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# Kinetics and Stereochemistry of Deuterium Exchange of the α-Hydrogen of an Amino Acid Moiety in Metal Complexes of Amino Acid Schiff Bases with *Ortho*-hydroxyacetophenone

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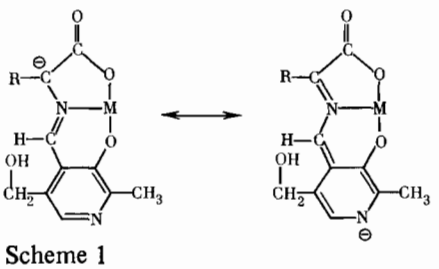
## Introduction

It is well known that in the presence of transition metal ions and pyridoxal, amino acids undergo many of those transformations which are catalyzed by pyridoxal-dependent enzymes [1].

Such reactions of amino acids as racemization and formation of the C–C bond are catalyzed in the presence of transition metals by the simplest analogue of pyridoxal-salicylaldehyde [2]. The key intermediate particle in all these model transformations is a metal complex of an amino acid Schiff base and pyridoxal or its analogues [3].

In these complexes the amino acid moiety is a CH-acid. Therefore under the action of bases the amino acid moiety donates an α-hydrogen and becomes a carbanion. This carbanion is commonly believed to be planar and resonance-stabilized [3], as is shown in Scheme 1 for complexes of pyridoxal Schiff bases.

Equality of the rates of deuterium exchange and racemization of the amino acid moiety in Λ and Δ bis-[N-salicylidene-(S)-valinato] cobaltate(III) complexes is an indirect evidence in favour of the intermediate formation of a planar carbanion in deuterium



Scheme 1

exchange in metal complexes of Schiff bases of salicylaldehyde and amino acids [4]. In such a carbanion, evidently, substantial steric interactions occur between the aldimine H and the substituent of the amino acid moiety [4] (Fig. 1).

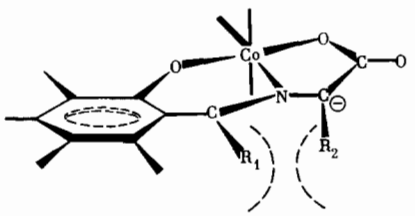


Fig. 1. Schematic representation of steric intramolecular interaction in the formation of a planar carbanion of an amino acid moiety in metal complexes of Schiff bases of salicylaldehyde or *ortho*-hydroxyacetophenone and amino acids.

It is obvious that an increase in the volume of $R_1$ and $R_2$ must lead to an enhancement of steric nonbonding interaction in this intermediate particle with simultaneous destabilization of the latter. In the limiting case the carbanion ceases to be planar and the conjugation between the carbanion centre and phenyl ring will become interrupted.

The possibility of formation of a non-planar chiral carbanion of an amino acid Schiff base is of considerable interest in connection with the stereochemistry of highly enantioselective processes catalyzed by pyridoxal enzymes [5].

Thus, for example, deuterium exchange of amino acids, which proceeds with retention of the configuration on the active site of a number of pyridoxal enzymes [6], may be thought of as going through intermediate formation of an non-planar chiral carbanion which retains its configuration during a period of time sufficiently long for the amino acid carbanion to accept a deuteron from the medium from the side the proton has left it.

Intermediate formation of such a carbanion in metal complexes can be ascertained by measuring the dependence of the rate and stereochemistry of the exchange of the α-hydrogen of the amino acid moiety of the complex on the volume of the groups $R_1$ and $R_2$.

In the present work we report on our attempt to find a slowly inverting non-planar carbanion in metal

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complexes of amino acid Schiff bases with *ortho*-hydroxyacetophenone As subjects for the investigation, we have synthesized a racemic ion of bis[N-7-methylsalicylideneglycinato] cobaltate(III) (BMSGC), synthesized and separated diastereomeric ions of Λ and Δ* bis[N-7-methylsalicylidene-(S)-alaninato]-cobaltate(III) (BMSAC), and have also prepared sodium [N-7-methylsalicylidene-(S)-alaninato, N-7-methylsalicylideneglycinato] cobaltate(III) (MSAGC) The rates of deuterium exchange and epimerization of the amino acid moieties in these complexes, as well as in (N-7-methylsalicylidene-S-alaninato)copper-(II) (MSAC), were quantitatively investigated The obtained data were compared with the parameters of similar processes for the complexes of Λ and Δ bis[N-salicylidene-(S)-alaninato] cobaltate(III) (BSAC) and bis[N-salicylidenglycinato] cobaltate(III) (BSGC)

## Experimental

Amino acids were purchased from Reanal, Budapest Enantiomeric purity of alanine was determined by GLC [7] Sephadex LH-20 was purchased from Pharmacia Fine Chemicals Incorporated

$Al_2O_3$ Brokman II neuter for chromatography was purchased from Reanal Budapest

