# Asymmetric Synthesis of Threonine and Partial Resolution and Retroracemization of α-Amino Acids via Copper(II) Complexes of Their Schiff Bases with (*S*)-2-*N*-(*N'*-Benzylprolyl)aminobenzaldehyde and (*S*)-2-*N*-(*N'*-Benzylprolyl)aminoacetophenone. Crystal and Molecular Structure of a Copper(II) Complex of Glycine Schiff Base with (*S*)-2-*N*-(*N'*-Benzylprolyl)aminoacetophenone

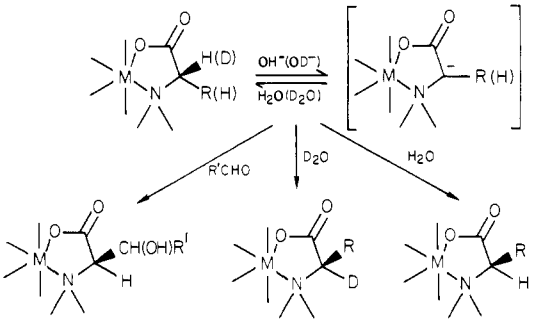
**Yu. N. Belokon',* I. E. Zel'tzer, V. I. Bakhmutov, M. B. Saporovskaya, M. G. Ryzhov, A. I. Yanovsky, Yu. T. Struchkov,* and V. M. Belikov**

*Contribution from the Nesmeyanov Institute of Organoelement Compounds, USSR Academy of Sciences, Vavilov 28, Moscow, USSR.* *Received November 18, 1981*

**Abstract:** The work described here is concerned with the search for universal chiral reagents for the asymmetric synthesis, resolution, and retroracemization of amino acids. Reaction of *N*-benzyl-(*S*)-proline with *o*-aminobenzaldehyde or *o*-aminoacetophenone has given (*S*)-2-*N*-(*N'*-benzylprolyl)aminobenzaldehyde ((*S*)-BPAB) or (*S*)-2-*N*-(*N'*-benzylprolyl)aminoacetophenone ((*S*)-BPAAPh). These chiral reagents have interacted with α-amino acids (aa) and Cu(II) ions to form complexes [(*S*)-BPAB–aa]$Cu^{II}$ and [(*S*)-BPAAPh–aa]$Cu^{II}$ in which Schiff bases (*S*)-BPAB–aa or (*S*)-BPAAPh–aa act as tetradentate ligands and coordinate the copper ion by the nitrogen atoms of the pyrrolidine fragment, the deprotonated amide group, and the amino acid fragment and by the oxygen atom of the carboxylate. Such a structure was supported by data on elemental analysis, the molecular weight measurements, and electron, IR, and CD spectra. It was finally confirmed by an X-ray diffraction analysis of [(*S*)-BPAAPh–Gly]$Cu^{II}$. One equivalent of (*S*)-BPAB has reacted with 2 equiv of (*R,S*)-aa and 2 equiv of Cu(II), having given preferential formation of copper complexes of Schiff bases with (*S*)-aa. After their extraction with chloroform the amino acid enriched with the *R* enantiomer remained in the aqueous solution. In this manner partial resolution of racemic amino acids (Ala, Nva, Phe, Val, Thr) has been carried out with enantiomeric purity 4–50%. (*S*)-BPAB or (*S*)-BPAAPh treatment of a racemic amino acid in the presence of Cu(II) ions (reagents ratio 1:1:1) and $CH_3O^-$ ions permits enantiomeric enrichment via conversion of the *R* into the *S* enantiomer (retroracemization). Thus (*S*)-Ala, (*S*)-Nva, (*S*)-Leu, (*S*)-Val, (*S*)-Phe, and (*S*)-PhGly of enantiomeric purity 36, 12, 22, 54, 42, and 35%, respectively, were obtained from racemic samples. $CH_3O^-$-catalyzed reaction of [(*S*)-BPAB–Gly]$Cu^{II}$ or [(*S*)-BPAAPh–Gly]$Cu^{II}$ with acetaldehyde has given rise to a mixture of diastereometric complexes, which upon removal of Cu(II) by $H_2S$ gave (*R*)-threonine of 60% or 97–100% enantiomeric purity and the threo/allo ratio 6:1 or 19:1, respectively, and permitted recovery of an unchanged initial chiral reagent (*S*)-BPAB or (*S*)-BPAAPh.

Chiral recognition of amino acid enantiomers in vivo underlies a number of essential biological processes.[1] Designing simple chemical systems to imitate this property of enzymes is an attractive means of developing efficient biomimetic catalysts and reagents. From this standpoint, enantioselective effects in chiral complexes of transition metals[2] are of particular interest. Indeed, such complexes may feature conformationally rigid arrangements of ligands, and X-ray diffraction analysis provides reliable data on their structure. Accordingly, the interligand interactions responsible for the enantioselectivity of these systems may be estimated, sometimes quantitatively,[3] and thus the search for useful

Scheme I




synthetic reagents based on these complexes is greatly facilitated.

Chiral complexes of transition metals were employed for resolution[4] and asymmetric synthesis of amino acids, e.g., threonine from glycine and acetaldehyde,[5,6] asymmetric decarboxylation,[7] asymetric transformation of amino acids in Co(III) complexes,[8] and enantioselective substitution of deuterium for the α-proton

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of amino acids.[9] At the key step of all these reactions (except decarboxylation), the $\alpha$-proton of the amino aicd is removed under the action of a base; the resulting carbanion[10] reacts with the electrophile in an enantioselective manner determined by the chiral environment in the complex (Scheme I).

