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A NEW SYNTHESIS OF (R)- AND (S)-2-^{2}H-AMINO ACIDS, INCLUDING (R)- AND (S)-2-$^2H_1$-GLYCINE VIA STEREOCHEMICALLY INERT Co(III) COMPLEXES

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Abstract—Chemical synthesis of deuterated optically active 2-^{2}H-amino acids via chiral complexes [Co(3-X-Sal-(S)-2-^{1}H-aa)$_2$]Na, where X is H, Me; aa is valine, norvaline, tyrosine, methionine, alanine and glycine; Sal is salicylaldehyde, is described.

The technique includes preparation of a mixture of Λ and Δ diastereomeric complexes of [Co(3-X-Sal-(S)-2-^{1}H-aa)$_2$]Na which are separated on Al_2O_3.

Then under the action of NaOD in D_2O the 2-^{1}H of the amino acid moiety is exchanged by deuterium, the resulting mixture of deuterated diastereomers is again separated on Al_2O_3, and optically active 2-^{2}H aa are isolated after electrochemical reduction of pure deuterated diasteroisomers. S and R-2-$^2H_1$-glycines are obtained by stereospecific ^{1}H-^{2}H exchange of glycine moiety in Λ and Δ [Co(3-Mesal-gly)$_2$]Na.

OPTICALLY active and racemic deuterated amino acids can be prepared enzymatically by carrying out D-exchange and transamination reactions in D_2O in the presence of certain enzymes.[1,2] Enzymatic methods suffer such disadvantages as narrow substrate specificity and lack of available pure enzymes.

The majority of chemical methods of preparing deuterated amino acids gives racemic products.[3-5]

In two recent publications chemical synthesis of optically active deuterated amino acids was reported.[6,7] In one of these methods the D label is introduced into the molecule by reducing unsaturated precursors of amino acids by means of chiral phosphine–rhodium catalysts in the D_2 atmosphere. The disadvantage of this method resides in the difficulty of obtaining chiral phosphine ligands, and the narrow range of the amino acids thus synthesised. The second chemical method consists in base-catalysed deuterium exchange of the α-hydrogen of amino acid chelates in chiral complexes Λ and Δ [Co(en)$_2$-(S)-aa]X_2 type. Chromatographic separation of the formed diastereomeric complexes followed by their reduction gives optically pure 2-^{2}H-aa.[7] Unfortunately, the separation and deuteration of the complexes are time consuming operations and may take several weeks.

We supposed that the replacement of Λ and Δ [Co(en)$_2$-(S)-aa] by Λ and Δ bis-[N salicylidene (S)-aminoacidato] cobaltate (III) ions (Λ and Δ [Co(Sal-(S)-aa)$_2$]Na) would yield optically pure 2-^{2}H-aa along the same pathway but considerably faster. This should be expected in view of the following reasons:

(a) The second order rate constant for the exchange of the glycine α-hydrogen under the action of OD^- in [Co(Sal-gly)$_2$]Na at 25°[8] is 63 times higher than in [Co(en)$_2$gly]X_2 at 30°.[9] It may be assumed that in other complexes [Co(Sal-(S)-aa)$_2$]Na the α-hydrogen will also be more labile than in [Co(en)$_2$-(S)-aa]X_2.

(b) Λ and Δ[Co(Sal - (S) - aa)$_2$]Na separation on Al_2O_3 takes several hours.

(c) The introduction of Me group into the position 3 of salicylaldehyde makes it possible to effect enantiospecific exchange in the complexes Δ[Co(3 - Me - Sal - (S) - aa)$_2$]Na[8].

The general pathway of the synthesis suggested is represented in Scheme I and consists in preparing a mixture of Λ and Δ[Co(Sal - (S) - 2 - ^{1}H - aa)$_2$]Na (Λ(SS) and Δ (SS)), separating the diastereomers on Al_2O_3 and deuterating separately Λ(SS) and Δ(SS) in D_2O under the action of OD^-. The separation of the mixture of the deuterated diastereomers of the Λ and Δ series obtained by preparative tlc yields optically pure (R) - 2 - ^{2}H - aa and (S) - 2 - ^{2}H - aa after the electrochemical reduction of the Λ(RR) and Δ(SS) isomers respectively. The experimental procedure of (R)- and (S) - 2 - ^{2}H - aa preparation by this method, starting from the synthesis of the initial complexes, takes, on an average, one week.

The enantiospecific exchange of the α-hydrogen of the gly and S-ala in Λ and Δ[Co(3 - Me - Sal - gly)$_2$]Na and Δ[Co(3 - Me - Sal - (S) - 2 - ^{1}H - ala)$_2$]Na yields (S)- and (R) - 2 - $^2H_1$ - gly and (S) - 2 - ^{2}H - ala, obviating the stage of chromatographic separation of the deuterated diastereomers.

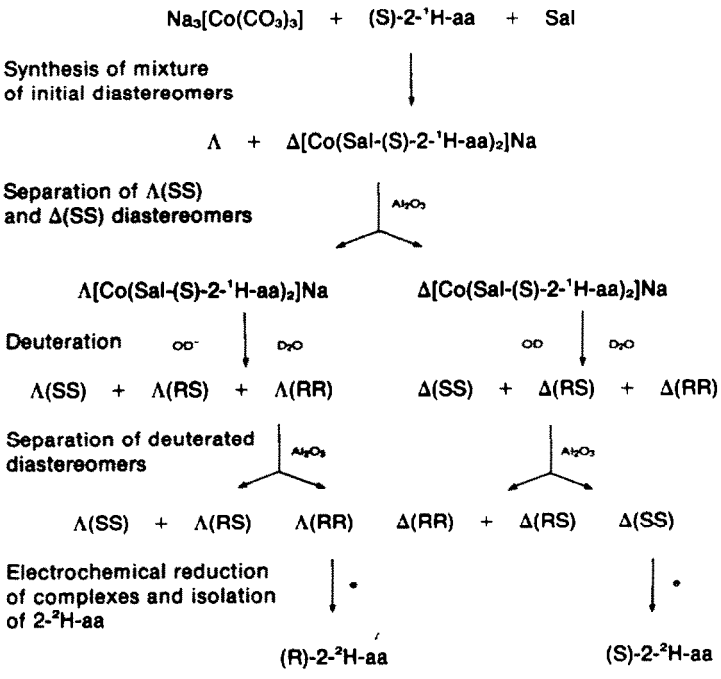
RESULTS AND DISCUSSION

General method of preparing 2-^{2}H-aa

(a) *Synthesis and separation of initial diastereomers.* The interaction of $Na_3[Co(CO_3)_3]$ with (S) - 2 - ^{1}H - aa and salicylaldehyde (Sal) or 3-methyl-salicylaldehyde (3 Me - Sal) gives a mixture of diastereomeric complexes Λ and Δ[Co(3 - X - Sal - (S) - 2 - ^{1}H - aa)$_2$]Na with a yield of 70–90%.†

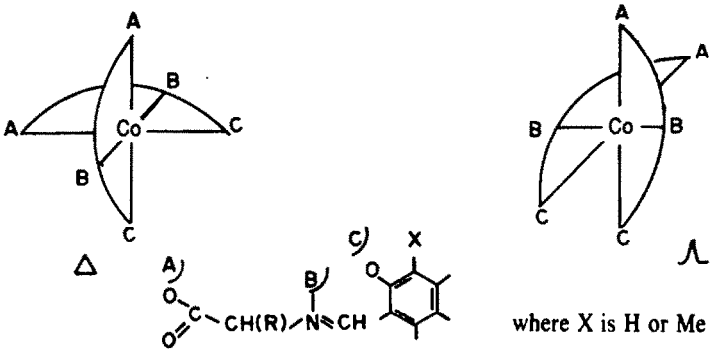
According to the X-ray analysis data[8,10] the Co^{3+} ion in these complexes has an octahedral coordination and

† Λ and Δ correspond to the left- and right-hand spiral arrangement of the ligands with respect to the axis C_2.[8,11]



Scheme 1.

the arrangement of two tridentate ligands is such as shown below.



