STEREOCHEMISTRY OF [SARCOSINATOBIS((*S*)-(+)-VALINATO)]--COBALT(III) COMPLEXES WITH THREE DIFFERENT CHIRAL CENTRES

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Dedicated to Professor S. Škramovský on the occasion of his 75th birthday.

After reaction of Λ-*cis*(N)-*cis*(O)-K[Co((*S*)-(+)-valinato)$_2$CO$_3$] with sarcosine, or oxidation of the Co^{2+} ion with hydrogen peroxide in the presence of (*S*)-(+)-valine and sarcosine in a molar ratio of 1 : 2 : 1, Λ- and Δ-*mer* isomers of the [sarcosinatobis((*S*)-(+)-valinato)]cobalt(III) complex were isolated chromatographically. Their absolute configuration was derived from circular dichroism curves or from the Cotton effect observed in the $^1T_{1g} \leftarrow {}^1A_{1g}$ transition region. It has been demonstrated on the basis of ^{1}H-NMR spectra that the Λ-isomer obtained by displacement of the carbonate group is the Λ-*cis*(N)-*trans*-(O)-isomer with an *S*-configuration of the secondary nitrogen atom in sarcosine. The Λ-isomer obtained by oxidation of the reaction mixture exhibits forced *R*-configuration of the secondary nitrogen atom and *trans*(N)-*cis*(O)-geometry. The stereochemical selection of geometric isomers is primarily determined by the steric requirements of the N—CH_3 group of sarcosine. The degree of stereoselectivity, expressed by the ratio Λ : Δ, of the isomers is low (1·2) and corresponds only to small structural differences following from axial or equatorial disposition of two isopropyl groups.

Study of steric effects has yielded valuable information on differences in diastereoisomer stabilities[1,2]. In amino acid metal complexes, these differences can stem from alkyl groups located either on the carbon skeleton of the chelate ring or on the donor atom. The former case applies particularly to non-polar chain amino acids (proline[3], valine[4], isoleucine[5]), while sarcosine (N-methyl glycine) is a typical representative of the latter group. The effect of substitution on the nitrogen atom increases the complexity of the metal complex stereochemistry and is manifested by a strict isomer selection, dictated by strong interactions between vicinal N—CH_3 groups[6].

In the present paper is studied the stereochemistry of a cobalt(III) complex with three different chiral centres in which interchelate non-bonding interactions take place, due to sterical requirements of the sarcosine (Sar) N—CH_3 group and the (*S*)-(+)-valine (Val) isopropyl group. The question of forced configuration of the sarcosine donor atoms is further investigated.

EXPERIMENTAL

Chemicals: (*S*)-(+)-valine ($[\alpha]_D$ +21·5° in 20% HCl); aluminium oxide for chromatography according to Brockmann (activity III); aluminium oxide G according to Stahl (containing 10% plaster).

Instruments: Electronic absorption spectra were measured on an Optica-Milano CF-4 instrument and the optical rotation on a Polamat A instrument (Zeiss). A Roussel Jouan 185 Model II instrument was used for the measurement of circular dichroism. ^{1}H-NMR spectra were obtained on a Varian XL-100 instrument using sodium 2,2-dimethyl-2-silapentane-5-sulphonate as an external standard. Electrophoresis was carried out on a Tatrachema instrument (0·05M--$NaClO_4$ electrolyte, Whatman No 1 paper). An apparatus from the Shandon company was employed for preparative thin-layer chromatography (100 . 20 cm plates and a sorbent thickness of 2 mm).

Λ-*cis*(N)-*cis*(O)-K[Co((*S*)-(+)-Val)$_2CO_3$] was prepared and characterized according to the literature[7,8].

[Co(Sar) ((*S*)-(+)-Val)$_2$]