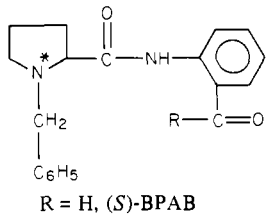
In a recent series of investigations it was demonstrated that both the kinetic CH acidity of the amino acid fragment[11] and the enantioselectivity of C–C[11] and C–D[11,12] bond formation may be increased significantly with the help of Co(III) chiral complexes of Schiff bases of salicylaladehyde or pyridoxal with amino acids.

Asymmetric induction in these complexes is brought about by chiral arrangement of ligands within a substitution-inert framework of the complexes.

However, biomimetic reagents and catalysts should be based on substitution-labile complexes capable of easy ligand exchange and consequent metal ion centered racemization. For sustained asymmetry of a labile system, pyridoxal and salicylaldehyde were substituted by their chiral analogues,[13,14] which has made it possible to use Cu(II) and Zn(II) complexes for asymmetric transamination of amino acids,[14] retroracemization of dipeptides,[13] and asymmetric synthesis of threonylglycine with >95% enantiomeric excess.[13]

The present study is concerned with the search for chiral reagents for the asymmetric synthesis, retroracemization, and resolution of amino acids via chiral metal Schiff base complexes.

In this work we have synthesized (*S*)-2-*N*-(*N'*-benzylprolyl)-aminobenzaldehyde (BPAB) and (*S*)-2-*N*-(*N'*-benzylprolyl)-aminoacetophenone (BPAAPh)



R = H, (*S*)-BPAB
R = $CH_3$, (*S*)-BPAAPh

and established the structure of copper complexes of Schiff bases of amino acids with these reagents.

The kinetic CH acidity of the amino acid fragment and enantioselective effects of these complexes were also studied. The effects observed were used to resolve amino acid enantiomers, for retroracemization of racemic amino acids and for an asymmetric synthesis of threonine from glycine and acetaldehyde.

The origin of the enantioselective effects in the complexes studied is discussed on the basis of X-ray diffraction data concerning the copper complex of the (*S*)-BPAAPh Schiff base with glycine.

## Experimental Section

The amino acids of "ch" (pure) grade were supplied by Reanal (Budapest) and Reakhim (Moscow). The enantiomeric purity of the amino acids was determined by GLC[15] and found to be >95%.

$CH_3ONa$ was prepared by adding metallic Na into anhydrous $CH_3OH$ under argon with cooling.

$^1H$ NMR spectra were recorded on Perkin-Elmer R-32 and Soviet-made RYa-2309 spectrometers. IR spectra were recorded in KBr on a UR-20; electron spectra were obtained on a Specord UV–Vis spectrophotometer. CD curves were recorded on a JASCO J-20 spectropolarimeter. Optical rotation was determined on a Perkin-Elmer 241 polarimeter. Paper electrophoresis of the complexes was carried out in 0.025 M pyridinium acetate at pH 6 on a Labor instrument. The molecular weight of the complexes was determined by vapor osmometry at 37 °C in dry $CHCl_3$ on a Dampfdruck osmometer (Knauer).

**Synthesis of *N*-Benzyl-(*S*)-Proline.** A solution of 4.6 g (0.04 mol) of (*S*)-Pro in 30 mL of $H_2O$, 20 mL of 2 N NaOH, 1 mL of 10% solution of tetrabutylammonium hydroxide, and 0.1 g of KI was placed into a three-necked flask, and while the mixture was stirred under argon, 5.8 mL (0.05 mol) of freshly distilled benzyl chloride was added. The mixture was stirred further at 65 °C for 2 h and then, upon addition of two milliliters (0.017 mol) of benzyl chloride and 5 mL of 2 N NaOH for 1 h, neutralized by 9 mL of 1 N HCl to pH 7 and evaporated in vacuo. Addition of ethanol resulted in a white precipitate which was filtered away. The filtrate was evaporated in vacuo and the residue chromatographed on silica gel in $C_2H_5OH$–$CHCl_3$ (1:1) (3 × 25 cm column). The second fraction, which absorbed at 254 nm and contained *N*-benzyl-(*S*)-proline, was collected. The solvent was removed in vacuo and the product dried under reduced pressure over $P_2O_5$ and paraffin. The yield was 3.6 g (0.017 mol), 42%: mp 164–165 °C, $[\alpha]^{20}_{589}$ −29.07° (*c* 0.01 g/mL, anhydrous $C_2H_5OH$) [lit.[16] mp 164 °C, $[\alpha]^{20}_{589}$ −28.4° (*c* 0.01 g/mL, anhydrous $C_2H_5OH$)]; $^1H$ NMR ($CD_3OD$) $\delta$ 1.35–3.65 (m, 6 H, $CH_2$ (pro)), 3.7–3.9 (m, 1 H, $\alpha$-H (Pro)), 4.35 (s, 2 H, $CH_2$), 7.5 (m, 5 H, Ar).

The first fraction, which also absorbs at 254 nm, is *N,N*-dibenzylproline: $^1H$ NMR ($CD_3OD$) $\delta$ 1.2–3.2 (m, 6 H, $CH_2$ (Pro)), 4 (m, 1 H, $\alpha$-H (Pro)), 3.8–4.5 (m, 4 H, $CH_2$), 7.1 (m, 5 H, Ar), 7.3 (m, 5 H, Ar). The IR spectrum of this compound contains no band at 1730 $cm^{-1}$ typical of the ester bond stretching mode.

**Synthesis of *o*-Aminobenzaldehyde** was carried out according to the procedure described earlier,[17] mp 39 °C (lit.[17] mp 38–39 °C).

**Synthesis of *o*-nitroacetophenone** was performed according to the procedure described earlier[18] bp 156 °C (13 mmHg), $n^{21}D$ 1.5513 (lit.[18] bp 158–159 °C (16 mmHg), $n^{20}D$ 1.551).