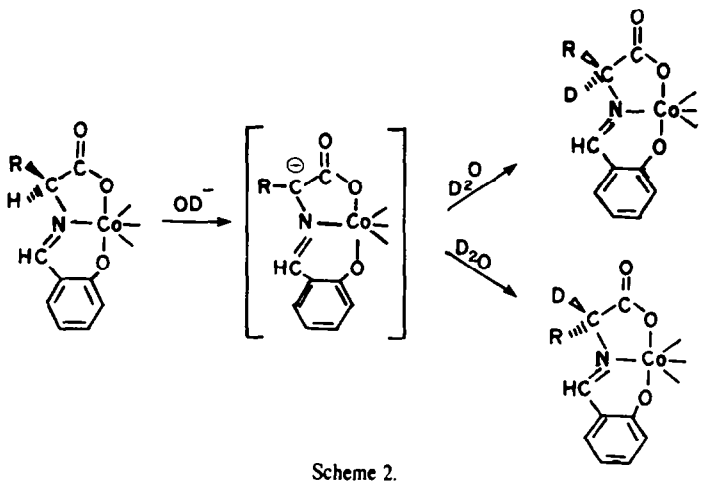
Complete separation of the diastereomers can be easily performed chromatographically on aluminium oxide.[8] To preclude oxidation[12] and racemisation of the amino acid moiety in the course of separation, the adsorbent was pretreated with a phosphate buffer solution, as described in the Experimental. Irrevocable losses of the complexes, when chromatographing them on Al_2O_3, range from 50% for the column chromatography to 25% for the preparative tlc. Partial separation of certain diastereomers can be attained on Sephadex LH-20. However, only for the diastereomers of sodium Λ and Δ bis-[N-salicylidene - (S) - valinato]cobaltate(III) the separation on Sephadex LH-20 is complete.

In the present work the diastereomeric complexes of sodium Λ and Δ bis-[N - salicylidene - (S) - norvalinato]cobaltate(III) BSNC; sodium Λ and Δbis - [N - salicylidene - (S) - methionato]cobaltate (III) BSMC; sodium Λ and Δ bis - [N - salicylidene (S) - tyrosinato]cobaltate(III) BSTC were synthesised and separated for the first time.

The complexes of sodium Λ and Δ bis - [N - salicylidene - (S) - valinato]cobaltate(III) BSVC; sodium Λ and Δ bis - [N - 3 - methyl - salicylidene - (S) - alaninato]cobaltate(III) MSAC; sodium Λ and Δ bis - [N - 3 - methyl - salicylidene - glycinato]cobaltate(III) MSGC had been synthesised earlier, starting from $Co(OH)_3$.[8, 13] In this work they were synthesised, starting from $Na_3[Co(CO_3)_3]$. The structure of these compounds has been confirmed by the comparison of their ORD curves, UV-ViS and ^1H NMR spectra with the parameters of the specimens obtained.[8, 13] Absolute configuration of the isomers can be assigned easily by comparing their ORD curves with those of sodium Λ and Δ bis - [3 - methyl - salicylidene - (S) - threoninato]cobaltate(III) MSTC, the absolute configuration of which was earlier determined by the X-ray analysis technique.[8, 10]

ORD curves of Λ(SS) and Δ(SS) MSTC; Λ(SS) and Δ(SS) BSNC are presented by way of illustration in Fig. 1.

(b) *Deuterium exchange of the α-hydrogen of an amino acid moiety and epimerisation of complexes in* D_2O *under the action of* OD^-. The amino acid moiety in the complexes Λ and Δ[Co(Sal - (S) - 2 - ^1H - aa)$_2$]Na is a



Scheme 2.

CH-acid; therefore under the action of OD^- the α-hydrogen of the amino acid moiety is exchanged by $D^{\oplus}$ in accordance with Scheme 2.

When the exchange of H by D is not enantiospecific, the process gives a mixture of diastereomers Λ(SS); Λ(RS) and Λ(RR) or Δ(SS) Δ(RS) and Δ(RR).[13,14] To preclude oxidation of the ligand,[12] the deuterium exchange reaction should be conducted under Ar. The ease of the deuterium exchange of the α-hydrogens of the amino acid moiety of the Λ or Δ[Co(3 - X - Sal - (S) - 2 - ^{1}H - aa)$_2$]Na depends on the structure of the amino acid and increases in the series Tyr, Val, Nva, Met, Ala.

The extent of the exchange of the 2-^{1}H of the amino acid moiety by deuterium was monitored by the ^{1}H NMR method. The conditions of deuterium exchange for each compound are presented in Table 1.

(c) *Separation of diastereomers after deuteration.* The mixture of the [Co(3- X - Sal - (S) - 2 - ^{2}H - aa)$_2$]Na diastereomers, which forms in the course of the deuterium exchange is separated by preparative tlc. To preclude ^{2}H–^{1}H re-exchange in the course of this

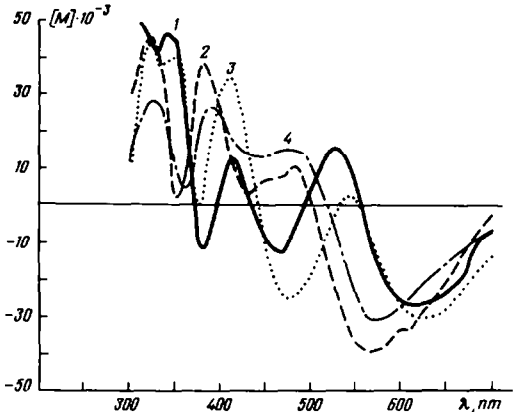


Fig. 1. ORD curves in water (t = 25°)
1. Λ[Co(Sal-(S)-2-^{1}H-NVa)$_2$]Na
2. Δ[Co(Sal-(S)-2-^{1}H-NVa)$_2$]Na
3. Λ[Co(Sal-(S)-2-^{1}H-Thr)$_2$]Na
4. Δ[Co(Sal-(S)-2-^{1}H-Thr)$_2$]Na.

