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PREPARATIVE ASYMMETRIC SYNTHESIS OF (R)- AND (S)-α-METHYLSERINE Ni(II) COMPLEX WITH A SCHIFF BASE OF α-ALANINE AND (S)-2-[(N-BENZYLPROLYL)AMINO]BENZOPHENONE

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The kinetic and thermodynamic diastereoselectivity of the hydroxymethylation of the alanine fragment in the Ni(II) complex of the Schiff base of alanine and (S)-2-[(N-benzylprolyl)amino]benzophenone (BBP) was studied. Optically pure (R)- and (S)-α-methylserines were synthesized.

Much attention has lately been given to the synthesis of the enantiomerically pure amino acids with unusual structure and to the exploraton of their biological properties [1]. α-Methyl-substituted analogs of protein amino acids occupy a special position among these compounds: being direct analogs of natural amino acids, they display the same biological activity, while their substitution for native amino acids in biologically active peptides imparts to the latter resistance to hydrolytic enzymes, which makes it possible to produce pharmaceutical preparations with prolonged action [2].

The asymmetric synthesis of α-methyl-substituted amino acids was carried out in [3, 4].

We have developed general methods in our laboratory for the asymmetric synthesis of α-amino acids using chiral regeneratable carbonyl-containing reagents: (S)-2-[(N-benzylprolyl)amino]benzaldehyde (BBA) and (S)-2-[(N-benzylprolyl)amino]benzophenone (BBP). It was shown that the alkylation of the Ni(II) complexes with Schiff bases of α-alanine and BBP or BBA by alkyl halides makes it possible to synthesize α-methyl-substituted amino acids in an optically active form [5-7]. In contrast to [3, 4], no expensive or difficultly accessible reagents are necessary in this case. The synthesis of BBP has already become highly developed [8], which ensures the high availability of this reagent. Unfortunately, the range of amino acids which can be synthesized using BBP is limited to reactive alkyl halides of the benzyl and allyl halide type [6, 7]. The use of BBA makes it possible to extend considerably the range of synthesizable α-methylamino acids [5]. However, the synthetic possibilities have not been completely exhausted.

The present work reports the investigation of the hydroxymethylation of the Ni(II) complex with a Schiff base of alanine and BBP (Ala-Ni-BBP) and a preparative synthesis of the two enantiomers of α-methylserine.

RESULTS AND DISCUSSION

Condensaton of formaldehyde with Gly-Ni-BBP proceeds readily and smoothly in the presence of Et_3N or MeONa used as bases [9]. The reaction of formaldehyde with Ala-Ni-BBP in the presence of Et_3N does not proceed, and an almost 20-fold excess of formaldehyde and a

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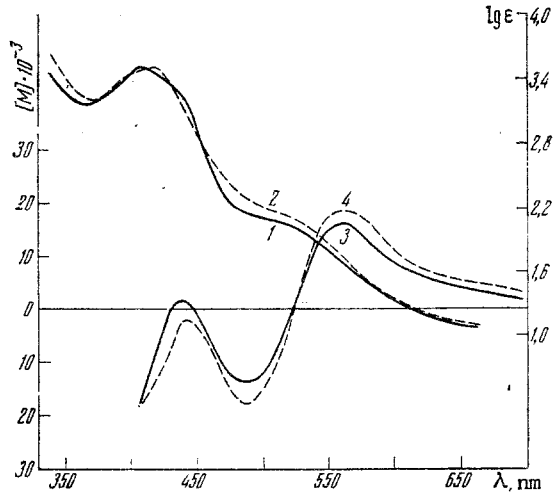


Fig. 1. Electronic absorption spectra (1, 2) and DOR curves (3, 4) of (S'R)-α-MeSer-Ni-BBP (1, 3) and (S'S)-α-MeSer-Ni-BBP (2, 4) in methanol.

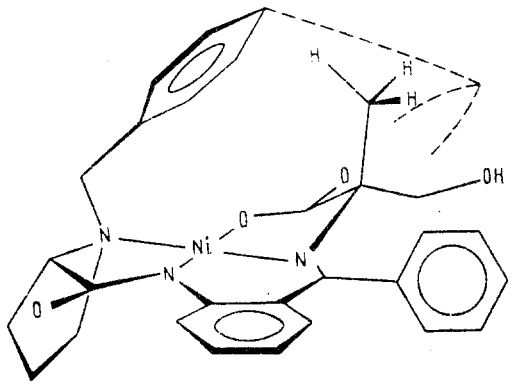
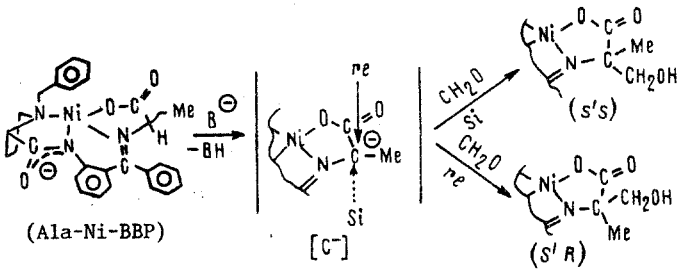