**Synthesis of *o*-aminoacetophenone.** *o*-Aminoacetophenone was obtained by reduction of *o*-nitroacetophenone as described earlier,[17] bp 105 °C (1 mmHg) [lit.[19] bp 110 °C (1.5 mmHg).

**Synthesis of (*S*)-2-*N*-(*N'*-Benzylpropyl)aminobenzaldehyde ((S)-BPAB).** To 0.642 g (3 mmol) of *N*-benzyl-(*S*)-proline was added dropwise 0.6 mL (8.35 mmol) of freshly distilled $SOCl_2$ while the mixture was cooled (solid $CO_2$/acetone). The mixture was allowed to stand for 3 h at room temperature and was used without purification. *o*-Aminobenzaldehyde (0.363 g, 3 mmol) in 25 mL of $CH_2Cl_2$ and 50 mL of water was placed into a pH-stat cell so that the electrodes were immersed in water. While the organic and the aqueous layers were stirred separately, the product of the reaction between $SOCl_2$ and *N*-benzyl-(*S*)-Pro in 2 mL of dry $CH_2Cl_2$ was added dropwise to the organic layer over 10 min. The pH (8) of the aqueous layer was maintained by adding 2 N KOH. The reaction mixture was then stirred for 35–40 min until the automatic feeding of the alkali stopped. The layers were then separated, and the aqueous layer was washed with $CH_2Cl_2$ (3 × 15 mL). The organic extracts were mixed, the solvent was evaporated in vacuo, and the residue was chromatographed on silica gel (2.5 × 30 cm column) in a $CHCl_3$–benzene–ether–ethanol–acetic acid system (10:10:10:2.5:2.5) to collect the second fraction absorbing at 254 nm and containing the reaction product. After evaporation of the solvent in vacuo, the residue was mixed with 25 mL of $H_2O$ and $Na_2CO_3$ was added until pH reached 9. (*S*)-BPAB was extracted with chloroform (3 × 30 mL) which was then evaporated in vacuo, giving a crystalline residue. The yield of the raw product was 0.2 g (0.08 mmol), 27%. Recrystallization from petroleum ether (bp 40–70 °C) gave (*S*)-BPAB: mp 96–98 °C; $[\alpha]^{25}_{436}$ −352.00°, $[\alpha]^{25}_{546}$ −157.33, $[\alpha]^{25}_{578}$ −134.67 (*c* 1.5 × $10^{-3}$ g/mL, $CHCl_3$); UV ($CHCl_3$) $\lambda_{max}$ (log $\epsilon$) 267 (3.953), 274 (3.940), 336 nm (3.720); IR (KBr) $\nu$ 3220 (NH), 1700 (CO, amide I), 1520 (CO, amide II), 1680 (CHO), 1580, 1500, 1450 (Ar) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.6–2.7 (m, 6 H, $CH_2$ (Pro)), 3.22 (m, 1 H, $\alpha$-H (Pro)), 7–7.33 (m, 7 H, Ar), 9.78 (s, 1 H, CHO), 12 (s, 1 H, NH—C=O); AB system: $CH_2$ group 3.51, 3.84 (*J* = 12 Hz); $H^3$, $H^6$ of *o*-aminobenzaldehyde fragment 7.44, 8.56 (*J* = 10

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Table I. Parameters of the Complexes and Enantiomeric Purity of Amino Acids Isolated from [(S)-BPAB-aa]$Cu^{II}$

| species | mp, °C | $[M]^{25}_{\lambda}$ in 96% $C_2H_5OH$[a] 436 nm | 546 nm | 578 nm | $\lambda_{max}$ (log $\epsilon$) in 96% $C_2H_5OH$ | purity,[b] % |
|---|---|---|---|---|---|---|
| [(S)-BPAB-Gly]$Cu^{II}\cdot 0.5C_2H_5OH\cdot{}^1/_2H_2O$ | 120–130 | −954 | −1908 | −619 | 250 (4.322), 360 (3.695), 540 (1.976) | |
| [(S)-BPAB-(S)-Val]$Cu^{II}\cdot H_2O$ | 140–147 | +559 | −7478 | −4220 | 254 (4.446), 360 (3.528), 500–520 (1.960) | 100 (S) |
| [(S)-BPAB-(R)-Val]$Cu^{II}\cdot C_2H_5OH$ | 115–125 | −644 | +1395 | +1985 | 254 (4.440), 360 (3.517), 500–520 (2.020) | 80 (R) |
| [(S)-BPAB-(S)-Thr]$Cu^{II}\cdot 1.5H_2O$ | 135–145 | −328 | −5651 | −3174 | 254 (4.450), 360 (3.640), 520 (1.970) | 100 (S) |
| [(S)-BPAB-(R)-Thr]$Cu^{II}\cdot H_2O$ | 135–145 | −1044 | +178 | +764 | 254 (4.442), 360 (3.606), 500–520 (2.030) | 88 (R) |
| [(S)-BPAAPh-Gly]$Cu^{II}\cdot 1.5H_2O$ | 120–135 | −361 | −1804 | −241 | 250 (4.401), 345 (3.600), 540 (1.980) | |

[a] There is no dependence of $[M]^{25}_{\lambda}$ on the species concentration. [b] Enantiomeric purity of isolated amino acids.

Hz). Anal. Calcd for $C_{19}H_{20}N_2O$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.40; H, 6.44; N, 9.17.

