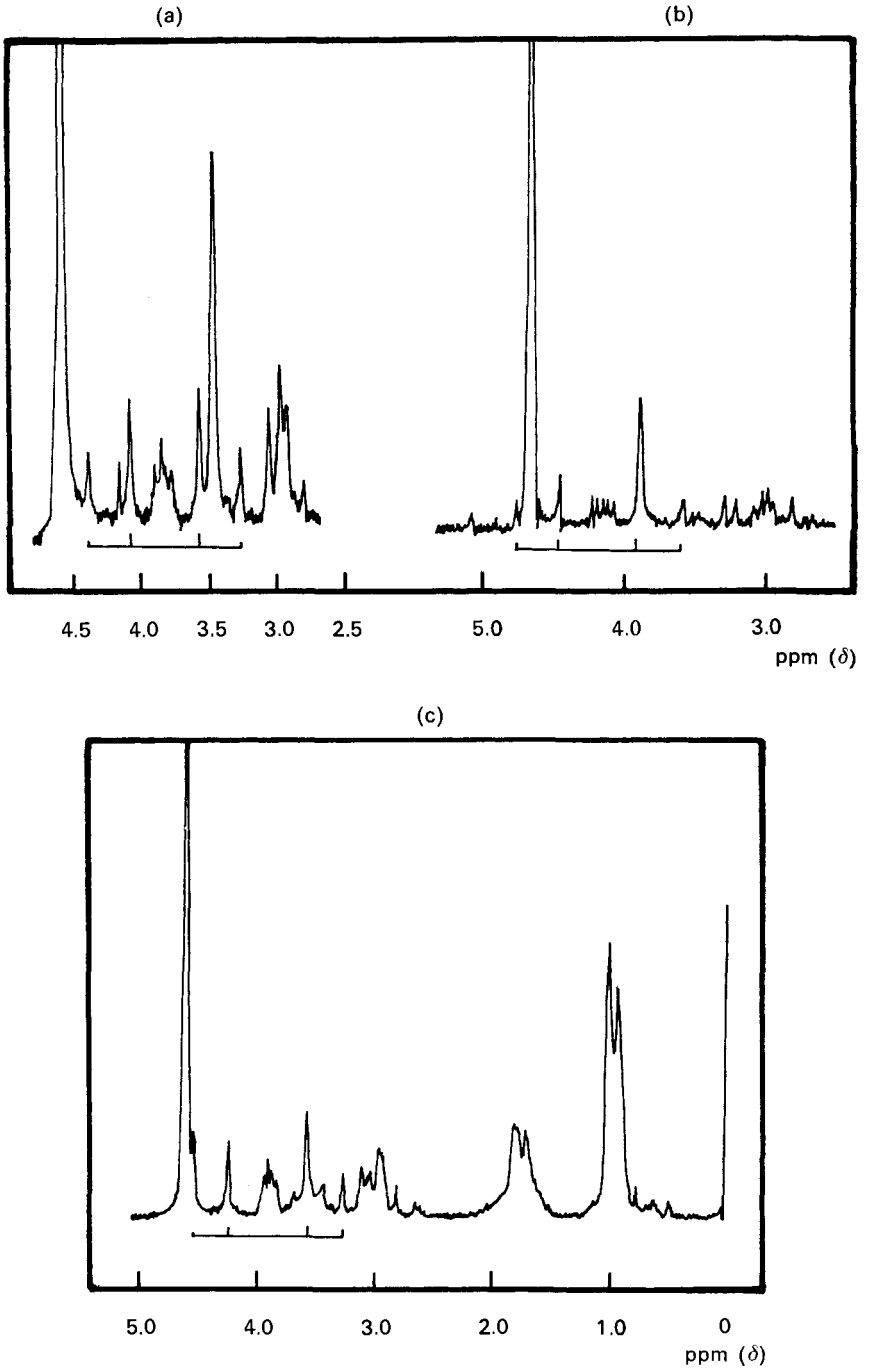
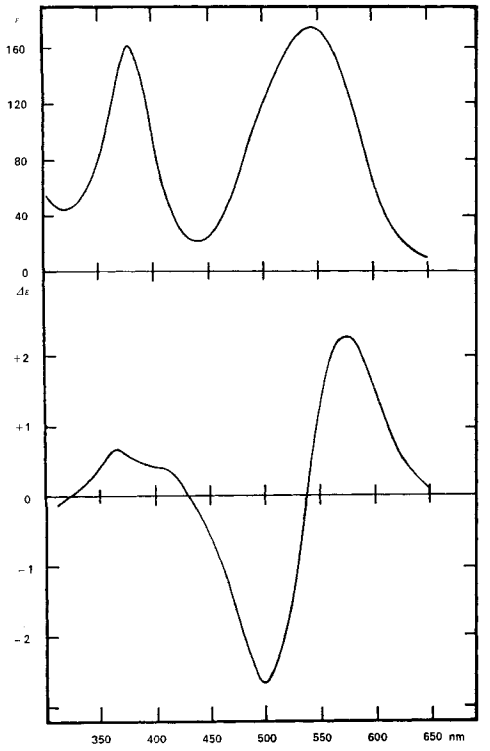