Table 1. Conditions of deuterating Λ and Δ[Co(Sal-(S)-aa)$_2$]Na in D_2O at 25°C and optical purity of the obtained (R) and (S) 2-²H-aa, as determined by GLC

Designation of complex	Compound	Enantiomeric purity of initial S-aa	OD^-M (pD)	Experiment time (hr)	Separated diastereomers (ratio)	Optical purity of obtained 2-²H-aa
Λ(SS) BSTC	Λ[Co(Sal-(S)-Tyr)$_2$]Na	99%	0.082	22	$\frac{\Lambda(SS)+\Lambda(RS)}{\Lambda(RR)}=\frac{1}{1.8}$	68% (R)-Tyr*
Δ(SS) BSTC	Δ[Co(Sal-(S)-Tyr)$_2$]Na		0.082	92	$\frac{\Delta(RR)+\Delta(RS)}{\Delta(SS)}=\frac{1}{1.8}$	94% (S)-Tyr*
Λ(SS) BSVC	Λ[Co(Sal-(S)-Val)$_2$]Na	99.9%	0.082	7.5	$\frac{\Lambda(RR)+\Lambda(RS)}{\Lambda(RR)}=\frac{1.5}{1}$	96% (R)-Val
Δ(SS) BSVC	Δ[Co(Sal-(S)-Val)$_2$]Na		0.082	2.8	$\frac{\Delta(RR)+\Delta(RS)}{\Delta(SS)}=\frac{1}{1}$	98.8% (S)-Val
Λ(SS) BSNC	Λ[Co(sal-(S)-NVa)$_2$]Na	99.1%	0.032	1.5	$\frac{\Lambda(SS)+\Lambda(RS)}{\Lambda(RR)}=\frac{1}{1.05}$	93.4% (R)-NVa
Δ(SS) BSNC	Δ[Co(Sal-(S)-(S)-NVa)$_2$]Na		0.032	1.2	$\frac{\Delta(RR)+\Delta(RS)}{\Delta(SS)}=\frac{1}{1.7}$	94% (S)-NVa
Λ(SS) BSMC	Λ[Co(Sal-(S)-Met)$_2$]Na	99%	0.01	12	Λ(SS): Λ(RS): Λ(RR) = 1:1.5:2.7	82% (R)-Met
Δ(SS) BSMC	Δ[Co(Sal-(S)-Met)$_2$]Na		0.01	18	Δ(RR): Δ(RS): Δ(SS) = 1:1.5:2.7	90% (S)-Met
Λ(SS) MSAC	Λ[Co(Me-Sal-(S)-Ala)$_2$]Na	99%	(10.5)	12	Λ(SS): Λ(RS): Λ(RR) = 1:2.5:1.75	90% (R)-Ala

*Polarimetric determination.

process, it is necessary to pretreat aluminium oxide as described in the Experimental. For the same purpose the complexes are eluted from the plate after the separation with 0.2M NaH_2PO_4. For MSAC and BSMC it is possible to attain complete separation of three dastereomers Λ(SS); Λ(RS) and Λ(RR), as well as of Δ(SS); Δ(RS) and Δ(RR). In this case maximum R_f is observed for the Λ(SS) and Δ(RR) isomers. Λ(RR) and Δ(SS) are eluted the last.

The ORD curves of the deuterated Λ(SS) BSMC are mirror images of the ORD curves of the deuterated Δ(RR) BSMC. The same is true for the ORD curves of the Λ(RR) and Δ(SS) BSMC.

Comparison of the values of molecular rotation (M) of the initial diastereomeric complexes with the M values of the deuterated diastereomers shows that, as should be expected, no substantial racemisation of the complexes with respect to the metal ion takes place in the course of D exchange.

The separation of deuterated diastereomers MSAC and BSMC gives fraction Λ(RS) or Δ(RS) with R_f values intermediate between those of the Λ(RR) and Δ(SS) or Λ(SS) and Δ(RR) isomers. The ORD curves of the intermediate fraction of BSMC show that the configuration of the complexes Λ or Δ is preserved. Enantiomeric analysis of the amino acid obtained after the electrochemical decomposition of these fractions proves that they contain a racemic amino acid.

Thus, for example, in the case of Δ(RS) BSMC 2-^{2}H-Met is separated, containing 50.4% (R)-2-^{2}H-Met and 49.6% (S) - 2 - ^{2}H - Met, while Λ(RS) BSMC gives 2 - ^{2}H - Met containing 48.9% (R) and 51.1% (S) form. From the ^{1}H NMR spectra of the deuterated Λ(RS) MSAC (43.7% (R) and 56.3% (S) - 2 - ^{2}H - ala) it can be seen that the signal of the Me group of the 2 - ^{2}H - ala moiety is a doublet instead of a singlet as in the case of deuterated Λ(SS) MSAC and Λ(RR) MSAC. This indicates the complex symmetry to be C_1 rather than C_2.

For the rest of the complexes it is possible to separate only Λ(RR) and the mixture of Λ(SS) and Λ(RS) or Δ(SS) and the mixture of Δ(RR) and Δ(RS).

The fraction containing the mixture of diastereomers has maximum R_f. The fact that this fraction is indeed a mixture of diastereomers is confirmed by the comparison of the ^{1}H NMR spectra of this fraction with the spectra of the initial and deuterated diastereomers. As should be expected, the signal due to the α-H of the amino acid is absent in both fractions of the deuterated BSVC. With this sole exception the spectra of the fraction having the smaller R_f are identical to the spectra of the non-deuterated Δ(SS) BSVC. The ORD curve of this deuterated fraction is a mirror image of Δ(SS). These data are in agreement with the structure of this compound as [Co(Sal - (R) - 2 - ^{2}H - Val)$_2$]Na.

In the spectrum of the fraction having the greater R_f two signals are observed instead of the aldimine proton singlet expected for the complex of symmetry C_2. Val isolated after the electrochemical reduction of this fraction contains 70% (S)-Val and 30% (R)-Val. Thus, there can be no doubt that the product is a mixture of Λ (RS) and Λ (SS) BSVC diastereomers.

The preservation of deuterium in the course of separation of the deuterated Λ and Δ [Co(3 - X - Sal - R(S) - 2 - ^{2}H - aa$_2$]Na diastereomers was monitored by the ^{1}H NMR technique.

(d) *Electrochemical reduction of the complexes and isolation of (S) and (R) - 2 - ^{2}H - aa.* Isolation of (S) or (R)-2-^{2}H from the complexes was carried out after the electrochemical reduction of the latter to labile complexes of Co^{2+}.[8] Mass spectrometry data confirm that in the course of reduction ^{2}H-^{1}H re-exchange of the amino acid moiety does not take place.

Thus, for example, according to the ^{1}H NMR data, in the initial mixture of deuterated BSMC diastereomers 2-^{1}H is not observed, which corresponds to >95% replacement of 2-^{1}H by 2-^{2}H in the Met moiety. 2-^{2}H-Met isolated from this mixture after its electrochemical reduction contains 2–3% 2-^{1}H-Met according to GC–MS data. Hence, the reduction of the complex is not accompanied by ^{2}H–^{1}H exchange.