**Synthesis of (S)-2-N-(N'-Benzylprolyl)aminoacetophenone ((S)-BPAAPh).** (S)-BPAAPh was obtained from N-benzyl-(S)-proline and o-aminoacetophenone similarly to (S)-BPAB. Yield of the raw product was 42%. Recrystallization from petroleum ether gave (S)-BPAAPh with mp 115–116 °C; $[\alpha]^{25}_{436}$ −270.00°, $[\alpha]^{25}_{546}$ −126.19°, $[\alpha]^{25}_{578}$ −110.71° (c 8.4 × $10^{-4}$ g/mL, $CHCl_3$); UV ($CHCl_3$) $\lambda_{max}$ (log $\epsilon$) 261 (4.000), 330 (3.616), 270 nm (h) (3.890); IR (KBr) $\nu$ 3220 (NH); 1695 (CO, amide I), 1520 (CO, amide II), 1670 (ketone CO), 1580, 1490, 1450 (Ar) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.27–2.44 (m, 6 H, $CH_2$ (Pro)), 2.5 (s, 3 H, $CH_3C{=}O$), 3.22 (m, 1 H, α-H (Pro)), 6.89–7.5 (m, 7 H, Ar); AB system: $CH_2$ group 3.53, 3.93 ($J$ = 14 Hz); $H^3$, $H^6$ of o-aminoacetophenone fragment 7.75, 8.61 ($J$ = 10 Hz). Anal. ($C_{20}H_{22}N_2O_2$): C, H, N.

**Synthesis of Copper Complexes of Schiff Bases of (S)-BPAB and (S)-BPAAPh with Amino Acids.** The complexes were obtained with the use of a general technique: 0.4 mmol of aa in 0.4 mL of 1 N $CH_3ONa$ and 3 mL anhydrous $CH_3OH$, 0.3 mmol of (S)-BPAB or (S)-BPAAPh, and Wolfen-Zeosorb 3-Å molecular sieve were put into a flask and stirred at room temperature for 15 min. Upon removal of the sieve by filtering, 0.4 mmol of $CuSO_4\cdot 5H_2O$ in 1 mL of water was added, the mixture was stirred for 45 min (30 min for threonine), and then 0.3 mL of 1 N $CH_3ONa$ and 30 mL of 1:1 $H_2O/CHCl_3$ were added. For (S)-BPAAPh all the manipulations were carried out under argon. The complex was extracted by $CHCl_3$ (3 × 15 mL) and purified on silica gel (2 × 25 cm column) and LH-20 in $C_2H_5OH$. The yields of the complexes were 40–81% (no attempts to improve the yields were made); the elemental analysis and molecular weight data fully support the expected structure of the complexes. Table I contains their mp, $[M]^{25}$, and $\lambda_{max}$ (log $\epsilon$).

**Isolation of (S)-BPAB and (S)-BPAAPh and Amino Acids from the Complexes.** The complexes were decomposed according to a general procedure: 0.02 mmol of the complex was dissolved in 0.2 mL of $CH_3OH$, 5 mL of 1 N HCl was added, and the mixture was allowed to stand for 10 min at room temperature, during which time it turned yellow. Then the internal amino acid reference and 15 mL of $H_2O$ were added, and $H_2S$ was bubbled through the mixture. Upon filtration, the filtrate was mixed with 1 mL of 25% $NH_4OH$ to pH 9–10 and BPAB or BPAAPh was extracted by $CHCl_3$ (3 × 20 mL). The recovery yields were determined spectrophotometrically by the absorption at 336 nm for BPAB and at 330 nm for BPAAPh and found to be 60–100%. The aqueous amino acid solution was desalted on Dowex-50 ($H^+$ form). Enantiomeric and quantitative analysis of the amino acids were carried out by the GLC.[15,20] Yield of the amino acids was 80–100%.

**Structure of the [(S)-BPAAPh-Gly]$Cu^{II}$ Complex.** The [(S)-BPAAPh-Gly]$Cu^{II}$ crystals are monoclinic. At 20 °C $a$ = 10.8845 (7) Å, $b$ = 6.9868 (3) Å, $c$ 13.490 (1) Å, $\beta$ = 93.818 (8)°, $V$ = 1023.6 (2) Å$^3$, $d_{found}$ = 1.496 g/cm$^3$, $Z$ = 2, space group $P2_1$.

The unit cell parameters and the reflection intensities were measured with a Hilger-Watts four-circle automatic diffractometer ($\lambda_{CuK}$, graphite monochromator, $\theta$–$2\theta$ scan, $\theta \le 66°$, 1633 reflections with $F^2 \ge 2\sigma$). The structure was solved by the heavy atom method and refined by the full-matrix least-squares technique in the anisotropic approximation. The methyl group hydrogen atoms were located in a difference Fourier synthesis, the rest of the hydrogen atoms (except those of the water molecule) were placed into geometrically calculated positions. In the final cycles of refinement, the contribution of the hydrogen atoms was taken into account when calculating $F_{calcd}$ but their thermal and positional parameters were not refined (all the H atoms had isotropic temperature factor $B_{iso}$ = 5 Å$^2$). The final $R$ factor was 0.0326 (weighted $R$ factor = 0.0454). The absolute configuration of [(S)-BPAAPh-Gly]$Cu^{II}$ was determined with the help of Hamilton's test allowing for anomalous scattering by the Cu atom for the inverted structure; $R$ = 0.0340, $R_w$ = 0.0474. This corresponds to 99.5% reliability of the absolute configuration. The S configuration[21] of the (S)-proline fragment asymmetric center is identical with that for free (S)-proline and its derivatives.[22] All the calculations were carried out on an Eclipse S/200 computer with modified EXTL programs.