*o*-Hydroxyacetophenone was purchased from Reachim (USSR)

$Na_3[Co(CO_3)_3]$ was prepared according to the technique given in [8]

Isotopic purity of $D_2O$ was 99 9%

NaOD solution in $D_2O$ was prepared by adding metallic Na under Ar to $D_2O$ after the removal of $CO_2$ from it Concentration of $OD^-$ in $D_2O$ was determined by potentiometric titration

Carbonate buffer solution in $D_2O$ was prepared by dissolving $NaHCO_3$ (0 4104 g) and $Na_2CO_3$ (0 78 g) in 50 ml of $D_2O$

The pD values of the carbonate buffer solution were determined with a glass electrode on a Radiometer SBR2(SB-4)TTT1 from pD = pH + 0 4, where pH is the observed pH of solution [9]

UV–Vis spectra and ORD curves were recorded on a 'Specord UV–Vis' spectrophotometer and on a 'Jasco ORD/UV-5' spectropolarimeter, respectively $^1$H NMR spectra were recorded on Soviet-made spectrometer 'P I-2309' Electrochemical reduction of the complexes was carried out on a Soviet-made potentiostat 'П-5827'

*Synthesis of Initial Compounds*

*Synthesis of sodium Λ and Δ bis[N-7-methylsalicylidene-(S)-alaninato] cobaltate(III) (BMSAC)*

Synthesis was carried out by using a Bailar Procedure for the synthesis of sodium bis-[N-salicylideneaminoacidato] cobaltate(III) [10] 3 56 g (40 mmol) of S-ala, 5 54 g (40 mmol) of hydroxyacetophenone and 7 2 (23 mmol) of $Na_3[Co(CO_3)]_3$ gave 3 9 g (39 8%) of a mixture of BMSAC diastereomers

*Separation of Λ and Δ-bis[N-7-methylsalicylidene-(S)-alaninato] cobaltate(III)*

3 9 g of the mixture of BMSAC diastereomers in 10 ml of $C_2H_5OH$ were placed on a column with $Al_2O_3$ (2 9 cm × 30 cm) The elution rate was 0 7 ml/min BMSAC separated into 2 brown bands Complete separation was attained in 36 h The fractions were evaporated and additionally desalted on a column of Sephadex LH-20 (2 5 cm × 18 cm) in a benzene-alcohol system (1 1)

Dry residue obtained fraction I–1 5 g (Λ(SS)), fraction II–0 37 g (Δ(SS))

The elemental analysis, parameters of the electronic spectra and molecular rotation of Λ and Δ BMSAC are presented in Table I

The $^1$H NMR spectra are given in Figs 4 and 5 The ORD curves of the diastereomers are given in Fig 2

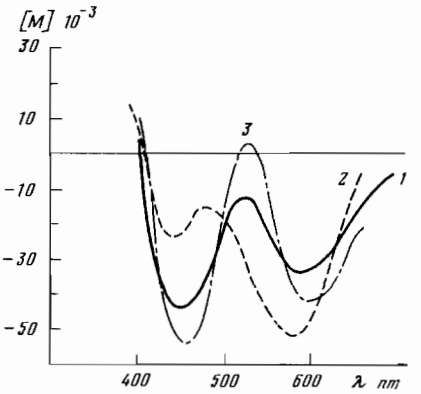



Fig 2 ORD curves in water (t 25 °C), 1) sodium Λ[N-7-methylsalicylidene-(S)-alaninato, N-7-methylsalicylideneglycinato] cobaltate(III), 2) sodium Δ bis[N-7-methylsalicylidene-(S)-alaninato] cobaltate(III), 3) sodium Λ bis[N-7-methylsalicylidene-(S)-alaninato] cobaltate(III)

*Synthesis and separation of diastereomers of sodium Λ and Δ bis[N-salicylidene-(S)-alaninato]-cobaltate(III) (BSAC)*

These were carried out as described above The parameters of the obtained compound were fully in agreement with the data reported in the literature [11]

*Here and hereafter the symbols Λ and Δ are used to denote the left- and right-handed helical arrangement of the ligands in relation to the $C_2$ axis, respectively

TABLE I Parameters of the Complexes of $Co^{3+}$ with Schiff Bases of *Ortho*-hydroxyacetophenone and Amino Acids, Synthesized in the Present Work