Optical purity of the 2-^{2}H-aa obtained by the procedure described above and determined by the glc technique directly after the isolation of the aa from the complexes, without additional crystallization of the aa, lies in the range of 90 to 98% (Table 1). The only exception is (R)-2-^{2}H-Tyr (its optical purity being 64%). The main results of the work are summarized in Table 1.

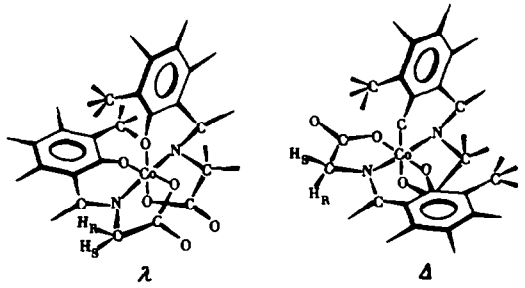
Synthesis of (R) *and* (S) - 2 - ^{2}H - *glycine and synthesis of* (S) - 2 - ^{2}H - *alanine without separation of deuterated diastereomeric complexes*

In Λ and Δ MSGC the Me substituent of the sal fragment of the neighbouring ligand shields, respectively, the pro-R and pro-S hydrogens of the glycine moiety[8] (Fig. 2). Therefore, as has been shown earlier, the exchange of diastereotopic α-protons of the glycine moiety in the complexes Λ and Δ-MSGC proceeds at a different rate.[8]

This allowed, after the exchange of *ca* 50% of the H of the glycine moiety, the isolation of (R)-2-^{2}H$_1$ glycine from Δ MSGC and (S)-2-^{2}H$_1$ glycine from Λ MSGC after the reduction of the complex. The glycine isolated from the Λ MSGC had the following specific rotation (after recalculation for the optically pure initial Λ-MSGC): $[\alpha]_{350} = -1.32°$; $[\alpha]_{300} = -2.89°$; $[\alpha]_{275} = -4.53°$; $[\alpha]_{250} = -7.8°$ ($c = 0.015$ g in 1 ml H_2O; $t = 22°$). The glycine isolated from the Δ MSGC had the specific rotation (after recalculation for the optically pure initial Δ-MSGC): $[\alpha]_{275} = +1.27°$; $[\alpha]_{250} = +4.7°$; $[\alpha]_{238} = +8.95°$ ($c = 0.011$ g in 1 ml H_2O; $t = 22°$).

Pure chiral (S)-2-^{2}H$_1$ glycine has, according to the literature data,[15] the following specific rotation values: $[\alpha]_{364} = -1.3°$; $[\alpha]_{275} = -11.0°$; $[\alpha]_{250} = -17.8°$ ($c = 0.114$ g in 5 ml H_2O. According to Refs. 16 and 17 (R)-2-^{2}H$_1$ glycine has $[\alpha]_{238}^{20} = +38.8°$ or $+36.5°$.

An additional confirmation of the fact that Λ and Δ MSGC give, respectively (S) and (R)-2-^{2}H$_1$ glycines is furnished by ^{1}H NMR spectra of camphanoyl derivatives of the racemic and chiral glycines. The 90 MHz ^{1}H NMR



Λ Δ

Fig. 2. Schematic representation of shielding of pro-(S) and pro-(R) hydrogens of glycine fragment in Δ MSGC and Λ MSGC.

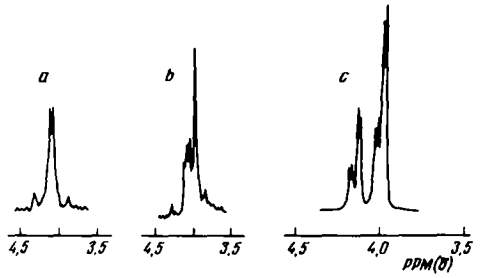


Fig. 3. 1.90 MHz ^{1}H NMR spectrum of camphanoyl derivative of racemic glycine. 2. 90 MHz ^{1}NMR spectrum of camphanoyl derivative of chiral (S)-2-^{2}H glycine (1 and 2 are recorded with decoupling from N–H protons ($CECl_3$; HMDS). 3. 360 MHz ^{1}H NMR spectrum of camphanoyl derivative of chiral glycine ($CDCl_3$; HMDS).

and 360 MHz ^{1}H NMR spectra of the caphanoyl derivative of (S)-2-^{2}H glycine from Λ MSGC are presented in Fig. 3. The same Figure shows the 90 MHz ^{1}H NMR spectrum of the caphanoyl derivative of achiral glycine. α-Protons of the glycine moiety of this compound are diastereotopic and appear at 90 MHz as AB system (J_{gem} – 18 Hz).

(S)-2-$^2H_1$-glycine was isolated after *ca* 40% exchange of the α-hydrogens. Therefore in the ^{1}H NMR spectrum of the camphanoyl derivative of this compound there are signals due to the initial achiral glycine, on which signals at 3.98 and 4.12 ppm (with respect to HMDS) are superimposed. These signals can be assigned to (S)-2-$^2H_1$ and (R)-2-$^2H_1$ glycines, respectively.[15] The 360 MHz ^{1}H NMR spectrum of this compound allows one to find the relative quantities of 2-$^1H_2$ gly, 2-$^2H_1$ gly, and 2-$^2H_2$ gly in per cent of the total amount of the gly to be equal to 24%, 72% and 4% respectively. The ratio of (S)-2-$^2H_1$ glycine and (R)-2-$^2H_1$ glycine (after recalculation for the enantiomerically pure complex) in 3:1. Thus, using chiral Λ and Δ MSGC, one can obtain (S) and (R) $^2H_1$-glycines with the enantiomeric purity of 20–40%.

The Me substituent in position 3 of the phenyl ring in the complexes Δ [Co(3 - Me - Sal - (S) - 2 - ^{1}H-aa)$_2$]Na shields the *si* side of the amino acid carbanion.[8] This leads to the preferable attack of D_2O from the *re* side of

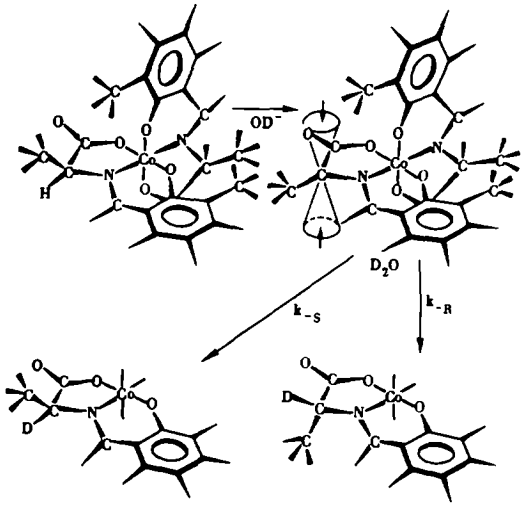


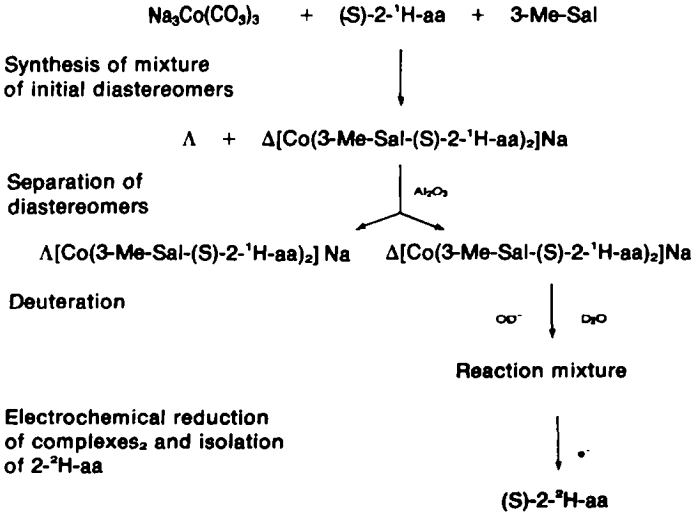
Fig. 4. Schematic representation of steric shielding of intermediate carbanion in sodium Δ bis [3 - methyl - salicylidene - (S) - alaninato]cobaltate(III).