Table II. Enantiomeric Composition of Amino Acids after Retroracemization

| run no. | amino acid | enantiomeric purity of the obtained aa,[a-c] % |
|---|---|---|
| 1 | (R,S)-Ala | 0[d] |
| 2 | (R,S)-Nva | 12 (S)[d] |
| 3 | (R,S)-Leu | 22 (S)[d] |
| 4 | (R,S)-Phe | 42 (S)[d] |
| 5 | (R,S)-Val | 54 (S)[d] |
| 6 | (R,S)-PhGly | 35 (S)[d] |
| 7 | (R,S)-Ala | 36 (S)[e,f] |
| 8 | (R,S)-Ala | 33 (S)[e,g] |

[a] (S)-BPAB((S)-BPAAPh)/aa/$Cu(OAc)_2$ = 1:1:1; in 0.1 N $CH_3ONa$ under argon at 25 °C, 1 h. [b] According to enantiomeric GLC analysis. [c] The chemical yield of amino acids is 75–100%; the recovery of the chiral reagent is 60–80%. [d] Retroracemization with (S)-BPAB. [e] Retroracemization with (S)-BPAAPh. [f] Reaction in 0.5 N $CH_3ONa$. [g] Reaction in 0.5 N $CH_3ONa$ for 3 h.

**Attempted Exchange of Amino Acid Fragment in Copper Complexes of Schiff Bases of (S)-BPAB with (S)-Val. 1. Exchange in a Homogeneous System.** To 2.1 × $10^{-2}$ mmol of [(S)-BPAB-(S)-Val]$Cu^{II}$ was added 3 mL of 7.8 × $10^{-2}$ M solution of glycine in 0.1 N $CH_3ONa$. After the solution was allowed to stand for 2.5 h at 25 °C, 30 mL of a $CHCl_3$–$H_2O$ (1:1) mixture was added and the complex was extracted with $CHCl_3$. The complex was decomposed as described above, the amino acids obtained were analyzed by TLC on cellulose in a 1-butanol–acetone–$NH_4OH$–$H_2O$ system (10:10:5:2) and by GLC. No glycine was found. The GLC sensitivity to glycine is 4 × $10^{-8}$ mmol.

**2. Exchange in a Two-Phase System, $CHCl_3$–$H_2O$.** To 3.3 × $10^{-3}$ mmol of [(S)-BPAB-(S)-Val]$Cu^{II}$ in 2.5 mL of $CHCl_3$ was added 1 mL of 0.1 M glycine in water (n-tetrabutylammonium hydroxide was added until pH 8 of the aqueous solution). The mixture was allowed to stand for 26 h at room temperature, and the organic layer was separated from the water layer. Chloroform was evaporated and the complex decomposed as described above. The amino acids obtained were analyzed by TLC on cellulose in a 1-butanol–acetone–$NH_4OH$–$H_2O$ (10:10:5:2) system and by GLC. No glycine was found.

**Epimerization of [(S)-BPAB-(S)-Val]$Cu^{II}$ and [(S)-BPAB-(R)-Val]$Cu^{II}$ under the Action of $CH_3ONa$.** To 8.5 × $10^{-3}$ mmol of [(S)-BPAB-(S)-Val]$Cu^{II}$ or [(S)-BPAB-(R)-Val]$Cu^{II}$ in an argon atmosphere was added 1 mL of 0.01 N $CH_3ONa$ in $CH_3OH$, and the solution was placed into a polarimeter cell ($l$ = 0.2 cm) thermostated at 25 °C. The optical rotation angle variations were monitored at 578 nm; when the reaction stopped (the rotation angle ceased to change), the complex was decomposed as described above.

**Retroracemization of amino acids** was carried out according to a general procedure.

**1. Retroracemization in the Presence of (S)-BPAB.** To 0.1 mmol of the racemic amino acid, 0.1 mmol of BPAB, 0.1 mmol of copper acetate, and 0.1 g of Wolfen-Zeosorb 3-Å molecular sieves was added under argon, 4.3 mL of anhydrous $CH_3OH$ and 0.2 mL of 1 N $CH_3ONa$. After being stirred for 1 h at room temperature, the reaction mixture was added to 0.5 mL of 1 N $CH_3ONa$ (final concentration 0.1 N) under argon and allowed to stand for 1 h at room temperature. The mixture

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Table III. Resolution of Amino Acids by (*S*)-BPAB

| amino acid | distribn of Cu(II), % | | distribution of aa: % found[a] | | distribution of aa: % calcd[b] | | enant excess[c] (ee), % | |
|---|---|---|---|---|---|---|---|---|
| | $H_2O$ | $CHCl_3$ | $H_2O$ | $CHCl_3$ | $H_2O$ | $CHCl_3$ | $H_2O$ | $CHCl_3$ |
| (*R,S*)-Ala | 65 | 35 | 70 | 30 | 67 | 33 | 6.3 (*R*) | 13 (*S*) |
| (*R,S*)-Nva | 56 | 44 | 57 | 43 | 56 | 43 | 4.2 (*R*) | 5.5 (*S*) |
| (*R,S*)-Phe | 59 | 41 | 50 | 49.5 | 43 | 57 | 37 (*R*) | 28 (*S*) |
| (*R,S*)-Val | 51 | 49 | 52 | 48 | 50 | 50 | 43 (*R*) | 43 (*S*) |
| (*R,S*)-Thr | 78 | 22 | 87 | 13 | 86 | 14 | 8 (*R*) | 51 (*S*) |

[a] GLC data indicate that no losses of amino acids are involved. [b] Calculated from the ee of the amino acid in $H_2O$ and $CHCl_3$ (see Experimental Section). [c] According to enantiomeric GLC analysis.

