COBALT(III) COMPLEXES OF (2S,3S)-ISOLEUCINE AND (S)-NORLEUCINE. EFFECT OF DIFFERENT LIGAND ALKYL CHAIN ARRANGEMENTS ON ISOMERS DISTRIBUTION*

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The geometrical and optical isomers were prepared of complexes of cobalt(III) with (2*S*,3*S*)-isoleucine and (*S*)-norleucine by two methods: by the oxidation of $CoSO_4$ in the presence of the corresponding amino acid by hydrogen peroxide and by the substitution of the NH_3-groups in $[Co(NH_3)_6]Cl_3$. The isomers were identified by electronic absorption spectra, infrared spectra, and optical rotation. The branching of the amino acid carbon chain increases the ratio of *mer* to *fac* isomers. In the case of (2*S*,3*S*)-isoleucine, a stereoselective coordination of both the Λ-*mer* and Λ-*fac* isomers take place. The different yields of Λ and Δ isomers are discussed in the light of different nonbonding interactions in the individual diastereoisomers.

Because of the nature of donor atoms, the complexes of α-amino acids with cobalt(III) exist as facial (*fac*, 1, 2, 3 or *cis*) and meridional (*mer*, 1, 2, 6 or *trans*) isomers. The arrangement of the chelate rings by itself gives rise to a chirality center on the cobalt atom and thus four isomeric forms can exist. The ratio of the isomers prepared depends[1-3] on the method used, on the nature of the amino acid carbon chain, and is different for optically active and racemic amino acids. The effect of the different arrangement of the amino acid carbon chain in ligands with the same number of carbon atoms in the molecule or, alternatively the effect of an additional assymetry center on the ratio of the isomers obtained is not known as yet. In an effort to cast light on these problems we studied the cobalt(III) complexes of isoleucine (Ile) and norleucine (Nle), both optically active and racemic. For reasons of comparison we also present the data on (*S*) and (*RS*)-leucine (Leu), respectively.

EXPERIMENTAL

Reagents and apparatus: (*S*)-leucine was a product of Lachema, $[\alpha]_D$ +16·1°, (*S*)-norleucine was from Busch $[\alpha]_D$ +24°, and (2*S*,3*S*)-isoleucine, $[\alpha]_D$ +40·5°, was an alloisoleucine-free product of Koch-Light.

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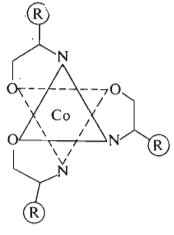
The electronic absorption spectra were measured in the Optica-Milano CF-4 photometer. The infrared spectra (KBr-disc) in the 400—4000 cm^{-1} range were measured in the Perkin-Elmer spectrophotometer. For optical rotation measurements the Opton polarimeter was employed.

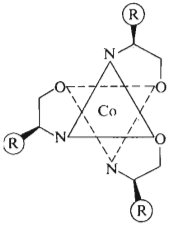
The preparation of complexes was effected *a*) by the direct oxidation method[4], *b*) by the substitution reaction from $[Co(NH_3)_6]Cl_3$, the amino acid, and KOH (*cf.*[5]), and *c*) by the substitution reaction from $[Co(NH_3)_6]Cl_3$ and the amino acid in the presence of active charcoal.

The solution of 0·02 mol of $[Co(NH_3)_6]Cl_3$ in 50 ml of water was heated at 60°C with 0·06 mol of the corresponding amino acid. Activated charcoal (0·5 g) was added and the mixture was heated until no more ammonia was evolved. The mixture was then cooled down to room temperature and passed over a glass filter. The residue on the filter was washed with hot methanol until the filtrate became colorless. The cooled filtrates were taken to dryness *in vacuo* and the dry residue was extracted again with hot methanol. This solution was taken to dryness *in vacuo* and the mer isomers were obtained. The residue on the filter was extracted first with concentrated hydrochloric acid, then dried, and extracted further with concentrated sulfuric acid. The obtained red-colored filtrates were diluted with water and afforded the water-insoluble *fac* isomers.