| Code | Complex | Elemental analysis | | | | | | Electronic Spectra in $H_2O$ $\Lambda$ nm ($\epsilon$) | Molecular Rotation in $H_2O$ [*M*] (nm) |
|---|---|---|---|---|---|---|---|---|---|
| | | %C | | %H | | %N | | | |
| | | Calc | Found | Calc | Found | Calc | Found | | |
| BMSAC | $\Lambda$[Co(7-Me-Sal-ala)$_2$]Na·4$H_2O$ | 46 81 | 46 58 | 5 36 | 4 63 | 4 96 | 4 82 | 690(127) 364(4830) 229(47940) | –4820(578) |
| BMSAC | $\Delta$[Co(7-Me-Sal-ala)$_2$]Na·4$H_2O$ | 45 36 | 45 28 | 5 5 | 4 87 | 4 81 | 4 61 | 680(160) 368(7057) 248(53653) | –7850(578) |
| MSGAC | $\Lambda$[Co(7-Me-Sal-ala) (7-Me-Sal-gly)]Na·4$H_2O$ | 45 82 | 45 74 | 3 64 | 3 77 | 5 09 | 5 08 | 680(250) 366(8750) 230(72700) | –4620(578) |
| BMSGC | [Co(7-Me-Sal-gly)$_2$]Na·2$H_2O$ | 44 79 | 45 18 | 4 89 | 4 81 | | | | |
| MSAC | Cu(7-Me-Sal-ala)·2$H_2O$ | 40 07 | 39 60 | 4 70 | 4 12 | 4 67 | 4 08 | 680(81) 367(3225)* | –477 5(436)* |

*Determination of the parameters was carried out in 96% $C_2H_5OH$

*Synthesis of sodium [7-methylsalicylidene-(S)-alaninato, 7-methylsalicylidenglycinato] cobaltate-(III) (MSAGC)*

This was carried out according to the same procedure from 0 89 (10 mmol) of (S)-ala, 0.75 g (10 mmol) of glycine, 1 12 g (20 mmol) of KOH and 2 72 g (20 mmol) of hydroxyacetophenone there were obtained 2 g of a product which was a mixture of compounds, further separated by preparative TLC on $Al_2O_3$ 2 g of the product were separated on 5 plates, 18 × 24 cm each, coated with a 1mm layer of $Al_2O_3$ The eluent was $C_2H_5OH$ Each development gives 3 brown bands $Al_2O_3$ containing these bands was removed from the plate and its elution with 50–60 ml of $C_2H_5OH$ allowed 3 fractions $R_{fI} > R_{fII} > R_{fIII}$ to be isolated Each of these fractions was evaporated, treated with a benzene/alcohol mixture (III), filtered, evaporated, and dried over $P_2O_5$ in vacuo Obtained. fraction I–0 1 g, fraction II–0 3 g, fraction III–0 2 g

The $^1H$ NMR spectra and ORD curves of these fractions have shown that fraction I is $\Lambda$[Co(7-Me-Sal-(S)-ala)$_2$]Na, fraction III is [Co(7-Me-Sal-gly)$_2$]-Na, and fraction II is a mixed complex MSAGC

The structure of [Co(7-Me-Sal-ala)(7-Me-Sal-gly)]-Na has been confirmed by comparison of the ORD curves of BMSAC and fraction II (which allowed configuration to be assigned to the obtained compound, see Fig 2), by the UV-Vis and elemental analysis data (Table I)

$^1H$ NMR of MSAGC $\delta$($CD_3OD$ in relation to HMDS) 1 73 (d) ($CH_3$-C-), 2 77 (s) ($CH_3$-C=N),



4 62 (s) (-$CH_2$-), 4 88 (q) (-C-), 6 07–7 55 (m) (Ar)

*Synthesis of sodium bis-[N-7-methylsalicylidene-glycinato] cobaltate(III) (BMSGC)*

This was carried out according to the Ballar procedure for the synthesis of sodium bis-N-salicylidenaminoacidatocobaltate(III) [10] 1 5 g (20 mmol) of glycine, 2 72 g (20 mmol) of hydroxyacetophenone and 2 91 g (10 mmol) of $Co(NO_3)_2 \cdot 6H_2O$ were air oxidized to give after purification on a LH-20 Sephadex column (alcohol/benzene (3 1) 0 5 g BMSGC (9 3%)

The elemental analysis and parameters of the electronic spectra of BMSGC are presented in Table I

$^1H$ NMR spectrum of BMSGC $\delta$($CD_3OD$, HMDS), 2 77 (s) ($CH_3$-C=N), 6 29–7 61 (m) (Ar), 4 79 (s) ($CH_2$)

*Synthesis of [N-7-methylsalicylidene-(S)-alaninato] copper(II) (MSAC)*

This was carried out according to the procedure given in [12] The obtained complex was purified on Sephadex LH-20 in a mixture alcohol benzene (5 1) The data of the elemental analysis, parameters of the electronic spectra, and molecular rotation of

TABLE II. Degree of Deuterium Exchange of α-Hydrogen and Enantiomeric Composition of the Amino Acid, Isolated after Treating a Number of Complexes with Base in $D_2O$.