Table IV. Epimerization of [(*S*)-BPAB–Thr]$Cu^{II}$ and Preparation of Thr from [(*S*)-BPAB–Gly]$Cu^{II}$ and [(*S*)-BPAAPh–Gly]$Cu^{II}$

| run no. | species | reactn conditions[a]: *t*, h | reactn conditions[a]: base concn, M | concn of reagents: $C_{complex} \times 10^3$, M | concn of reagents: $C_{CH_3CHO}$, M | chem yield,[b] %: Thr/allo-Thr | chem yield,[b] %: Thr | chem yield,[b] %: allo-Thr | ee,[c] %: Thr | ee,[c] %: allo-Thr |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | [(*S*)-BPAB-(*S*)-Thr]$Cu^{II}$ | 4 | 6.12 $Et_3N$ | 7.5 | 0.27 | 2.2 | | | 95 (*S*) | 58 (*R*) |
| 2 | [(*S*)-BPAB-(*R*)-Thr]$Cu^{II}$ | 5 | 6.12 $Et_3N$ | 10 | 0.27 | 0.6 | | | 5 (*R*) | 94 (*R*) |
| 3 | [(*S*)-BPAB-Gly]$Cu^{II}$ | 22.5 | 6.12 $Et_3N$ | 11 | 0.27 | 0.8 | 38 | 48 | 51 (*S*) | 57 (*S*) |
| 4 | [(*S*)-BPAAPh-Gly]$Cu^{II}$ | 24 | 4.89 $Et_3N$ | 7 | 0.21 | 1.1 | 20 | 18 | 41 (*S*) | 80 (*S*) |
| 5 | [(*S*)-BPAB-Gly]$Cu^{II}$ | 0.5 | 0.1 $CH_3ONa$ | 6.2 | 0.35 | 4.9 | 70 | 14 | 58 (*R*) | 12 (*S*) |
| 6 | [(*S*)-BPAB-Gly]$Cu^{II}$ | 1 | 0.1 $CH_3ONa$ | 6.2 | 0.35 | 5.6 | 80 | 14 | 56–60 (*R*)[d] | racemic |
| 7 | [(*S*)-BPAB-Gly]$Cu^{II}$ | 4 | 0.1 $CH_3ONa$ | 5.6 | 0.35 | 5.8 | 56 | 10 | 61 (*R*) | 16 (*R*) |
| 8 | [(*S*)-BPAB-Gly]$Cu^{II}$[e] | 19 | 0.1 $CH_3ONa$ | 7.2 | 0.35 | 9.7 | 91 | 9 | 65 (*R*) | 30 (*R*) |
| 9 | [(*S*)-BPAAPh-Gly]$Cu^{II}$ | 1 | 0.1 $CH_3ONa$ | 2.7 | 0.27 | 3.8 | 62 | 16 | 92 (*R*) | 100 (*R*) |
| 10 | [(*S*)-BPAAPh-Gly]$Cu^{II}$ | 4 | 0.1 $CH_3ONa$ | 3.1 | 0.27 | 19 | 76 | 4 | 97–100 (*R*) | 100 (*R*) |

[a] In $CH_3OH$ under argon at 25 °C. [b] According to quantitative GLC analysis. [c] According to enantiomeric GLC analysis. [d] Results of four experiments fall into this range. [e] At −5 °C.

was then decomposed by 5 mL of 1 N HCl with addition of an internal amino acid reference as described above. The yields of (*S*)-BPAB and amino acids, as well as the enantiomeric composition of the latter, are given in Table II.

**2. Retroracemization in the Presence of (*S*)-BPAAPh.** To 0.1 mmol of the racemic amino acid, 0.1 mmol of (*S*)-BPAAPh, 0.1 mmol of copper acetate, and 0.1 g of Wolfen-Zeosorb 3-Å molecular sieves was added under argon, 4.8 mL of anhydrous $CH_3OH$ and 0.2 mL of 1 N $CH_3ONa$. The reaction mixture was stirred under argon for 1 h at room temperature and added under argon to 5 mL of 1 N $CH_3ONa$ (final concentration 0.5 N), and this solution was allowed to stand at room temperature for (a) 1 h or (b) 3 h. Decomposition was performed by 10 mL of 1 N HCl as described above with addition of an internal amino acid reference. The yields of (*S*)-BPAAPh and amino acids, as well as the enantiomeric composition of the latter, are given in Table II.

**Resolution of Amino Acids in the Presence of (*S*)-BPAB.** Amino acids were resolved by the following procedure: 0.2 mmol of the racemic amino acid, 2 mL of anhydrous $CH_3OH$, 0.2 mL of 1 N $CH_3ONa$, and 0.1 g of Wolfen-Zeosorb 3-Å molecular sieves were put into a flask and stirred for 15 min. Upon removal of the molecular sieves, 1 mL of 0.2 M aqueous $CuSO_4$ was added and the mixture was stirred for 45 min. Upon addition of 0.1 mL of 1 N $CH_3ONa$ and, in a few minutes, 50 mL of $CHCl_3$–$H_2O$ mixture (1:1), the aqueous and the organic layers were separated. The aqueous layer was washed with $CHCl_3$, the organic layer with $H_2O$. To the aqueous layer was added the internal amino acid reference, and then Cu(II) ions were removed on Dowex A-1 ($K^+$ form) and the mixture was desalted on Dowex 50 ($H^+$ form) resin. In the case of Nva, Leu, and Phe, it was the suspension of copper complexes of the amino acids in water that was deposited on the Dowex A-1.

The chloroform solution was evaporated to dryness and the complex decomposed as described above. The quantitative and the enantiomeric composition of the amino acids were determined by GLC (Table III).

**Determination of Cu(II) Ions in Aqueous Solutions.** Copper ions were eluted from Dowex A-1 by ~50 mL of 1 N HCl; the solution was evaporated to dryness. The residue was mixed with 5 mL of concentrated $NH_4OH$ and diluted with water to 25 mL. The amount of copper was determined spectrophotometrically at the absorption maximum of copper ammonium complexes at 625 nm (Table III). The amount of copper in the complex was calculated as the difference between the total amount of copper taken for the experiment and the amount determined in the aqueous solution.