A) To a solution of 3·9 g (0·01 mol) Λ-*cis*(N)-*cis*(O)-K[Co((*S*)-(+)-Val)$_2CO_3$] in 60 ml of water were added 0·89 g (0·01 mol) of sarcosine. The mixture was heated to 50°C for 8 h. On cooling and filtration a substance was obtained whose properties correspond, in accordance with the literature[9], to Λ-fac-[Co((*S*)-(+)-Val)$_3$]. The filtrate was passed through an ion-exchanger column (Dowex 50W X8, 200—400 mesh, H^+-cycle). The column was eluted with water and the fractions were controlled electrophoretically. On decreasing the volume of the eluate containing electroneutral components, a substance separated whose properties corresponded[9] to Δ-*fac*--[Co((*S*)-(+)-Val)$_3$]. The filtrate was further subjected to thin-layer chromatography on Al_2O_3—G with a 90 : 10 ethanol–water mixture. Three substances were detected chromatographically, with R_F 0·95, 0·80 and 0·39. A substance with R_F 0·95 was separated by chromatography of the mixture on an Al_2O_3 column (according to Brockmann, a 50×2 cm dry column) in the same solvent; the substance was identified as Λ-*mer*-[Co((*S*)-(+)-Val)$_3$] by comparing its properties with the literature data[9]. The remaining two substances, which could not be separated on the column, were separated by thin-layer chromatography (Al_2O_3—G), applying a saturated solution of the mixture in 90% ethanol along the entire length of the plate. On development in a 90 : 10 ethanol–water system the mixture separated into two bands. These were separated mechanically with the sorbent layer and were extracted with 90% ethanol. The extracts were filtered and evaporated. The substances obtained: $(+)_{589}$-[Co(Sar)((*S*)-(+)-Val)$_2$] (R_F 0·80), electronic absorption spectrum: 378 nm (ε 158), 545 nm (ε 90); and $(-)_{589}$-[Co(Sar)-((S)-+)-Val)$_2$] (R_F = 0·39), electronic absorption spectrum: 375 nm, (ε 145), 544 nm (ε 103). For $(+)_{589}$-$C_{13}H_{26}N_3O_6Co$. .3 H_2O (433·3) calculated: 35·99% C, 7·38% H, 9·69% N; found: 35·86% C, 6·92% H, 9·59% N. For $(-)_{589}$-$C_{13}H_{26}N_3O_6Co$.2 H_2O (415·3) calculated: 37·56% C, 7·22% H, 10·11% N; found: 37·50% C, 7·02% H, 9·99% N.

B) To a solution of 3·16 g (0·01 mol) $Ba(OH)_2$, 2·4 g (0·02 mol) of (*S*)-(+)-valine and 0·89 g (0·01 mol) of sarcosine in 50 ml of water, a solution of 2·81 g (0·01 mol) $CoSO_4$.7 H_2O in 20 ml of water and 5 ml of 30% H_2O_2 were added at an elevated temperature and with stirring. The mixture was heated for 30 min, the $BaSO_4$ separated was filtered off and the filtrate was passed through an ion-exchange column. On evaporation of the eluate, Δ-fac-[Co((*S*)-(+)-Val)$_3$] separated. The subsequent procedure was identical to that employed with the substitution reaction. The substances obtained: Λ-*mer*-[Co((*S*)-(+)-Val)$_3$], $(+)_{589}$-[Co(Sar)((*S*)-(+)-Val)$_2$], the electronic absorption spectrum: 375 nm (ε 145), 543 nm (ε 92) and $(-)_{589}$-[Co(Sar)((*S*)-(+)-Val)$_2$], the

electronic absorption spectrum: 378 nm (ε 152), 545 nm (ε 90). For $(+)_{589}$-$C_{13}H_{26}N_3O_6Co.1{\cdot}5H_2O$ (406·3) calculated: 38·39% C, 7·14% H, 10·34% N; found: 38·41% C, 7·15% H, 10·32% N. For $(-)_{589}$-diastereoisomer was found: 38·44% C, 7·11% H and 10·29% N. In order to determine the product distributions, the reactions were carried out with a concentration of 0·01 mol Co (at appropriate molar ratios) and the products were analyzed for cobalt.

RESULTS AND DISCUSSION

Chromophor $Co(N)_3(O)_3$ predicts the existence of two geometric isomers of the sarcosinatobis((*S*)-(+)-valinato)cobalt(III) complex, *fac* and *mer*, each of which represents a pair of Λ- and Δ-diastereoisomers. Coordination of two different amino acids increases the number of *mer* isomers from two to six, so that the existence of eight isomers, four of them geometrical, can be expected (the individual isomers differ in the mutual position of the two valines, see Fig. 1). Since the secondary nitrogen atom in sarcosine becomes chiral on coordination and attains absolute configuration *R* or *S*, the total number of stereoisomers increases to sixteen.