Fig. 3. *^{1}H-NMR. spectra of* a) *Na*-cis-*N*-[*Co*((S)-*AMA*)gly], b) *Na*-trans-*N*-*Na*[*Co*((S)-*AMA*)gly] *and of* c) *Na*-cis-*N*-[*Co*((S)-*AMA*)(R)-*leu*] *in* D_2O *at 60 MHz*

Table 3. *Chemical shifts and coupling constants of methylenic protons of the glycinate group in* $Na[Co((S)\text{-}AMA)(AA)] \cdot n\,H_2O$

Complex	δ_A [ppm]	δ_B [ppm]	Coupling constants [Hz]
cis-gly	4.22	3.46	18.3
trans-gly	4.59	3.94	18.3
cis-(*R*)-leu	4.32	3.48	18.4
trans-(*R*)-leu	4.54	3.81	18.5
cis-(*S*)-leu	4.30	3.50	18.5
trans-(*S*)-leu	4.54	3.81	18.4



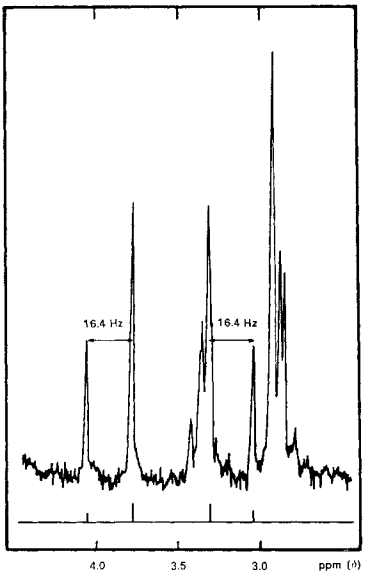


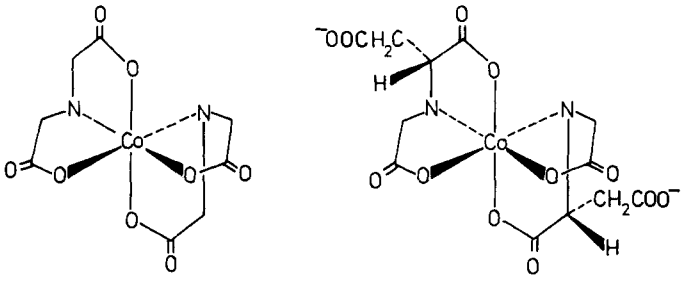
Fig. 4. *VIS., CD. and* ^1H*-NMR. spectra* (in D_2O at 60 MHz) *of* $Na_3[Co((R)\text{-}AMA)_2]$

maximum at 17100–17300 cm^{-1} and a negative maximum between 20100 and 20700 cm^{-1}. The fact that the lowest energy CD. maximum is positive for all the *cis*-N- and *trans*-N-isomers suggests that the absolute configuration of the coordination skeleton is the same in both series of complexes. Consequently this generic configuration seems to be determined by the geometry of the coordinated quadridentate ligand and is independent of the *cis* or *trans* arrangement and the chirality of the amino acid. Therefore only the complexes with structures **3** and **4** or **5** and **6** are formed, but a

Table 4. *Characteristics of the VIS. and CD. spectra of complexes of the type* $[CoN_2O_4]$

Complex	Visible spectrum		Circular dichroism	
	$\tilde{\nu}_{max}$ cm^{-1}	ε_{max} $M^{-1}\,cm^{-1}$	$\tilde{\nu}_{max}$ cm^{-1}	$\Delta\varepsilon_{max}$ $M^{-1}\,cm^{-1}$
cis-$[Co(IDA)_2]^-$ [a]	17800	152	17100	+2.72
			19600	−2.94
	26300	135	26300	+0.79
cis-$[Co((R)\text{-}AMA)_2]^{3-}$	18400	176	17460	+2.29
			20150	−2.64
	26500	162	27400	+0.68

[a] Ref. [12].