the carbanion (Fig. 4). Thus, ($K_{-S}/K_{-R} \approx 1$) and the mixture of diastereomers, which is formed in deuteration of Δ (SS) MSAC contains a large excess of the Δ (SS) form. This is confirmed by comparison of the ^{1}H NMR spectra of the mixture (Fig. 5) and of the initial Δ (SS) MSAC as well as by the tlc data.

The mixture of diastereomers can be reduced directly electrochemically. (S)-2-^{2}H ala isolated by the conventional method had 90% (S) and 10% (R). This corresponds to the ratio K_{-S}/K_{-R} *ca* 10. The same ratio of the rate constants of the D_2O attack from the *re* and *si* sides of the carbanion was observed also for Δ Co(3 - Me - Sal - (S) - 2 - ^{1}H - Val)$_2$ K.[8] From this it follows that the kinetic enantioselectivity of deuterium exchange in Λ and Δ[Co(3 - Me - Sal - S - (R) - aa)$_2$]Na can also be employed for the synthesis of a wide range of chiral 2-^{2}H-aa according to Scheme 3.

CONCLUSION

The general method of synthesis elaborated in the present work can be applied for preparing a wide range



Scheme 3.

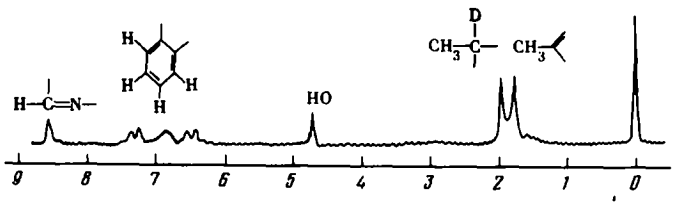


Fig. 5. 90 MHz ^1H NMR spectrum of Δ[Co(3 - Me - Sal - (S) - 2 - ^1H - ala)$_2$]Na deuteration product.

of neutral (S) and (R) 2-^2H-aa, with the exception of proline and other N-substituted aa which cannot form Schiff bases. The preparation of deuterated acidic and basic aa in accordance with this method requires protection of the carboxyl and amino groups in the side chain of the aa.

EXPERIMENTAL

All amino acids were purchased either from "Reachim" (USSR) or from "Reanal Budapest". The enantiomer purity of all amino acids, except tyrosine, was determined by glc. Sephadex LH-20 was purchased from "Pharmacia Fine Chemicals Incorporated". Al_2O_3 Brokmann II, neutr for column chromatography was purchased from "Reanal Budapest". For preparative TLC Al_2O_3 (neutr L-5/40) was purchased from "Chemapol Praha".

Al_2O_3 was pretreated in the following manner

(a) For column chromatography 160 g of Al_2O_3 (Brokmann II) was mixed with a soln of 5 g NaH_2PO_4 in 300 ml H_2O and the mixture was evaporated for 2 hr at 80° and 20–25 mm. After drying for 2 hr at 100° and 1 mm the adsorbent was ready for use.

(b) For preparative tlc 160 g of Al_2O_3 (neutr L-5/40) was mixed with a soln of 20 g NaH_2PO_4 in 300 ml H_2O and dried as described above. Salicylaldehyde was predistilled under argon; 3 - methyl - salicylaldehyde was prepared according to the technique given in Ref. 18 and purified chromatographically on Sephadex LH-20 in a dichloroethane/ethanol system (4:1).

$Na_3[Co(CO_3)_3]$ was prepared according to the technique given in Ref. [19]. Isotopic purity of D_2O was 99.9%. Isotopic purity of CD_3OD was 99%. Soln of NaOD in D_2O was prepared by addition of metallic Na under argon to D_2O from which CO_2 was preliminarily removed. Carbonate buffer soln in D_2O was prepared by dissolving $NaHCO_3$ (0.4104 g) and Na_2CO_3 (0.78 g) in 50 ml of D_2O. Concentration of OD^- in D_2O was determined by potentiometric titration. The pD of the buffer carbonate solution was determined with a glass electrode on a "Radiometer SBR-2/SB-4/TTT1" from pD = pH + 0.4, where pH is the observed pH of solution.[20] UV-Vis spectra and ORD curves were recorded respectively on a "Specord UV-Vis" spectrophotometer and a "Jasco ORD/UV-5" spectropolarimeter. ^1H NMR spectra were recorded on a Soviet-made apparatus "P5-2309" and on a "Brucker WH-360". Electrochemical reduction of the complexes was carried out on a Soviet-made potentiostat "П-5827".

Synthesis of sodium Λ and Δ - bis - N - salicylidene - (S) - aminoacidato cobaltate (III)

Synthesis of BSTC, BSVC, BSMC was carried out according to the technique of Bailar from Na_3 [$Co(CO_3)_3$] Sal and (S) - 2 - ^1H-aa.[21]

Thus, for example, according to this technique, from 1.81 g (0.005 mole) of Na_3 [$Co(CO_3)_3$], 1.22 g (0.01 mole) of Sal and 1.17 g (0.01 mole) of (S) - 2 - ^1H - Val there were obtained 2 g (0.0036 mole) of Λ + Δ[Co(Sal - (S) - 2 - ^1H - Val)$_2$]Na. The yield was 72%.

Synthesis of BSNC, MSAC and MSGC was carried out according to a modification of the technique of Bailar. Described below is an experimental procedure for the case of preparing BSNC from Sal and S-NVa.

Synthesis of sodium Λ and Δ - bis - N - salicylidene - (S) - norvalinato cobaltate (III)

A soln of (S)-NVa (1.17 g, 0.01 mole) and KOH (0.56 g, 0.01 mole) in 100 ml of EtOH was heated to complete dissolution of S–NVa, cooled down to temp., 1.22 g (0.01 mole) of Sal in 5 ml of EtOH was added, the mixture was stirred in the presence of molecular sieves Wolfen–Zeosorb-3 A for 10 min, then separated from the sieves and added simultaneously with 1 N HNO_3 (20 ml) under vigorous stirring under Ar to 1.81 g (0.005 mole) of $Na_3[Co(CO_3)_3]$ and 0.1 g of active charcoal in 20 ml of absolute EtOH.