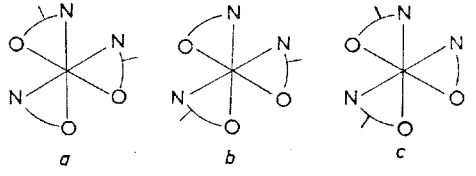
In order to differentiate the basic geometrical arrangement (*fac* or *mer*), the different ligand-field symmetry, *i.e.* C_{3v} for the *fac*- and C_{2v} for the *mer*-isomer, was utilized. The electronic absorption spectra of all products with composition [Co(Sar)((*S*)-(+)-Val)$_2$] exhibited splitting of the first absorption band corresponding to the magnetic-dipole allowed $^1T_{1g} \leftarrow {}^1A_{1g}$ transition, which is characteristic of the meridional arrangement of the donor atoms[10].

Chromatography enabled separation of stereoisomers whose circular dichroism spectra, given in Fig. 2, verified meridional arrangement of the donor atoms and permitted the determination of the absolute configuration of the isomers obtained. The low-energy $^1T_{1g} \leftarrow {}^1A_{1g}$ transition in octahedral complexes is split into three components with ligand-field symmetry C_{2v} (the *mer*-isomer) and into only two components with C_{3v} symmetry (the *fac*-isomer)[11]. It follows from study of the circular dichroism spectra of cobalt(III) complexes of diamines that components A_2 and E_a, into which the octahedral low-energy transition in complexes with D_3 symmetry is split, have opposite signs[12]. Applying the Mason procedure[13,14], it is then possible to compare the main bands of $(+)_{589}$ isomers, $\Delta\varepsilon = +0{\cdot}67$ and $+0{\cdot}65$ corresponding to the $^1T_{1g} \leftarrow {}^1A_{1g}$ transition, with the positive dominant band of (+)-Co(en)$_3^{3+}$

FIG. 1

Geometric Isomers of [Co(Sar)((*S*)-(+)-Val)$_2$]

a) *cis*(N)-*trans*(O), *b*) *trans*(N)-*cis*(O), *c*) *cis*(N)-*cis*(O).



(en is ethylenediamine) for the same transition, which has Λ-configuration[15]; dominant bands of $(-)_{589}$ isomers, $\Delta\varepsilon = -0{\cdot}63$ and $-0{\cdot}49$, can be compared with the dominant band of $(-)$-$Co(en)_3^{3+}$, whose absolute configuration is Δ. It thus follows that isomers of $(+)_{589}$-[Co(Sar)((*S*)-(+)-Val)$_2$] have absolute configuration Λ, while $(-)_{589}$-[Co(Sar)((*S*)-(+)-Val)$_2$] isomers have configuration Δ.

Formation of facial isomer was not detected in the reaction mixture, similar to [$Co(Sar)_3$][6]. On the other hand, these were prepared[7] for [Co(Gly)((*S*)-(+)-Val)$_2$] (Gly is the glycine anion), from which it can be concluded, as was verified by study of models, that non-bonding interactions due to the presence of the N-CH_3 group exclude isomers with a facial arrangement of the donor atoms.

The study of Dreiding models indicated that the main source of non-bonding interactions is the sarcosine N—CH_3 group. In no structure studied (including Δ-isomers) does mutual interaction of isopropyl groups occur. On the other hand, the orientation of the N—CH_3 group with respect to the isopropyl groups is a factor which to a certain degree determines the selection of the geometric isomers. These interactions on the one hand enable the existence of certain geometric isomers and, on the other hand, force a certain configuration of the sarcosine secondary nitrogen atom. For example, the Λ-*cis*(N)-*cis*(O) isomer can only exist if the sarcosine nitrogen atom has configuration *R*, as strong interactions between the N-CH_3 group and the isopropyl group occur with the *S*-configuration, similar to the Λ-*trans*(N)-*cis*(O) isomer (Fig. 3*a*, *b*). In contrast, the Λ-*cis*(N)-*trans*(O) isomer (Fig. 3*c*) is free from interactions with