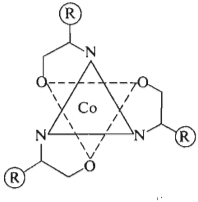
Chromatographic separation. The methanolic solution of the Λ and Δ *mer*-siomers was evaporated *in vacuo* with a small quantity of aluminum oxide and the dry, triturated residue was placed on top of the column. A 100 × 4 cm column of aluminum oxide was used for the chromatography. A 80% solution of 2-propanol served as solvent. Fractions 5 ml in volume were collected and their optical rotation at 578, 436 and 305 nm was measured. The Λ and Δ isomers were obtained by repeated chromatography and selection of fractions. The analyses of the complexes prepared are given in Table I.



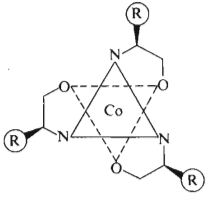
mer-Λ



mer-Δ



fac-Λ



fac-Δ

RESULTS AND DISCUSSION

Two methods were used for the preparation of complexes of isoleucine and leucine which have not been obtained before: the oxidation of the complex Co(II) (amino-acid)$_3$ by hydrogen peroxide[4] and the substitution of the NH_3 groups in $[Co(NH_3)_6]$. $.Cl_3$ in an alkaline medium[5]. We have also used for the synthesis of the complexes substitution of the NH_3 groups in the ammonia complex in the presence of activated charcoal, without the adjustment of pH. This modified method was found useful in a number of cases[6] where the synthesis of the amino acid complexes was unsuccessful or where mild conditions were required.

The oxidation of the Co(II) amino acid complexes by hydrogen peroxide leads exclusively to the synthesis of the *mer* isomers. It was shown electrophoretically that the reaction mixture contained both in the case of isoleucine and norleucine a product of anionic character, most likely $[Co(\text{amino acid})_2(OH)_2]^-$. A product of this type can be regarded as an intermediary product of oxidation of cobalt(II)

TABLE I

Characteristics of Complexes and Yields of Optical Isomers

Product	Found			$[M]_D$	Yield (%)
	% C	% H	% N		
Λ, Δ-*mer*-[Co((*SS*)-Ile)$_3$].3 H_2O[a]	43·16	8·20	8·35	—	—
Δ-*mer*-[Co((*SS*)-Ile)$_3$].3 H_2O[a]	43·08	8·38	8·40	−6 265°	12
Δ-*fac*-[Co(*SS*)-Ile)$_3$].3 H_2O[a]	43·00	8·50	8·43	−5 980°	20
Λ, Δ-*mer*-[Co((*S*)-Nle$_3$].3 H_2O[a]	42·88	8·47	8·28	—	—
Λ, Δ-*fac*-[Co((*SS*)-Ile)$_3$.2 H_2O[b]	44·48	8·42	8·66	—	—
Λ-*fac*-[Co((*SS*)-Ile)$_3$].2 H_2O[b]	44·28	8·38	8·57	+1 684°	80
Λ-*mer*-[Co((*SS*)-Ile)$_3$].2 H_2O[b]	44·61	8·28	8·70	+2 087°	88
Λ-*fac*-[Co((*S*)-Nle)$_3$].2 H_2O[b]	44·62	8·44	8·66	+ 871°	56
Λ-*mer*-[Co((*S*)-Nle)$_3$.2 H_2O[b]	44·41	8·40	8·70	+1 740°	53
Δ-*mer*-[Co((*S*)-Nle)$_3$].2 H_2O[b]	44·57	8·26	8·58	−3 527°	47
Δ-*fac*-[Co((*S*)-Nle)$_3$].1·5 H_2O[c]	45·26	8·00	8·71	−2 740°	44
Λ, Δ-*fac*-[Co((*S*)-Nle)$_3$].H_2O[d]	46·19	8·19	9·01	—	—
Λ-*fac*-[Co((*S*)-Leu)$_3$].3 H_2O[e]	—	—	—	—	61
Δ-*fac*-[Co((*S*)-Leu)].2 H_2O[e]	—	—	—	—	39
Λ-*mer*-[Co((*S*)-Leu)$_3$].2 H_2O[e]	—	—	—	—	62
Δ-*mer*-[Co((*S*)-Leu)$_3$].2 H_2O[e]	—	—	—	—	38