| Code | Complex | t °C | Time, min | Concentration of $OD^-$ (pD) | Degree of deuterium exchange, % | S-aa, % | R-aa, % | S – [2-$^2$H]-aa / R – [2-$^2$H]-aa |
|---|---|---|---|---|---|---|---|---|
| BMSAC | Λ[Co(7-Me-Sal-(S)-ala)$_2$]Na | 21 | 145 | 0.156 | 50 | 91.3 | 8.7 | 4.8 |
| | | | 275 | | 61 | 87.5 | 12.5 | 3.9 |
| | | | 1365 | | 100 | 81.2 | 18.8 | 4.3 |
| BMSAC | Δ[Co(7-Me-Sal-(S)-ala)$_2$]Na | 21 | 145 | 0.158 | 82 | 84.5 | 15.5 | 4.3 |
| | | | 275 | | 100 | 82.3 | 17.7 | 4.7 |
| BMSAC | Λ[Co(7-Me-Sal-(S)-ala)$_2$]Na | 40 | 35 | 0.156 | 48.6 | 88.5 | 11.5 | 3.2 |
| | | 4 | 1270 | | 52.9 | 88.7 | 11.3 | 3.7 |
| BMSGC | [Co(7-Me-Sal-gly)$_2$]Na | 25 | 155 | (10.6) | 45 | | | |
| MSAC | Cu(7-Me-Sal-(S)-ala) | 21 | 130 | | 18.1 | 93 | 7 | 1.6 |
| | | | 250 | 0.158 | 28.7 | 88.3 | 11.7 | 1.5 |
| | | | 410 | | 31.8 | 84 | 16 | 1.0 |
| BSAC | Λ[Co(Sal-(S)-ala)$_2$]Na | 21 | 190 | (10.6) | 52 | 75.3 | 24.7 | 1.1 |
| MSGAC | Λ[Co(7-Me-Sal-(S)-ala) (7-Me-Sal-gly)]Na | 21 | 65 | 0.158 | 48 | 76.4 | 23.6 | 1.0 |
| | | | 145 | | 80 | 65.5 | 34.5 | 1.3 |

the complex are given in Table I. The enantiomeric purity of alanine isolated from the initial complex, as determined by GLC, was 99.2%.

*Deuterium Exchange of α-Hydrogen of Amino Acid Moiety in Λ and Δ[Co(7-Me-Sal-(S)-ala)$_2$]Na; [Co(7-Me-Sal-gly)$_2$]Na; Λ[Co(Sal-(S)-ala)$_2$]Na; Cu(7-Me-Sal-gly) and Λ[Co(7-Me-Sal-(S)-ala)(7-Me-Sal-gly)]Na*

Deuterium exchange of Λ and Δ BMSAC was carried out in 0.156 *N* and 0.158 *N* NaOD in $D_2O$.

The experiment was carried out in a thermostatted flask at the temperature of 4°, 21° and 40°C. After definite periods of time samples were taken under argon (see Table II) and neutralized with 1 *N* $H_3PO_4$.

The samples were evaporated, the residue was treated with a mixture of alcohol and benzene (1:1), filtered, the filtrate was evaporated, treated with a small quantity of $D_2O$ and dried in vacuo over $P_2O_5$.

The deuterium exchange was followed by using $^1$H NMR techniques and observing the change of the relative area of the α-proton of the amino acid moiety of the complexes and/or the diminution of the signal due to the ala isolated after the electrochemical reduction of the complexes [4]. The obtained data are summarized in Table II.

Deuterium exchange of Λ[Co(7-Me-Sal-(S)-ala)(7-Me-Sal-gly)]Na was carried out as described above, in 0.158 *N* NaOD in $D_2O$. The deuterium exchange was followed by using $^1$H NMR techniques and observing the change of the relative area of the α-proton of the ala isolated after the electrochemical reduction of the complex. The data are presented in Table II.

Deuterium exchange of Λ[Co(Sal-(S)-ala)$_2$]Na was carried out as described above in a buffer soln in $D_2O$ (pD 10.6). The data are presented in Table II.

Deuterium exchange of [Co(7-Me-Sal-gly)$_2$]Na was carried out as described above in a buffer soln in $D_2O$ (pD 10.6). The process was followed by using $^1$H NMR techniques and observing the diminution of the α-hydrogen signal of the glycine moiety.

*Deuterium exchange of Cu(7-Me-Sal-(S)-ala)*

A soln of 0.45 g (1.4 × $10^{-3}$ mol) of MSAC in 8 ml of 0.158 N NaOD in $D_2O$ and 1 ml of pyridine was stirred with argon in a thermostatted flask (21 °C). After definite periods of time samples were taken, neutralized with 1 *N* $H_3PO_4$, and the amino acid was isolated by a conventional ion-exchange procedure (on Dowex 50 × 8). The degree of the ala deuteration was analyzed by the $^1$H NMR technique. The obtained data are summarized in Table II.