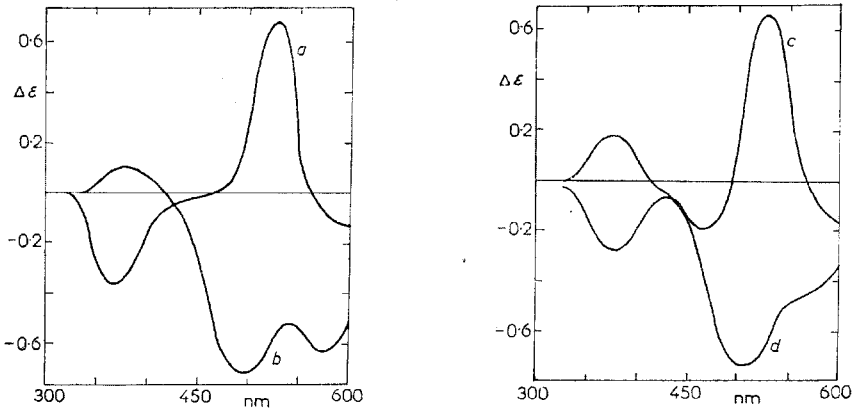


FIG. 2

Circular Dichroism Spectra of [Co(Sar)((*S*)-(+)-Val)$_2$]

a) Λ-, *b*) Δ-isomers prepared by the substitution reaction, *c*) Λ-, *d*) Δ-isomers obtained by oxidation.

both nitrogen atom configurations, *i.e.* *R* and *S*. The situation is very similar with Δ-isomers, only the axial character of the valine isopropyl groups leads to further interactions between these groups and the equatorial hydrogen atom from the NH_2--group in the neighbouring ring. However, even these interactions are connected with the secondary nitrogen atom configuration. The Δ-*cis*(N)-*cis*(O) isomer is free from all interactions when the sarcosine nitrogen atom has configuration *S*, similar to the Δ-*cis*(N)-*trans*(O) isomer where, however, the interactions between the NH_2-group and the isopropyl group (at the level of van der Waals radii) remain unchanged. In the Δ-*trans*(N)-*cis*(O) isomer with the *S*- or *R*-configuration of the secondary nitrogen atom, there also exist weak interactions at the van der Waals radius level between the N—CH_3 group and the equatorial hydrogen from the NH_2-group of the vicinal chelate ring (Fig. 3*d*).

In order to identify the geometric isomers, the ^{1}H-NMR spectra measured in D_2O, namely the signals of the sarcosine N—CH_3 groups and the methine protons of the coordinated valines, were employed. With the Λ-isomer obtained by the substitution

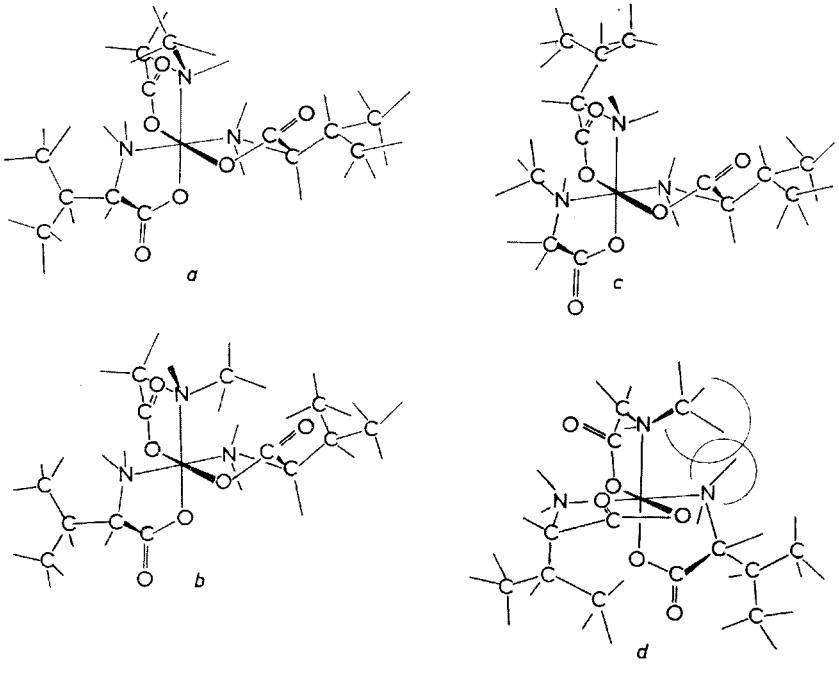


FIG. 3

Configuration of the [Co(Sar)((*S*)-(+)-Val)$_2$] Isomers

a) Λ-(*R*)-*trans*(N)-*cis*(O), *b*) Λ-(*S*)-*trans*(N)-*cis*(O), *c*) Λ-(*S*)-*cis*(N)-*trans*(O), *d*) Δ-(*S*)-*trans*(N)--*cis*(O).