The mixture was stirred for 2 hr at 60°, filtered, evaporated to dryness *in vacuo*, the residue was dissolved in a mixture of benzene with alcohol 2:1, filtered and evaporated. The residue was dried *in vacuo* over P_2O_5. The synthesis gave 2.3 g of a mixture of BSNC diastereomers. The yield was 88.4%.

Separation of sodium Λ and Δ - bis - N - salicylidene - S) - aminoacidato cobaltate (III)

All diastereomers were separated chromatographically on Al_2O_3 in alcohol.

(a) *Column chromatography of the diastereomers.* For preparing large quantities of BSNC, BSVC diastereomers column chromatography was employed. Described below is a typical experimental procedure for the case of separating Λ(SS) and Δ(SS) BSNC.

A mixture of BSNC diastereomers (1.8 g) in 10 ml of C_2H_5OH was placed on a column with Al_2O_3 (3 cm × 28 cm).

Elution was carried out with EtOH at the rate of 0.7 ml/min. BSNC gave two brown bands. The first band separated in the volume of 170 ml of the eluent and the second band, in 250 ml of the eluent. Complete separation of the diastereomers is attained in 13 hr. The fractions were evaporated and additionally purified from mineral salts on a column Sephadex LH-20 (2.5 cm × 18 cm) in a benzene:alcohol system (1:1).

The ORD curves of fractions I and II allow the assignment of the Λ and Δ configuration to them respectively. 0.6 g of dry Δ(SS) and 0.34 g of dry Λ(SS) were obtained.

For BSVC and BSNC the Λ(SS) isomer was always the first to emerge from the Al_2O_3 column.

Λ(SS) and Δ(SS) BSVC can be completely separated also on a Sephades LH-20. For this purpose on a column (3.5 cm × 28 cm) with LH-20 swollen in a benzene:alcohol mixture (3:1) 1.2 g of the mixture of diastereomers was applied. Elution was performed with a benzene:alcohol mixture (3:1) at the flow rate of 0.5 ml/min. Complete separation of Λ(SS) and Δ(SS) BSVC occurs in 90 hr. The fractions containing the diastereomers were evaporated. The residue was dried *in vacuo*. 0.5 g of Δ(SS); 0.06 g of a mixture of Λ(SS) and Δ(SS); and 0.4 g of Λ(SS) BSVC were obtained in the order of the emergence from the column.

(b) *Preparative tlc of the diastereomers on* Al_2O_3. BSTC, BSMC and MSAC diastereomers were separated by preparative tlc on Al_2O_3. Described below is a typical experiment for the case of separating Λ(SS) and Δ(SS) BSMC.

A mixture of BSMC diastereomers (1.7 g) was separated on ten plates, 18 cm × 24 cm each, coated with a 1 mm layer of Al_2O_3. The eluent was EtOH. 0.17 g of the complex was applied on each plate. In one development the mixture completely separates into two brown bands. The Al_2O_3 containing these bands was removed from the plate. The BSMC diastereomers were isolated from the Al_2O_3 by washing with 50–60 ml of 0.2 M NaH_2PO_4.

The solns containing similar isomers were combined and evaporated *in vacuo* at 40°. The dry residue was treated with a benzene:alcohol mixture (1:1) and filtered. The filtrate was evaporated and the residue was purified from mineral salts on a Sephadex LH-20 column (2.5 cm × 18 cm) in a benzene:alcohol

system (1:1). The soln containing the pure diastereomer was evaporated *in vacuo*. The residue was dried *in vacuo* over P_2O_5 at 50°. 0.78 g of Λ(SS) and 0.41 g of Δ(SS) BSMC were obtained.

For all the compounds employed in the present work the Λ(SS) isomer has a greater R_f on Al_2O_3 than the Δ(SS) isomer. The elemental analysis of the synthesised diastereomers of sodium Λ and Δ-bis [N-salicylidene - (S) - aminoacidato] cobaltate (III) is presented in Table 2.

Chemical shifts of the protons of the complexes employed in the present work are given in Table 4.

Parameters of the UV-Vis spectra of these compounds are given in Table 3.

Specific molecular rotation values of the complexes employed in the present work are given in Table 5.

Table 2. Elemental analysis of compounds [Co(Sal-(S)-aa)$_2$]·Na

Designation	Complexes	C (%)		H (%)		N (%)	
		Found	Calc.	Found	Calc.	Found	Calc.
Λ(ss) BSNC	[Co(Sal-(S)-NVa)$_2$]Na·2H$_2$O	51.81	51.81	4.92	4.67	4.78	5.03
Δ(ss) BSNC	[Co(Sal-(S)-NVa)$_2$]Na·3H$_2$O	49.96	50.1	4.65	4.52	4.71	4.87
Λ(ss) BSTC	[Co(Sal-(S)-Tyr)$_2$]Na·4H$_2$O	53.39	53.3	3.95	3.6	3.59	3.8
Δ(ss) BSTC	[Co(Sal-(S)-Tyr)$_2$]Na·3H$_2$O	54.64	54.7	3.85	3.7	3.93	3.98
Λ(ss) BSMC	[Co(Sal-(S)-Met)$_2$]Na·4H$_2$O	44.27	43.96	4.24	3.97	4.23	4.27
Δ(ss) BSMC	[Co(Sal-(S)-Met)$_2$]Na·2H$_2$O	46.62	46.52	4.44	4.2	4.47	4.52

Table 3. UV-Vis maxima and extinction coefficients of newly synthesized Λ and Δ[Co(Sal-(S)-2-^{1}H-aa)$_2$]Na diastereomers

Compounds	Λnm(ε)		
Λ [Co(Sal-(S)-2-^{1}H-NVa)$_2$]Na	504 (511)	374 (4234)	237 (44136)
Δ [Co(Sal-(S)-2-^{1}H-NVa)$_2$]Na	504 (502)	380 (5883)	248 (50225)
Λ [Co(Sal-(S)-2-^{1}H-Tyr)$_2$]Na	504 (612)	378 (5004)	225 (57150)
Δ [Co(Sal-(S)-2-^{1}H-Tyr)$_2$]Na	504 (456)	384 (6404)	223 (53088)
Λ [Co(Sal-(S)-2-^{1}H-Met)$_2$]Na	504 (656)	378 (4920)	238 (47970)
Δ [Co(Sal-(S)-2-^{1}H-Met)$_2$]Na	504 (496)	382 (6045)	250 (48825)

Table 4. Chemical shifts of protons (δ ppm) with respect to HMDS in CD_3OD) of the [Co(3-X-Sal-(S)-2-^{1}H-aa)$_2$]Na complexes employed in the present work