**Determination of Amino Acid Ratio in $CHCl_3$ and $H_2O$ from the Data of Enantiomeric Analysis.** The amino acid ratio in $H_2O$ and $CHCl_3$ was calculated according to

$$A_w/A_c = C/W$$

where $A_w$ is the enantiomeric excess of the amino acid in water, $A_c$ is the enantiomeric excess of the amino acid in the complex, $C$ is the amount of the amino acid in the complex in percent of its total amount, $W$ is the amount of the amino acid in water in percent of its total amount.

**Hydroxyethylation of the Complexes. Synthesis of Threonine. 1. Hydroxyethylation in the Presence of $Et_3N$ as a Base.** To 0.01 g (0.022 mmol) of [(*S*)-BPAB–Gly]$Cu^{II}$ under argon was added 0.3 mL of 1.78 M acetaldehyde solution in anhydrous $CH_3OH$ and 1.7 mL of $Et_3N$. The reaction mixture was allowed to stand for 22.5 h at 25 °C. When 5 mL of 1 N HCl and the internal amino acid reference had been added and the mixture allowed for stand for 10 min, acetaldehyde was extracted by ether (3 × 30 mL). Further treatment was the same as in decomposition of the complexes. The recovery of (*S*)-BPAB was 75%. Hydroxyethylation of [(*S*)-BPAAPh–Gly]$Cu^{II}$ was performed likewise but with addition of 0.5 mL of DMF. The recovery yield of (*S*)-BPAAPh was 75%. Enantiomeric composition and chemical yield of threonine were determined by GLc (Table IV).

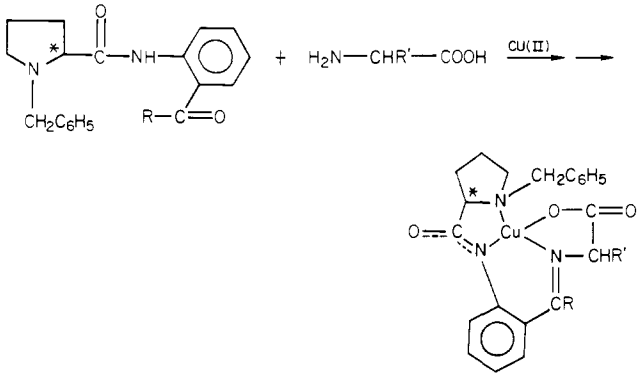
**2. Hydroxyethylation in the Presence of $CH_3ONa$ as a Base.** To 0.06 mmol of [(*S*)-BPAB–Gly]$Cu^{II}$ or [(*S*)-BPAAPh–Gly]$Cu^{II}$ were added 9 mL of 0.39 M solution of freshly distilled acetaldehyde in anhydrous $CH_3OH$ and 1 mL of 1 N $CH_3ONa$ in anhydrous $CH_3OH$ (final concentration 0.1 M) under argon. The reaction mixture was thermostated at 25 °C for (a) 30 min, (b) 1 h, or (c) 4 h, and then 10 mL of $H_2O$ and 6 mL of 1 N HCl were added. The recovery of (*S*)-BPAB or (*S*)-BPAAPh determined spectrophotometrically at the absorption maximum (336 and 330 nm, respectively) was 60–100%; the enantiomeric composition and the chemical yield of threonine and allothreonine were determined by GLC (Table IV).

**Epimerization of [(*S*)-BPAB-(*S*)-Thr]$Cu^{II}$ and [(*S*)-BPAB-(*R*)-Thr]$Cu^{II}$ under the Action of $Et_3N$.** To ~1.5 × $10^{-2}$ mmol of [(*S*)-BPAB-(*S*)-Thr]$Cu^{II}$ or [(*S*)-BPAB-(*R*)-Thr]$Cu^{II}$ were added 0.3 mL of 1.78 M solution of freshly distilled acetaldehyde in anhydrous $CH_3OH$ and 1.7 mL of $Et_3N$ (final concentration 6.12 M) under Ar. The mixture was thermostated at 25 °C for 4 h, mixed with 5 mL of 1 N HCl, allowed to stand for 10 min, and treated as described above. The enantiomeric composition of the amino acids was determined by GLC (Table IV).

## Results

**1. Synthesis of the Chiral Reagents (*S*)-BPAB and (*S*)-BPAAPh.** The product of the first stage is *N*-benzylproline obtained by condensation of proline with benzyl chloride. The procedure reported earlier[16] leads to the product of mono- as well as di-*N*-alkylation. We modified the procedure and managed to separate these species by preparative chromatography on silica gel. (*S*)-BPAB and (*S*)-BPAAPh were obtained by condensation

Scheme II




R = H, R' = H
R = H, R' = $CH(CH_3)_2$
R = H, R' = $CH(OH)CH_3$
R = $CH_3$, R' = H

of *N*-benzyl-(*S*)-proline chloroanhydride hydrochloride with *o*-aminobenzaldehyde or *o*-aminoacetophenone in a two-phase system $CH_2Cl_2$–$H_2O$ at pH 8 of the aqueous phase and separated from the initial *o*-aminobenzaldehyde or *o*-aminoacetophenone by preparative chromatography on silica gel. Elemental analyses and IR and $^1H$ NMR spectra confirm the structure of (*S*)-BPAB and (*S*)-BPAAPh.

**2. Synthesis and Properties of Copper Complexes of Schiff Bases of Amino Acids with (*S*)-BPAB and (*S*)-BPAAPh.** Interaction between (*S*)-BPAB and Gly, Val, or Thr or between (*S*)-BPAAPh and Gly in the presence of copper ions ($CuSO_4$) in solution of $CH_3ONa$ gives rise to complexes in 40–80% yield according to Scheme II.

The structure of [(*S*)-BPAB–aa]$Cu^{II}$ and [(*S*)-BPAAPh–aa]$Cu^{II}$ presented by Scheme II may be proved as follows:

(1) The elemental analyses of the complexes correspond, taking into account the solvation molecules of $H_2O$ and $C_2H_5OH$ to calculated values.