Fig. 2. Steric structure of (S'S)-α-MeSer-Ni-BBP (the dotted line designates part of the anisotropy cone, which is responsible for the magnetic screening of the methyl group of the amino acid fragment of the complex).

high concentration of MeONa in the reaction mixture are necessary for the reaction to occur. Under these conditions two new complexes are formed from Ala-Ni-BBP. In analogy with the data in [9], the hydroxymethylation mechanism of Ala-Ni-BBP can be represented by Scheme 1.

Scheme 1



The course of the reaction is readily monitored by TLC on SiO_2 (eluent chloroform–acetone, 7:1). After neutralization of the reaction mixture by dilute AcOH, extraction of products with chloroform, and preparative column chromatography, two diastereomeric α-MeSer-Ni-BBP complexes were isolated, as verified by elemental analysis and PMR spectral data.

Figure 1 shows the curves for the dispersion of optical rotation (DOR) and electronic spectra of diastereomers of α-MeSer-Ni-BBP. It is seen that the DOR curves of the diastereomeric complexes have a practically identical character, which precludes the use of the DOR

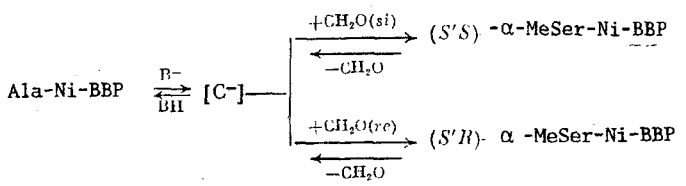
TABLE 1. Change in Diastereoselectivity of the Hydroxymethylation Reaction of Ala-Ni-BBP with Time

Time, min	Conversion Ala-Ni-BBP,%	S'S/S'R ratio
10	14	2,23
45	48,2	2,17
135	92,5	1,92
1140	91,4	1,25

method for assigning their absolute configurations. Such an assignment was made by comparison of PMR spectra of diastereomeric complexes. Figure 2 shows the steric structure of the S'S-diastereomer (in designating the absolute configuration of the complexes, S' in all cases refers to the absolute configuration of BBP) and it can be seen that the methyl group of the amino acid fragment is included in the screening zone of the phenyl ring of the N-benzyl group of the ligand and its signal is located in the stronger field region compared with the signal of the methyl group of the S'R-diastereomer (0.98 and 1.6 ppm, respectively). Based on this consideration, an S'R-configuration was ascribed to the diastereomer with a higher R_f on silica gel, while the S'S configuration was ascribed to the diastereomer with a lower R_f. (R)-α-Methylserine isolated from (S'R)-α-MeSer-Ni-BBP has a negative rotation angle, which agrees completely with the data in [10].

Study of the diastereoselectivity of the reaction of Ala-Ni-BBP with formaldehyde showed that it is subject to both kinetic and thermodynamic control. Table 1 shows the change in the ratio of the S'S- and S'R-diastereomers, depending on the time of reaction and conversion of the initial alanine complex. These data show that at a low degree of conversion of the starting complex (14%), the S,S'-diastereomer is in substantial predominance. It should be noted that the diastereomers with the S',S-configuration are also preferentially formed in the case of purely kinetic control during an irreversible alkylation of Ala-Ni-BPP by alkyl halides [5, 6]. However, the S'S/S'R ratio during the hydroxymethylation (2.23) is considerably lower than the ratio during the alkylation (7-10). It is possible that the change in the kinetic diastereoselectivity is due to a change in the volume of the electrophilic particle, and during the hydroxymethylation the electrophile CH_2O, having a relatively small volume is only inappreciably sterically hindered during an attack from the re-side of the carbanion, which is screened by a phenyl group (Scheme 1). With increase in the time of reaction, the conversion of Ala-Ni-BBP increases, but the diastereoselectivity thus decreases, and with long reaction times, the ratio between the stereoisomers approaches unity (Table 1). This fact can be explained by the assumption that the diastereomeric complexes convert into one another. In fact, when the individual diastereomers of α-MeSer-Ni-BBP and paraform are held in a solution of MeONa in methanol, their epimerization is observed at the amino acid fragment, which can be easily detected by TLC on SiO_2. In the absence of paraform, under these conditions, in addition to the interconversion of the α-MeSer-Ni-BBP diastereomers, their considerable dissociation to the diastereomers of the starting Ala-Ni-BBP is observed. These experimental data indicate the reversibility of the hydroxymethylation of Ala-Ni-BBP and a mechanism for the establishment of the equilibrium between the diastereomers of α-MeSer-Ni-BBP including their retroaldolic dissociation, can be represented with greater confidence by Scheme 2.