[a] For $C_{18}H_{42}CoN_3O_9$ (503·5) calculated: 43·00% C, 8·42% H, 8·39% N. [b] For $C_{18}H_{40}CoN_3O_8$ (485·5) calculated: 44·53% C, 8·32% H, 8·65% N. [c] For $C_{18}H_{39}CoN_3O_{7,5}$ (476·5) calculated: 45·37% C, 8·25% H, 8·82% N. [d] For $C_{18}H_{38}CoN_3O_7$ (467·5) calculated: 46·29% C, 8·21% H, 8·99% N. [e] Taken from paper[4].

complexes both by hydrogen peroxide and by atmospheric oxygen[7,8]. By contrast, the reaction between the amino acid and $[Co(NH_3)_6]^{3+}$ affords a mixture of *fac* and *mer* isomers.

As obvious from Table II, the branching of the carbon chain located at the α-carbon atom of the amino acid increases the *mer* to *fac* ratio. It appears that the presence of the sterically more bulky chain is an important factor preventing geometric isomerization[3,4]. This is in good agreement with the opinion assuming that the *mer* isomers are thermodynamically more stable than the *fac* isomers[4]. We have provided evidence of the higher stability of the *mer* isomers of the isoleucine and norleucine complexes by showing that the equilibration of the *mer* isomers with activated charcoal in methanol does not give rise to the *fac* isomers. The reaction of $[Co(NH_3)_6].Cl_3$ with racemic amino acids afforded mostly the *fac* isomers (84% of Λ, Δ-*fac*-Co(*RS*)-Ile)$_3$, 64% of Λ, Δ-*fac*-Co(*RS*)-Nle)$_3$).

The isolated geometrical isomers Co(Ile)$_3$ and Co(Nle)$_3$ show identical electronic absorption spectra with two characteristic absorption bands; they correspond to two spin-allowed transitions of the cobalt(III) complexes with facial (*cis-cis*) or meridional (*cis-trans*) arrangement of the donor atoms around[9] Co(III). The geometrical isomers were identified on the basis of differences in their absorption spectra which reflect different symmetries. We found a greater spliting of the band corresponding to the $^1A_{1g} \rightarrow {}^1T_{1g}$ transition in the case of the *mer*-(1,2,6) isomers showing rhombic symmetry whereas in the case of the *fac*-(1,2,3) isomers showing cubic symmetry the two absorption bands were entirely symmetric. The characteristics of the geometrical isomers together with those of the selected absorption maximums in the infrared region are given in Table II, together with the yields of the reactions.

TABLE II

Electronic Absorption Spectra (nm), Infrared Spectra (cm^{-1}), and Reaction Yields of Geometrical Isomers

Product	$\lambda_{max}(\varepsilon)^a$	$\nu(COO^-)_{as}$	$\nu(COO^-)_s$	$\nu(NH_2)$	Yield %
mer-[Co((*SS*)-Ileu)$_3$].3 H_2O	535 (168), 375 (110)	1 635 vs[b]	1 370 sh	3 110 s	64
fac-[Co((*SS*)-Ileu)$_3$].2 H_2O	530 (210), 370 (212)	1 620 vs	1 380 s	3 110 s	36
mer-[Co((*S*)-Nleu)$_3$].3 H_2O	535 (166), 375 (112)	1 615 vs	1 380 s	3 110 s	44
fac-[Co((*S*)-Nleu)$_3$].H_2O	530 (205), 375 (210)	1 630 vs	1 380 sh	3 095 sh	56
mer-[Co((*S*)-Leu)$_3$].2 H_2O	535 (170), 375 (112)	1 625 vs	1 360 sh	3 120 sh	59
fac-[Co((*S*)-Leu)$_3$].2 H_2O	530 (208), 370 (211)	1 630 vs	1 360 s	3 130 sh	41