*Alkaline Epimerization of the Amino Acid Moiety in Λ and Δ[Co(7-Me-Sal-(S)-ala)$_2$]Na*

Alkaline epimerization of Λ(SS) or Δ(SS) BMSAC was carried out in 0.17 *N* NaOH in a thermostatted flask at the temperature of 21 °C under argon. In 3 days equilibrium was established, the reaction mixture was neutralized with 1 *N* $H_3PO_4$, evaporated and separated into fractions by preparative TLC on $Al_2O_3$, using plates 18 cm × 24 cm in size. The eluent was $C_2H_5OH$. A single development gave 2 brown bands. $Al_2O_3$ containing these bands was removed from the plate and eluted with 100 ml of $C_2H_5OH$; fractions $R_{fI}$, $R_{fII}$ were thus isolated.

The concentration of these fractions was determined by UV–Vis technique The fraction I/fraction II ratio proved to be 1.2

The $^1$H NMR spectra and ORD curves showed that in the case of initial Λ-BMSAC fraction I is Λ[Co(7-Me-Sal-(S)-ala)$_2$]Na [Λ(SS)], its ORD curve being a mirror image of the ORD curve of fraction I from initial Δ-BMSAC, which is Δ[Co(7-Me-Sal-(R)-ala)$_2$]-Na [Δ(RR)]

Fraction II in the case of Λ-BMSAC is [Co(7-Me-Sal-(R)-ala)$_2$]Na[Λ(RR)], whose ORD curve is a mirror image of the ORD curve of fraction II of Δ-BMSAC, which is Δ[Co(7-Me-Sal-(S)-ala)$_2$]Na [Δ(SS)]

Enantiomeric composition of the amino acid after the deuteration was determined by GLC [7], by analyzing the amino acid isolated from the same samples which had been used for determining the degree of deuterium exchange of the amino acid moiety of the complexes.

Deuterium exchange rate constants were calculated from the formula

$$k_{obs} = \frac{\ln \frac{100}{100 - x}}{t}$$

where x is the quantity of non-deuterated amino acid in per cent of the total quantity, t is the time from the beginning of the experiment in sec

Second-order deuterium exchange rate constant

$$k_{ex} = \frac{k_{obs}}{[OD^-]}$$

where $OD^-$ is either NaOD concentration in $D_2O$ soln, or is found from the formula

$$pOD = pK_{D_2O} - pD$$

$pK_{D_2O}$ was adopted to be equal to 14 7 [9]

The $k_{-S}/k_{-R}$ ratio was calculated by assuming that this ratio is determined as

$$\frac{S[2\text{-}^2H]\text{-ala}}{R[2\text{-}^2H]\text{-ala}}$$

The quantity of R[2-$^2$H]-ala was assumed to be equal to the total quantity of R-ala in the mixture (in %) Hence, the quantity of S[2-$^2$H]-ala (in %) is S[2-$^2$H]-ala = Σ[2-$^2$H]-ala-R[2-$^2$H]-ala, where Σ[2-$^2$H]-ala is the degree of deuteration of ala in %

## Results and Discussion

*Synthesis of Diastereomeric Complexes of Bis(N-7-methylsalicylideneaminoacidato)cobaltate(III)*

Diastereomers of BMSAC and racemic MSGC were prepared by reacting (S)-ala or gly with $Na_3$[Co-$(CO_3)_3$] with *o*-hydroxyacetophenone (7-Me-Sal) as described above (see Experimental) Diastereomers were separated chromatographically on $Al_2O_3$

The elemental analysis of the obtained compounds corresponds to the complexes with the composition [Co(7-Me-Sal-(S)-2-$^1$H-ala)$_2$]Na and [Co(7-Me-Sal-gly)$_2$]Na (see Table I)

ORD curves of the obtained diastereomers of BMSAC are presented in Fig. 2 The calculated configuration components of the ORD curves [13] of fractions I and II of BMSAC and of sodium Λ-bis[N-salicylidene-(S)-alaninato]cobaltate(III) (BSAC) are presented in Fig 3

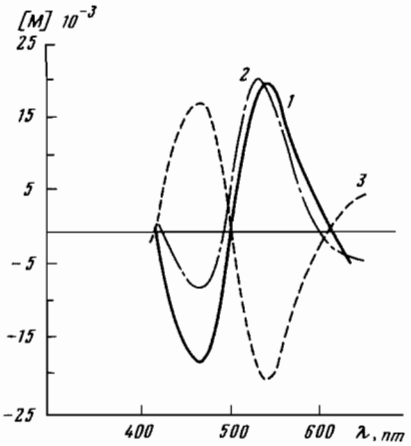



Fig 3 Configuration components of ORD curves, 1) fraction I of sodium bis[N-7-methylsalicylidene-(S)-alaninato]-cobaltate(III) Λ(SS), 2) fraction I of sodium bis[N-salicylidene-(S)-alaninato]cobaltate(III) Λ(SS), 3) fraction II of sodium bis[N-7-methylsalicylidene-(S)-alaninato]cobaltate-(III) Δ(SS)