Scheme 2



The ratio S'S/S'R = 1.25 for long reaction times (Table 1) thus reflects the thermodynamic equilibrium between the diastereomeric α-MeSer-Ni-BBP complexes formed in the reaction mixture. These diasteromeric pairs may consist of complexes as illustrated in Fig. 2, or their alternative structures in which the carboxyl group of α-methylserine is substituted in the coordination sphere of Ni(II) by an ionized hydroxymethyl group; the possibility of the formation of the latter at high MeONa concentrations is confirmed by the data in [9].

The hydroxymethylation of Ala-Ni-BBP and the chromatographic separation of the α-MeSer-Ni-BBP diastereomers can be readily carried out on a preparative scale (see Experimental). The decomposition of the diastereomeric complexes by the action of HCl in an aqueous-alcoholic solution gives enantiomerically pure (S)-α-MeSer and (R)-α-MeSer, whereby the chiral reagent can be isolated in high yield.

EXPERIMENTAL

The PMR spectra were recorded on Bruker WP 200 spectrometer and the DOR spectra on a Jasco ORD/UV-5 apparatus, the electronic absorption spectra were run on a Specord M-40 spectrophotometer, and the rotation angles were measured on a Perkin–Elmer WP-241 polarimeter.

In the investigation the (S)-alanine, (S)-proline, and 2-aminobenzophenone used were from the firm Reanal, silica gel for the preparative chromatography from Merck, and silica gel for column chromatography was Silpearl (CSFR); all the remaining reagents and solvents were Soviet-produced and were chemically pure or analytically pure grade. The solution of MeONa in MeOH was prepared by dissolving metallic sodium in methanol, the concentration of the base was determined by titration with a standard solution of HCl in water with phenolphthalein as indicator.

(S)-2-[(N-Benzylpropyl)amino]benzophenone (BBP) was synthesized from (S)-benzylproline and 2-aminobenzophenone by the method described in [8].

Complex of Ni(II) with the Schiff Base of Alanine and BBP (Ala-Ni-BBP). A 245 ml portion of a 2.82 N solution of MeONa in MeOH was added in the course of 5-10 min to a mixture of 33 g (0.086 mole) of BBP, 50 g (0.17 mole) of $Ni(NO_3)_2 \cdot 6H_2O$, 38 g (0.43 mole) of (S)-alanine and 250 ml of methanol heated to 60°C, and the mixture was allowed to stand at this temperature up to the end reaction [1-2 h; the monitoring was carried out by TLC on silica gel in a chloroform–acetone (7:1) system, according to disappearance of the spot of the initial BBP]. The hot solution was then neutralized with 30 ml of AcOH, and the mixture was poured into water. The dark-red crystalline precipitate of the complex was filtered off, washed with water, and dried in air. Yield, 42 g of a pure product. From the mother liquors another 1.6 g of the complex was obtained by extraction with chloroform. Yield quantitative.