7 ä

Figure 5

distinction between either both *cis*-N (**4** and **5**, Fig. 1) or both *trans*-N (**3** and **6**) forms is not possible on the basis of the CD. spectra only [9]. However additional information may be obtained from the NMR. spectra of *cis*-N-complexes [10]. It has been established that the coupling constants of the methylenic protons of a glycinate ring in cobalt(III) complexes are about 16 Hz if the ring lies in the plane containing the metal and the two nitrogen atoms, but about 18 Hz if the ring is out of this plane. These rules have already been applied to mixed complexes of amino-acids [11]. Fig. 3 shows the spectra of three examples. The coupling constants for the six compounds containing glycine and leucine are given in Table 3.

These results allow to propose that the isolated complexes derive from *cis*-O_5 (**2**, Fig. 1), and that their structure is given by **5** and **6** for all the mixed-ligand complexes obtained.

Fig. 4 represents the VIS., CD. and ^{1}H-NMR. spectra of the complex $[Co((R)\text{-}AMA)_2]^{3-}$[4]. According to the ^{1}H-NMR. spectrum, the glycinate ring is found in this complex in the CoNN plane and the two ligand molecules must be in an identical arrangement. The VIS. spectrum is consistent with a *cis*-N structure. Moreover, the

[4] The CD. spectrum of the complex with (*R*)-AMA shows the same sign pattern as the isomer of $[Co(IDA)_2]^-$ described in [12].

CD. spectrum of $[Co((R)\text{-}AMA)_2]^{3-}$ is very close to the spectrum reported for the *ΔΛ-cis*-bis(iminodiacetato)cobaltate(III) (**7**, Fig. 5) (Table 4).

All these informations suggest the structure **8** (Fig. 5) for the anion $[Co((R)\text{-}AMA)_2]^{3-}$, which also appears to be formed stereospecifically.

In all the examples reported so far, it has been shown that the iminodiacetate unit of aminopolycarboxylate ligands spans preferentially a face of the coordination octahedron [4]. This rule is obeyed also in the complexes formed by the aspartate-N-monoacetate ligand, the oxygen atoms of the two 5-membered chelate rings being in *cis*-position to one another, both in the 1:2 complex $[Co(AMA)_2]^{3-}$ and in the mixed ligand complexes $[Co(AMA)(AA)]^{-}$.

The authors wish to express their thanks to Dr. *P. Moser, Ciba-Geigy*, Basel, for his help in carrying out the CD. measurements.

REFERENCES

[1] *B. Güntert, S. Claude & K. Bernauer*, Helv. *58*, 780 (1975).
[2] *R. V. Snyder & R. J. Angelici*, J. inorg. nucl. Chemistry *35*, 523 (1973).
[3] *R. Nakon, P. R. Rechani & R. J. Angelici*, Inorg. Chemistry *12*, 2431 (1973).
[4] *K. Bernauer*, in Topics in Current Chemistry *1976*, Vol. 65, p. 1–35.
[5] *G. Colomb & K. Bernauer*, Helv. *60*, 468 (1977).
[6] *N. Koine, N. Sakota, J. Hidaka & Y. Shimura*, Bull. chem. Soc. Japan *43*, 1737 (1970).
[7] ibid. *42*, 1583 (1969).
[8] *N. Matsuoka, J. Hidaka & Y. Shimura*, Inorg. Chemistry *9*, 719 (1970).
[9] *J. I. Legg & J. A. Neal*, Inorg. Chemistry *12*, 1805 (1973).
[10] *J. L. Sudmeier, A. J. Senzel & G. L. Blackmer*, Inorg. Chemistry *10*, 90 (1971).
[11] *L. Koine, N. Sakota, J. Hidaka & Y. Shimura*, Inorg. Chemistry *12*, 859 (1973).
[12] *C. W. Van Saun & B. E. Douglas*, Inorg. Chemistry *8*, 1145 (1969).