Compound	H–C=N	Aromatic protons	CH_3–Ar	Amino acid fragment		
				α–CH	β–CH and γ–CH	δ–CH
Λ [Co(Sal-(S)-2-^{1}H-NVa)$_2$]Na	s 8.45	m 6.37–7.6		d 4.9(6)	m 1.31–2.4	t 1.05
Δ [Co(Sal-(S)-2-^{1}H-NVa)$_2$]Na	s 8.47	m 6.55–7.62		d 4.62(6.5)	m 1.5–2.55	t 1.12
Λ [Co(Sal-(S)-2-^{1}H-Tyr)$_2$]Na	*	m 6.19–7.26		d 4.64	m 3.13–3.52	
Δ [Co(Sal-(S)-2-^{1}H-Tyr)$_2$]Na	*	m 6.27–7.27		d 4.5	m 3.21–3.47	
Λ [Co(Sal-(S)-2-^{1}H-Met)$_2$]Na	s 8.35	m 6.28–7.34		t 4.93(7)	m 2.2–2.83	s 2.06 (S–CH_3)
Δ [Co(Sal-(S)-2-^{1}H-Met)$_2$]Na	s 8.39	m 6.37–7.41		t 4.74(6)	m 2.22–2.93	s2.06 (S–CH_3)
Λ [Co(3-Me-Sal-(S)-2-^{1}H-Ala)$_2$]Na	s 8.5	m 6.3–7.4	s 1.42	d 4.95(7.5)	d 1.85(7.5)	
Δ [Co(3-Me-Sal-(S)-2-^{1}H-Ala)$_2$]Na	s 8.5	m 6.2–7.37	s 1.75		d 2.0 (7.5)	d1.18(6.5)
Λ [Co(Sal-(S)-2-^{1}H-Val)$_2$]Na**	s 8.46	m 6.32–7.67		d 4.53(8)	m 1.98–2.83	
Δ [Co(Sal-(S)-2-^{1}H-Val)$_2$]Na**	s 8.51	m 6.39–7.78		d 4.42(7.5)	m 2.08–3	d 1.25(6.5) d 1.12(6.5)
[Co(3-Me-Sal-2-$^1H_2$-Gly)$_2$]Na	s 8.9	m 6.4–7.5	s 1.53	s 5.04		

*Signal of aldimine proton is superimposed onto the signals of aromatic protons.
**^{1}H NMR spectrum is recorded in D_2O (with respect to DSS).

Table 5. Specific and molecular rotations of the complexes employed in the present work (H_2O; 25°)

Type of compound	C·10^4 g/ml	[α] (Λ nm)	C·10^4 mole/l	[M] (Λnm)
Λ [Co(Sal-(S)-2-^{1}H-Val)$_2$]Na·3H$_2$O	4.16	−7320 (589)	7.25	−42015 (589)
Δ [Co(Sal-(S)-2-^{1}H-Val)$_2$]Na·2H$_2$O	3.4	−4334 (589)	6.1	−24140 (589)
Λ [Co(Sal-(S)-2-^{1}H-NVa)$_2$]Na·3H$_2$O	4.2	−6159 (589)	7.32	−35300 (589)
Δ [Co(Sal-(S)-2-^{1}H-NVa)$_2$]Na·2H$_2$O	4.0	−3747 (589)	7.19	−21000 (589)
Λ [Co(Sal-(S)-2-^{1}H-Met)$_2$]Na·2H$_2$O	4.0	−5975 (589)	6.45	−37045 (589)
Δ [Co(Sal-(S)-2-^{1}H-Met)$_2$]Na·4H$_2$O	3.56	−3483 (589)	6.09	−25600 (589)
Λ [Co(Sal-(S)-2-^{1}H-Tyr)$_2$]Na·3H$_2$O	4.0	−6600 (589)	5.698	−46200 (589)
Δ [Co(Sal-(S)-2-^{1}H-Tyr)$_2$]Na·4H$_2$O	4.0	−4072 (589)	5.55	−29300 (589)
Λ [Co(3-Me-Sal-(S)-2-^{1}H-Ala)$_2$]Na·3H$_2$O	4.0	−325 (578)	7.33	−1775 (578)
Δ [Co(3-Me-Sal-(S)-2-^{1}H-Ala)$_2$]Na·3H$_2$O	4.0	−2480 (578)	7.39	−13600 (578)

Deuteration of Λ *and* Δ [Co(3 - X - Sal - (S) - 2 - ^{1}H - aa)$_2$]Na

For removing the crystallisation water, before carrying out the experiment each complex was dissolved in a small quantity of D_2O. The resulting soln was evaporated *in vacuo* over P_2O_5.

The H exchange of the amino acid moiety proceeds under mild conditions at 25°. A typical experiment of Λ or Δ[Co(Sal - (S) - 2 - ^{1}H - aa)$_2$]Na deuteration is described below.

A 0.082N soln of NaOD in D_2O (10 ml) was placed into a 50 ml flask. 0.4–0.8 g of Λ or Δ [Co(Sal - (S) - 2 - ^{1}H - Val)$_2$]Na was placed into another 50 ml flask thermostatted at 25°. Both flasks, after the evacuation of air *in vacuo*, were filled with argon. This operation was repeated 3–4 times. Then the contents of the flasks were combined so that the presence of air was completely precluded. A portion of the homogeneous soln was transferred by means of a syringe under Ar into a cell of a "Perkin–Elmer-241" polarimeter, thermostatted at 25°, and the change in the rotation of the specimen at 578 nm was recorded (Fig. 6). After the rotation had practically ceased changing, the mixture was neutralised with a 1N D_2SO_4 in D_2O. The soln was evaporated at 40°. The dry residue was treated with a benzene:alcohol mixture (1:1), filtered, and the soln containing the mixture of deuterated diastereomers was evaporated *in vacuo* to dryness. The residue was treated with 1 ml of D_2O and dried *in vacuo* over P_2O_5 at 78° for 1 hr. The ^{1}H NMR spectrum in CD_3OD of the thus obtained mixture of deuterated diastereomers shows absence of the α-hydrogen signal of the valine fragment.

Other complexes were deuterated by following the same technique. The concentration of OD^- ions in each experiment and the duration of these experiments are presented in Table 1. The only difference in the experimental procedure for Λ(SS) and Δ(SS) BSTC and Λ(SS) MSAC was that these compounds were introduced into the reaction as DMF solns (0.8 g of the complex in ≈0.8 ml of DMF). If the HOD signal was superimposed on the α-hydrogen signal of the amino acid moiety, the ^{1}H NMR spectrum of the mixture of deuterated diastereomers was recorded either at 45° or with adding D_2SO_4 to their CD_3OD soln.

Separation of deuterated diastereomers

All deuterated diastereomers are separated by preparative tlc as described above. Thus, for example, the separation of 0.6 g of deuterated diastereomers requires four chromatographic plates 18 × 14 cm with 1 mm thickness of the Al_2O_3 layer.

Deuteration of 0.6 g of Λ(SS) BSVC gave 0.25 g of a mixed Λ(SS) + Λ(RS) fraction and 0.17 g of Λ(RR) BSVC fractions.

The product of deuteration of 0.6 g of Δ(SS) BSVC gives 0.2 g of the mixed Δ(RR) + Δ(RS) and 0.2 g of the Δ(SS) BSVC fractions.

The ^{1}H NMR spectra of all these fractions show absence of the signals of the α-hydrogen of the valine fragment.