Hydroxymethylation of Ala-Ni-BBP. A mixture of 61.8 g (0.12 mole) of Ala-Ni-BBP, 68.5 g (2.28 mole) of paraform, and 300 ml of a 3 N solution of MeONa in methanol was stirred for 3 h at 20°C. [The monitoring of the reaction was carried out by TLC on silica gel in a chloroform–acetone (7:1) system.] The reaction mixture was then neutralized by the addition of 58 ml of AcOH and was evaporated to dryness. To the residue 100 ml of chloroform was added and the insoluble part was filtered off and washed with chloroform up to the disappearance of the red color. The filtrate was washed with water and evaporated. The residue was chromatographed on a 92 × 7.5 cm column with silica gel, eluted with a mixture of chloroform with acetone (7:1), obtaining in the order of elution from the chromatographic column: a mixture of diastereoisomers of the starting Ala-Ni-BBP and the individual S'R (17.9 g; yield 27.5% of theoretical) and S'S- (41.6 g, 64.2% of theoretical) diastereomers of α-MeSer-Ni-BBP. Elemental analysis of (S'R)-α-MeSer-Ni-BPP. Found, %: C 64.18, H 5.11, N 7.47. $C_{29}H_{29}N_3NiO_4$. Calculated, %: C 64.23, H 5.39, N 7.75. $[\alpha]^{25}$ (λ, nm) (c 0.0275 in MeOH): +236.36 (578), +174.55 (546). Characteristic PMR signals [$CDCl_3$, δ, ppm (HMDS)]: 1.60 s (3H, Me), 2.0 m (2H, β-Pro), 4.40 d (1H, B-part of AB system, J = 13.1 Hz, benzyl H). (S'S)-α-MeSer-Ni-BPP. Found, %: C 64.49, H 5.30, N 7.47. $C_{29}H_{29}N_3NiO_4$. Calculated, %: C 64.23, H 5.39, N 7.75. $[\alpha]^{25}$ (λ, nm) (c 0.028 in MeOH): +270.71 (578), +173.57 (546). Characteristic PMR signals ($CDCl_3$, δ, ppm): 0.98 s (3H, Me), 1.85 m (2H, β-Pro), 4.33 d (1H, B-part of AB system, J = 13.1 Hz, benzyl H). The DOR curves and the electronic spectra of the two diastereomers are given in Fig. 1.

Dependence of the diasteroselectivity of the hydroxymethylation reaction on the degree of conversion was studied under conditions close to the preparative experiment conditions. Aliquots were withdrawn from the solution at given moments of time, neutralized by AcOH, then poured into water, and the complexes were extracted with chloroform. The extracts were evaporated and chromatographed on plates with silica gel, whereby individual fractions were isolated. The amounts of the complexes isolated from the plates were determined spectrophotometrically. The data on the changes in the diastereoselectivity in the course of hydroxymethylation are given in Table 1.

(R)-α-Methylserine [(R)-α-MeSer]. A solution of 17.9 g of (S'R)-α-MeSer-Ni-BBP in 150 ml of MeOH was added dropwise, with stirring, to a boiling solution of 2 N hydrochloric acid (200 ml). The green solution thus formed was concentrated in vacuo and water was added. The BBP·HCl precipitate was filtered off, washed with water, and dried in air. Yield 11.2 g (81.2%) of BBP·HCl. The mother liquors were combined, neutralized with a concentrated ammonia solution to pH 8 and BBP was extracted with chloroform [after evaporation 0.9 g (7.3%) of BBP was obtained]. The amino acids were isolated from the aqueous solution by ion-exchange chromatography on a KRS-12 sulfo-cation exchanger in acid form [9]. Yield 3.57 g (91%) of (R)-α-MeSer. After recrystallization from aqueous alcohol, 3.0 g (76.4%) of pure amino acid was obtained. (R)-α-MeSer. Found, %: C 40.32, H 7.64, N 11.82. $C_4H_9NO_3$. Calculated, %: C 40.33, H 7.62, N 11.75. $[\alpha^{25}]$ (λ, nm) (c 5.015 in 6N HCl): −3.75 (589), −3.87 (578), −4.33 (546) (compare [10]: $[\alpha]_D^{25}$ −3.4 (c 1.2 in 6 N HCl); [11]: $[\alpha]_D^{25}$ −3.78 (c 2.0 in 5 N HCl). PMR spectrum (D_2O, δ, ppm): 1.13 s (3H, Me), 3.4 and 3.67 (2H, AB system, J = 13.1 Hz, CH_2).

(S)-α-Methylserine [(S)-α-MeSer]. Similarly to the above-described procedure, from 41.5 g of (S'S)-α-MeSer-Ni-BBP, after recrystallization, 6.84 g (75%) of pure amino acid was obtained. (S)-α-MeSer. Found, %: C 40.52, H 7.49, N 11.82. $C_4H_9NO_3$. Calculated, %: C 40.33, H 7.62, N 11.75. $[\alpha]_D^{25}$ (c 4.86 in 6 N HCl); (λ, nm): +3.60 (589), +3.81 (578), +4.28 (546) (compare [11]: $[\alpha]_D^{25}$ +3.6 (c 2.5 in 5 N HCl)). PMR spectrum (D_2O, δ, ppm): 1.11 s (3H, Me), 3.4 and 3.65 (2H, AB-system, J = 13.1 Hz, CH_2).

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