Comparison of these curves shows that fraction I of BMSA, which has a greater mobility on $Al_2O_3$ than fraction II of BMSAC, has the same absolute configuration as Λ(SS) BSAC The absolute configuration of the latter can be easily determined in the manner described earlier for other diastereomeric ions of Λ and Δ bis-[N-salicylideneaminoacidato]cobaltate(III) [4] Hence, it follows that the configuration of fraction II of BMSAC is Δ(SS)

Λ(S) MSAGC was isolated by preparative TLC (on $Al_2O_3$) from the mixture of products resulting in the interaction of gly, (S)-ala, 7-Me-Sal and $Na_3$[Co-$(CO_3)_3$] The ORD curve of Λ(S) MSAGC is presented in Fig 2

*Kinetics and Stereochemistry of Deuterium Exchange of the α-Hydrogen of an Amino Acid Moiety of BMSAC, MSAC, BMSGC, MSAGC and BSAC*

α-Hydrogen of the alanine moiety of Λ(SS) and Δ(SS) BMSAC in 0 15 *N* NaOD ($D_2O$) is exchanged by deuterium The exchange is accompanied by a

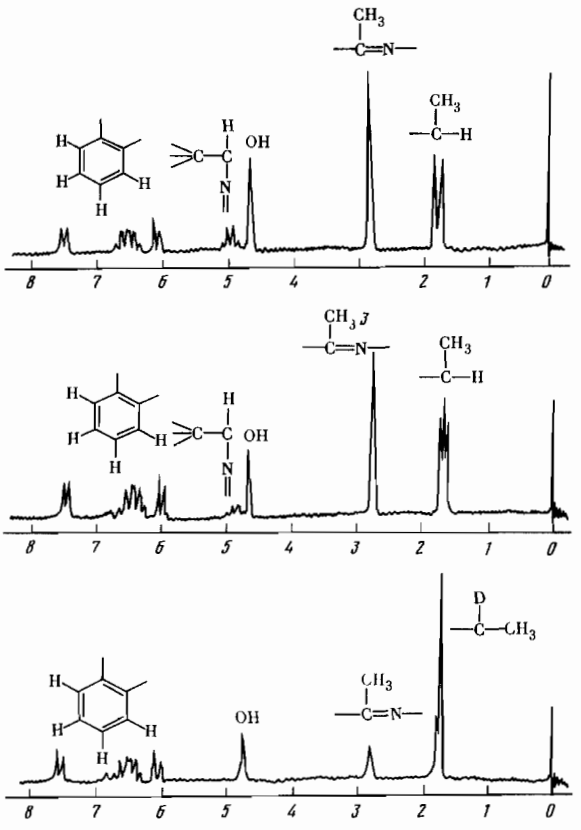


Fig 4 $^1$H NMR spectra ($CD_3OD$, HMDS), 1) spectrum of initial Λ(SS) BMSAC, 2) spectrum of Λ(SS) BMSAC in 2 5 hours in 0 156 *N* NaOD in $D_2O$, 3) spectrum of Λ(SS) BMSAC in 23 hours in 0 156 *N* NaOD in $D_2O$

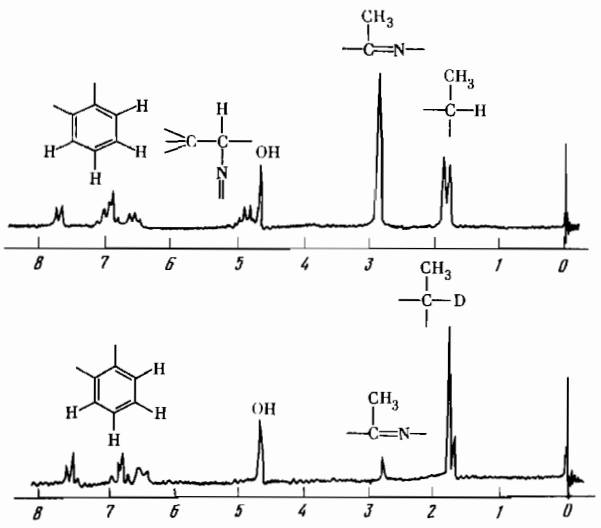


Fig 5 $^1$H NMR spectra ($CD_3OD$, HMDS), 1) spectrum of initial Δ(SS) BMSAC, 2) spectrum of Δ(SS) BMSAC in 4½ hours in 0 158 *N* NaOD in $D_2O$

diminution of the relative area of the signal of its α-proton (4 93 ppm and 4 89 ppm respectively) and by the transformation of the doublet of the $CH_3$ group (1 77 ppm and 1 81 ppm) into a singlet as for the cases of Λ and Δ BMSAC (see Figs 4 and 5)