[a] The electronic absorption spectra were measured in methanol (*mer* isomers) and in 96% H_2SO_4 (*fac* isomers). $[Co(NH_3)_6]Cl_3$ as starting material, catalysis by active charcoal, reaction time 10 h.
[b] vs very strong, sh shoulder, s strong

The geometrical isomers of the $Co(III)(amino\ acid)_3$ type are enantiomeric at the cobalt atom; at the same time the arrangement of the chelate rings around Co(III) gives rise to two configurations referred to in Piper's[10] terminology as Λ and Δ, which correspond to the left-handed and right-handed helicity formed around the three-fold (*fac* isomers) or pseudo three-fold axis of rotation (*mer* isomers), respectively. Since the ligands themselves are chiral, there exist isolated complexes in four diastereoisomeric forms: Λ-*mer*, Δ-*mer*, Λ-*fac*, and Δ-*fac* (Fig. 1). The different solubility of the Λ-*fac* and Δ-*fac* isomers in hydrochloric and sulfuric acid permits their resolution without difficulties. On the other hand, the *mer* isomers soluble in lower alcohols were resolved chromatographically on a alumina column. In the case of the complexes of isoleucine and norleucine (similarly to the case of complexes with other amino acids[4]), the less polar Δ-*mer* isomer with pseudoaxial arrangement of the alkyl chain was eluted as the first one; this indicates that the equatorial arrangement facilitates the adsorption of the complex on the surface of aluminum oxide. The optical isomers thus obtained differ in the sign of their optical rotation at 578 nm, as can be expect in view of their opposite helicity, similarly to other complexes of amino acids with trivalent cobalt[1,2]. To determine the absolute configuration of the isolated isomers, we employed the general rule according to which the isomer with a dominant positive Cotton effect in the region of the spin-allowed transition $^1\mathbf{A}_{1g} \rightarrow {}^1\mathbf{T}_{1g}$ is of Λ configuration[11].

The results given in Table I show that the direct synthesis, *i.e.* the oxidation of $CoSO_4$ in the presence of the amino acid affords almost the same quantity of Λ and Δ-*mer* Co((*S*)-Nle)$_3$ whereas in the case of (2*S*, 3*S*)-Ile predominantly the Λ isomer was obtained, both with the *fac* and the *mer* isomer. These results, which point to a relatively high degree of stereoselectivity in the case of (2*S*,3*S*)-Ile, can be explained on the basis of different non-bonding interactions between the individual diastereoisomers. Since the chelate rings formed by the α-amino acids are only little puckered (the deviation from planarity is approximately[12] 6°), the degree of these interactions depends only on the sterical volume of the substituents located in the α position of the amino acid. These substituents are arranged with respect to the C_3 axis in such a manner (Fig. 1) that the non-bonding interactions are greater in the *fac* isomers than in the case of the *mer* isomers. The Λ-isomers with the pseudoequatorial arrangement of the alkyl groups will then be more stable for sterical reasons than the Δ-isomers with a pseudoaxial disposition of these groups. These positions are occupied in the case of the complexes (2*S*,3*S*)-Ile and (*S*)-Leu (α-aminocaproic acid) by sterically bulky groups whereas the n-butyl chains of norleucine, being the sterically less demanding substituents, can be arranged in pseudoaxial positions. The *sec*-isobutyl group of isoleucine is sterically comparable with the isopropyl group of valine. However, no stereoselectivity except geometric stereoselectivity has been observed with any of the *mer* isomers of cobalt(III) complex of (*S*)-valine. These results lead us to assume that we must take into account, in

addition to the above mentioned sterical hindrances, also the possible interactions between the chirality centers in the chelate rings of the (2*S*,3*S*) -amino acid which obviously have an effect on the stereoselectivity.

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