BSTC, BSMC, MSAC and BSMC deuterated diastereomers were separated in a similar manner; the ratio of the isolated diastereomers is presented in Table 1.

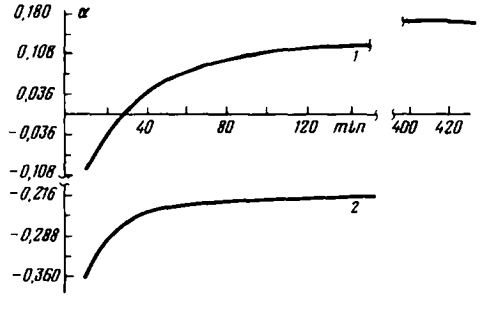


Fig. 6. Change of rotation of Λ and Δ[Co(Sal - (S) - 2 - ^{1}H - val)$_2$]Na samples in 0.082N solution of NaOD in D_2O (t = 25°; λ = 578 nm). 1. Λ[Co(Sal - (S) - ^{1}H - Val)$_2$]Na. 2. Δ[Co(Sal - (S) - 2 - ^{1}H - Val)$_2$]Na.

Isolation of (R) *and* (S) 2-^{2}H-aa

(a) Reduction of 0.2–2 g of the complexes was carried out electrochemically in 100 ml of a 0.2M NaH_2PO_4 soln. The solns obtained after the elution of deuterated diastereomers from tlc plates can be reduced directly electrochemically by using the technique given in Ref. 8.

(b) Amino acids were isolated from the mixture after the reduction in the following manner. The contents of the electrolytic cell were thoroughly extracted with ether to remove Sal and the aqueous soln was transferred onto a column with Dowex-50W × 8 (3 cm × 20 cm) in H^+ form. The column was washed with water to pH 3.0–4.0 (S) or (R)-2-^{2}H-aa was eluted with 3M ammonia. The eluate was evaporated *in vacuo*. The chemical yield amino acids is quantitative. Thus, for example, 0.2 g of Δ[Co(Sal - (S) - 2 - ^{2}H - Val)$_2$]Na gave 0.080 g of (S) - 2 - ^{2}H - Val with the enantiomeric purity of 98.8%. The enantiomeric and quantitative analysis of the amino acids were carried out without preliminary crystallisation of the latter.

(c) *Enantiomeric analysis of the amino acids.* Glc enantiomeric analysis of the amino acids was carried out in accordance with the technique given.[22] Enantiomeric purity of (R) and (S) 2-^{2}H-Tyr was determined polarimetrically.

(d) Quantitative analysis of the amino acids was carried out by glc in accordance with the procedure given.[23]

(e) *Mass spectrometric analysis.* The D content in the isolated Met was determined mass spectrometrically from the ratio of the peaks of molecular ions M_H and M_D for the isopropyl ester of N-trifluoroacetyl derivative (M = 287 and 288 respectively). The study was carried out on an AEI DBMS-1073 instrument with ionising voltage of 70 eV and ion source temp. of 200°. A glass capillary column LKB Am-Ac and a jet separator at t – 130° were employed.

Synthesis of (S) *and* (R)-2-^{2}H$_1$-*glycine*

(a) *Preparation of* Λ *and* Δ[Co(3 - Me - Sal - 2 - ^{1}H$_2$ - gly)$_2$]Na. Racemic [Co(3 - Me - Sal - 2 - ^{1}H$_2$ - gly)$_2$] Na was prepared and resolved in accordance with the technique given.[8]

The ^{1}H NMR spectra and the ORD curves as well as the elemental analysis data of Λ and Δ MSGC are in agreement with the data.[8] For preparing (S) and (R)-2-^{2}H$_1$-glycines Λ MSGC and Δ MSGC were used, respectively. The enantiomeric purity of Λ MSGC was 85.5% ($[M]_{650}$ = −9850); that of Δ MSGC was 66.2% ($[M]_{650}$ = +7500).

(b) Enantioselective exchange of (pro-S and pro-R) hydrogen of the glycine fragment in Λ MSGC and Δ MSGC and preparation of (S)-2-^{2}H$_1$ and (R)-2-^{2}H$_1$ glycines.

Λ or Δ MSGC (2 g) were dissolved in 200 ml of a carbonate buffer soln (pD 10.5) in D_2O under Ar. The technique of combining the buffer soln and MSGC was the same as for other complexes (see above). In 70 min at 25° the soln was neutralised with 1M H_3PO_4 and transferred to an electrolytic cell. After the reduction gly was isolated in a usual manner. The solution was passed through a column with active charcoal (0.5 cm × 1 cm) for decolorisation.

The initial Λ and Δ MSGC (2 g) gave, respectively, 0.5 g of 81% (S)-2-^{2}H glycine and 0.52 g of 85% (R)-2-^{2}H glycine. The glycine was additionally purified by crystallisation from a mixture of water and 96% alcohol (2.3 ml of H_2O and 1 ml of EtOH per g of glycine).

The specific rotation values of the samples of chiral glycine are given in the Section "Results and Discussion".

(c) *Preparation of* (−) *camphanoyl glycine.* Camphanoyl chloride[24] was prepared by a multistage method from camphoric acid (α_D^{20} = +48° in EtOH, m.p. 189–191°) and purified by sublimation before the use. Condensation of camphanoyl chloride with glycine was carried out according to the technique given.[15] The resulting (−) (1S, 4R) camphanoyl glycine had the m.p. = 73–75° (lit. 73.5–75°).[15]

360 MHz ^{1}H NMR spectrum of camphanoyl - (S) - 2 - ^{2}H$_1$ - glycine in $CDCl_3$ (δ ppm with respect to HMDS) 0.9 (C - CH_3-4'); 1.03 (C - CH_3 - 7); 1.06 (C - CH_3 - 7'); 1.6–2.52 (M. 5' – 6' H_2); 7.2 (d. NH 3.99 (q J_{vic} – 5.4 Hz; J_{gem} – 18 Hz pro - (R) - H); 4.15 (q J_{vic} – 5.4 Hz; J_{gem} – 18 Hz pro - (S) - H) 3.38 (d J_{vic} – 5.4 Hz; (S) - 2 - ^{2}H - gly) and 4.12 (d. J_{vic} 5.4 (R) - 2 - ^{2}H - gly).

Preparation of (S) - 2 - ^{2}H alanine by enantioselective exchange of α-hydrogen of alanine fragment of Δ[Co(3 - Me - Sal - (S) - 2 - ^{2}H - ala)$_2$]Na

A soln of 0.5 g of Δ (SS) MSAC in 0.5 ml of DMF under Ar (see above) was transferred into 10 ml of buffer soln (pD 10.5). In 16 hr at 25° the solution was neutralized with 1M H_3PO_4. The ^{1}H NMR spectrum of the deuteration product shows that the dominant diastereomer in the mixture is Δ[Co(3 - Me - Sal - (S) - 2 - ^{2}H - ala)$_2$]Na.) The soln obtained after neutralisation was placed into an electrolytic cell and after the reduction of the complex (S)-2-^{2}H-ala was isolated in a conventional manner. The enantiomeric purity of the product was 80%.

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