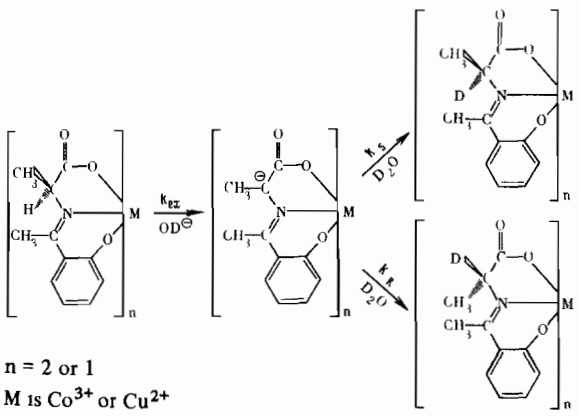
Protons of the methyl group of 7-Me-Sal also enter into the reaction of deuterium exchange, though more slowly than the α-protons of the alanine moiety Quantitatively the degree of deuteration of the alanine, as well as its enantiomeric composition, were determined after the electrochemical reduction of the deuterated diastereomers of BMSAC by analyzing the isolated alanine by $^1$H NMR and GLC methods MSAC and MSGAC also enter into the reaction of deuterium exchange, the degree to which this reaction proceeds can be judged by analyzing the alanine isolated from the complex after the reaction has been carried out

For the sake of comparison, deuterium exchange of Λ(SS) BSAC was carried out in a buffer solution in $D_2O$ (pD 10 6)

The degree of deuteration of this compound was determined in the same manner as for other complexes

As can be seen from the data presented in Figs 4 and 5, for both Λ(SS) and Δ(SS) BMSAC the exchange is accompanied by retention of the configuration of the amino acid moiety Thus, the spectrum of the fully deuterated Λ(SS) BMSAC (see Fig 4) contains an intensive singlet of the $CH_3$ group of the ala moiety with δ = 1 76 ppm and a less intensive singlet with 1 80 ppm At the same time the signal of this group for the fully deuterated Δ(SS) isomer is an intensive singlet with 1 80 ppm and a less intensive singlet with δ = 1 76 ppm

By analogy with other amino acid complexes of metals it may be supposed that deuterium exchange [2a, 4, 14] of Λ(SS) and Δ(SS) BMSAC and MSAC under the action of $OD^-$ in $D_2O$ proceeds through intermediate formation of an amino acid carbanion The entire exchange can thus be described by Scheme 2



n = 2 or 1
M is $Co^{3+}$ or $Cu^{2+}$

Scheme 2

TABLE III Parameters of Exchange of α-Hydrogen of an Amino Acid Moiety of Various Metal Complexes of Amino Acid Schiff Bases in $D_2O$ under the Action of $OD^-$

| Exp No | Code of complex | Complex | t °C | Concentration of $OD^-$ (pD) | $k_{ex}$ $M^{-1}$ $s^{-1}$ ** | $k_{-S}/k_{-R}$ |
|---|---|---|---|---|---|---|
| 1 | BMSAC | Λ[Co(7-Me-Sal-(S)-ala)$_2$] Na | 21 | 0 156 | 4 3 × $10^{-4}$ | 4 3/1 |
| 2 | BMSAC | Λ[Co(7-Me-Sal-(S)-ala)$_2$] Na | 40 | 0 158 | 2 01 × $10^{-3}$ | 3 2/1 |
| 3 | BMSAC | Λ[Co(7-Me-Sal-(S)-ala)$_2$] Na | 4 | 0 158 | 6 25 × $10^{-5}$ | 3 7/1 |
| 4 | BMSAC | Δ[Co(7-Me-Sal-(S)-ala)$_2$] Na | 21 | 0 158 | 1 25 × $10^{-3}$ | 4 5/1 |
| 5 | BSAC | Λ[Co(Sal-(S)-ala)$_2$] Na | 21 | (10 6) | 8 30 × $10^{-1}$ | 1/1 |
| 6 | BMSGC | [Co(7-Me-Sal-gly)$_2$] Na | 25 | (10 6) | 6 0 × $10^{-1}$ | |
| 7 | BSGC | [Co(Sal-gly)$_2$] Na | 25* | (10 6)* | 6 3* | |
| 8 | MSAC | Cu(7-Me-Sal-(S)-ala) | 21 | | 1 36 × $10^{-4}$ | 1/1 |
| 9 | MSAGC | Λ[Co(7-Me-Sal-(S)-ala)(7-Me-Sal-gly)] Na | 21 | 0 158 | 1 11 × $10^{-3}$ | 1/1 |

*Reference [4] **$k_{ex}$ determination error lies within 20%

Since deuterium exchange was carried out in $D_2O$, *i e* in a high-polarity medium the effects associated with 'internal return' of the proton [15] and 'isoracemization' [15] can be neglected

Hence, it follows that after the decomposition of the reaction mixture the entire isolated [2-$^1$H]-ala is obtained from the unreacted initial complex and has the configuration (S), while all the (R)-ala contains deuterium