reaction, the N—CH_3 group protons resonate at $\delta = 2{\cdot}54$ p.p.m., which corresponds (compared with another Λ-isomer) to equatorial character[16] of this group and to *S*-configuration of the nitrogen atom. Two doublets correspond to the α-methine protons (a consequence of their interaction with the β-CH protons), with $\delta = 3{\cdot}60$ and 3·77 p.p.m. ($J = 4$ Hz) and with an intensity ratio of 1 : 1. Two signals of α-CH protons can only exist when two valine chelate rings exist under geometrically and magnetically non-equivalent conditions; the corresponding structures are *cis*(N)-*cis*(O) and *cis*(N)-*trans*(O). However, it follows from the models that the *S*-configuration of the sarcosine secondary nitrogen atom is excluded in the *cis*(N)-*cis*(O) isomer, due to interaction between the equatorial N—CH_3 group and the isopropyl group in the vicinal chelate ring; hence, the isomer structure is Λ-*cis*(N)-*trans*(O).

The other Λ-isomer obtained by direct oxidation exhibited a signal in the spectrum corresponding to the resonance of the N—CH_3 protons at $\delta = 2{\cdot}47$ p.p.m., which is shifted upfield compared with the previous Λ-isomer; therefore, axial character can be attributed to the N—CH_3 group in this isomer. The absolute *R*-configuration of the secondary nitrogen atom then corresponds to the axial position. Only a single doublet corresponding to the resonance of α-CH protons, $\delta = 3{\cdot}60$ p.p.m. ($J = 4$ Hz), was observed in the spectrum. The presence of a single doublet is only possible when both valine rings are under geometrically and magnetically equivalent conditions. These conditions are met[17] with the valine rings in a mutual *trans*-position, which occurs in the *trans*(N)-*cis*(O) isomer. No unambiguous assignment of the signals was possible with Δ-isomers.

Reaction between Λ-*cis*(N)-*cis*(O)-K[Co((*S*)-(+)-Val)$_2CO_3$] and sarcosine is an example of acid hydrolysis of the carbonate group, proceeding without breakage of the metal–ligand bond[18], with subsequent decarboxylation, leading to formation of diaqua-complexes. It should then follow that the substitution yields exclusively

TABLE I
Per Cent Distribution of the Reaction Products

Product	Substitution	Oxidation
Λ-*fac*-[Co((*S*)-(+)-Val)$_3$]	5·3	—
Δ-*fac*-[Co((*S*)-(+)-Val)$_3$]	7·0	8·4
Λ-*mer*-[Co((*S*)-(+)-Val)$_3$]	29·3	41·2
Λ-*mer*-[Co(Sar) ((*S*)-(+)-Val)$_2$]	32·3	27·5
Δ-*mer*-[Co(Sar) ((*S*)-(+)-Val)$_2$]	26·2	22·9

Λ-*cis*(N)-*cis*(O)-[Co(Sar)((*S*)-(+)-Val)$_2$]. As the reaction proceeds with simultaneous isomerization, the presence of both Λ- and Δ-isomers is to be expected in the reaction mixture[19].

Both synthetic reactions yielded a complex mixture of substances. It can be seen in Table I that Λ-isomers predominate in the reactions. As the tris(sarcosinato)cobalt-(III) complex was detected in neither reaction mixture, the reactions described are not accompanied by disproportionation of [Co(Sar)((*S*)-(+)-Val)$_2$]. The degree of stereo-selectivity, measured on the basis of the Λ : Δ ratio, and as follows from the study of the models, is predominantly dependent on isopropyl group interactions, which are larger when these groups are located in the axial position (Δ-isomers). The Λ : Δ ratio in the substitution reaction is 1·23. This value, not very different from unity, indicates that the difference in the thermodynamical stability between the two stereo-isomers is given solely by fine structural differences stemming from axial and equatorial disposition of the isopropyl groups. Since these are complexes with two sterically bulky isopropyl chains, the degree of interaction is small compared with Co(AB)$_3$--type complexes. The presence of the sarcosine N—CH_3 group in the coordination sphere was chiefly manifested in the selection of geometric isomers, while the requirement of minimum interactions between N—CH_3 and the isopropyl group led to a forced configuration on the secondary nitrogen atom.

The ratio of Λ and Δ isomers of [Co(Sar)((*S*)-(+)-Val)$_2$] prepared by oxidation is virtually identical (1·20) as with the substitution reaction; this indicates that the same steric effects are apparently operative in all cases.

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