Time dependence of the rate of (S) and (R)[2-$^2$H] ala accumulation allows one to find $k_{ex}$ as well as the ratio of (S)[2-$^2$H] ala and (R)[2-$^2$H] ala, equal to $k_{-S}/k_{-R}$ Both for the diastereomers of BMSAC and for MSAC the ratio (S)[2-$^2$H] ala/(R)[2-$^2$H] ala practically does not depend on the degree of deuteration (see Table II) Average values of $k_{ex}$ and $k_{-S}/k_{-R}$ for BMSAC, MSAC and BSAC are given in Table III As can be seen from the data presented in Table III, BMSAC and BMSAC exchange α-hydrogen of (S)-ala by deuterium with the configuration being preserved, and $k_{-S}/k_{-R}$ lies within the range of 4 1–4 3 at 21 °C

The temperature dependence of the ratio $k_{-S}/k_{-R}$ is small it varies from 3 2 to 4 1 within the temperature range of 4 to 40 °C

This result shows a principal difference in the behaviour of BMSAC complexes from that of BSAC in the reaction of deuterium exchange of the amino acid moiety Thus, the complex Λ(SS) BSAC which in structure is closest to BMSAC exchanges α-hydrogen with complete racemization (Table III) Exchange of hydrogen with racemization is observed also for Λ and Δ bis[N-salicylidene-(S)-valinato] cobaltate(III) complexes BSVC [4]

Thus, replacement of aldimine hydrogen for the methyl group leads to preservation of the configuration of the amino acid moiety in deuterium exchange in the Λ(SS) and Δ(SS) BMSAC complexes

Steric effects of the final state of the reaction cannot account for the retention of the configuration both for Λ and Δ BMSAC

Thus, enantimeric analysis of ala isolated after the electrochemical reduction of the equilibrium mixture of diastereomers, obtained after alkaline epimerization of Λ and Δ BMSAC (in accordance with Scheme 3), gives the ratio

$$\frac{\Lambda(RR)}{\Lambda(SS)} = \frac{\Delta(SS)}{\Delta(RR)} = 2/1$$

$$\Lambda(SS) \underset{H_2O}{\overset{OH^-}{\rightleftharpoons}} \Lambda(RR)$$

$$\Delta(SS) \underset{H_2O}{\overset{OH^-}{\rightleftharpoons}} \Delta(RR)$$

Scheme 3

Thus, a thermodynamically controlled process gives excess R-ala from Λ BMSAC Consequently, the reasons for the preservation of the configuration of (S)-ala in the deuterium exchange of Λ(SS) BMSAC can be of kinetic character only

However, the data on the stereochemistry of deuterium exchange of the amino acid moiety in the MSAC and MSGAC complexes show that the intermediately forming carbanion cannot be a slowly inverting chiral one It is obvious that any steric interactions of the groups $R_1$ and $R_2$ (Fig 1) of the intermediate carbanion must be the same in the case of BMSAC and in the case of MSAC and MSGAC, a chiral slowly inverting carbanion could be formed in these two cases as well Indeed, although the rate of deuterium exchange in MSGAC is considerably decelerated as compared to BSAC (Table III), both MSAC and MSGAC do exchange their α-hydrogen with complete racemization of the amino acid moiety (Table III)

Evidently, the reason why the configuration S-ala is preserved in the deuterium exchange of the ala moiety in the case of both Λ and Δ BMSAC lies in an unusually great influence of the neighbouring chiral S-ala moiety on the relative rates of $D_2O$ attack on

the *re* and *si* sides of the intermediate planar or rapidly inverting carbanion of the amino acid moiety of BMSAC

What can be said about the probability of formation of a slowly inverting non-planar chiral carbanion? The probability of this phenomenon is, evidently, small in view of the following considerations comparison of the rate of deuterium exchange of racemic ions of bis-[N-salicylideneglycinato] cobaltate(III) (BSGC) and bis-[N-7-methylsalicylideneglycinato] cobaltate(III) (BMSGC) shows that kinetic CH-acidity of the glycine moiety of BMSGC is 10 times smaller than that of the glycine moiety of BSGC (Table III, Experiments No 6 and No 7) The same difference in the CH-acidity is observed when one compares BSAC and BSGC (Table III, Experiments No 5 and No 7) It is obvious that in both cases diminution of the rate constant is caused by the replacement of the intraligand steric H–H interaction in the carbanion by the interaction H–$CH_3$ On the other hand, replacement of the interaction H–$CH_3$ for $CH_3$–$CH_3$ as one goes from BSAC to BMSAC leads to the diminution of the deuterium exchange rate constant by $3 \times 10^3$ times (Table III, Experiments No 1, No 4, No 5) Thus, even if considerable steric hindrances are created to the formation of the carbanion, leading to the diminution of the CH-acidity by 3 orders of magnitude, we cannot positively state the formation of a slowly inverting non-planar chiral carbanion in the system of amino acid Schiff bases and *ortho*-hydroxyacetophenone

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