(2) Decomposition of all the complexes resulted in the amino acid and the chiral reagent in a 1:1 ratio.

(3) Electrophoresis in 0.025 M pyridinium acetate (pH 6) suggests that the complexes carry no electric charge. They are well soluble in chloroform and may be extracted from the reaction mixture with it.

(4) The molecular weights of [(*S*)-BPAB–Gly]$Cu^{II}$, [(*S*)-BPAB–(*S*)-Val]$Cu^{II}$, and [(*S*)-BPAB–(*S*)-Thr]$Cu^{II}$ determined by vapor osmometry in anhydrous $CHCl_3$ at 37 °C are close to the calculated values.

(5) IR spectra of all the complexes are identical. The 3220-c (NH), 1690-c (CO, amide I), and 1520-$cm^{-1}$ (CO, amide II) bands present in the parent (*S*)-BPAB and (*S*)-BPAAPh disappear in the complexes; the bands 1580, 1500, and 1450 $cm^{-1}$, which correspond to the stretching modes of aromatic rings, are retained. The broad absorption at 1600–1680 $cm^{-1}$ may be attributed to overlapping of the bands of the coordinated carboxylate, the CH=N bond, and the ionized amide group.

(6) All the complexes are reddish brown. Their electronic spectra are virtually identical (see Table I). The electronic spectra in the region of copper d–d transitions display a broad maximum at 500–600 nm, where two maxima are observed in the CD spectra (Figure 1). Calculation with the use of empirical parameters suggests that $\lambda_{max}$ for $CuON_3$ chromophore is 580 nm (with Billo's parameters[23]) or 460 nm (with Kurganov's parameters[24] and disregard for the axial coordination of the solvent). Comparison of the experimental and the calculated values, therefore, testifies to the structure in which the Schiff base of the amino acid and (*S*)-BPAB or (*S*)-BPAAPh is coordinated to the copper ion by

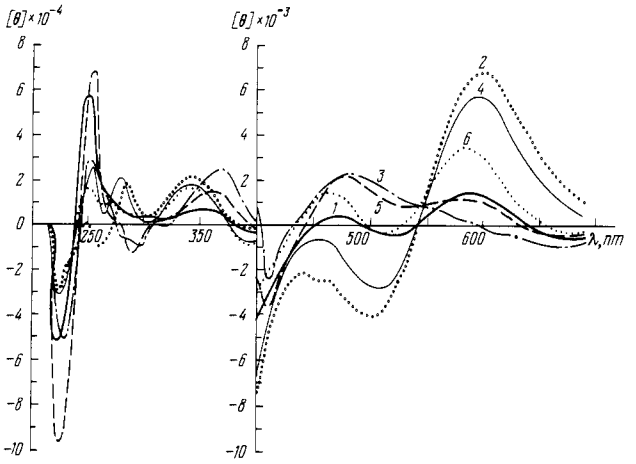



**Figure 1.** CD spectra in 96% $C_2H_5OH$: (1) [(*S*)-BPAB–Gly]$Cu^{II}$; (2) [(*S*)-BPAB–(*S*)-Val]$Cu^{II}$; (3) [(*S*)-BPAB–(*R*)-Val]$Cu^{II}$; (4) [(*S*)-BPAB–(*S*)-Thr]$Cu^{II}$; (5) [(*S*)-BPAB–(*R*)-Thr]$Cu^{II}$; (6) [(*S*)-BPAAPh–Gly]$Cu^{II}$.

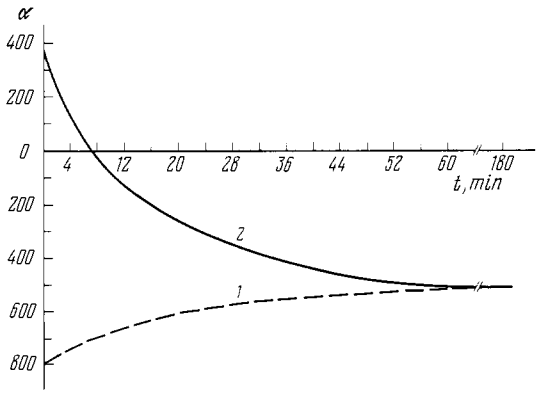



**Figure 2.** Time-dependent variation of specific optical rotation at 578 nm of [(*S*)-BPAB–(*S*)-Val]$Cu^{II}$ (1) and [(*S*)-BPAB–(*R*)-Val]$Cu^{II}$ (2) under the action of 0.01 N $CH_3ONa$ at 25 °C.

one oxygen and three nitrogen donor atoms including one of the deprotonated amide group.

(7) The CD spectra of all the complexes exhibit exciton couplets at 230–260 nm (Kuhn dissymmetry factor is up to $2.7 \times 10^{-3}$) with the negative and the positive constitutent situated at shorter and at longer wavelengths, respectively (Figure 1). This indicates that the chirality of the mutual arrangement of benzyl groups and coordinated phenyl fragments probably responsible for the observed Cotton effects is similar in all the complexes. This serves as an indirect evidence that pyrrolidine nitrogen atom acquires the same configuration in all the compounds.

Conclusive proof of the complexes structure was obtained by X-ray diffraction analysis of [(*S*)-BPAAPh–Gly]$Cu^{II}$.

As in the recently studied copper complex of the Schiff base of 1-(*N*,*N*-dimethylaminomethyl)-2-formylcymanthrene with (*S*)-Ala-(A)-Ala,[25] the Cu atom in [(*S*)-BPAAPh–Gly]$Cu^{II}$ has a distorted tetragonal-pyramidal coordination. The carboxyl and three nitrogen atoms form the base of the pyramid; the Cu atom is shifted from this plane by 0.1647 (4) Å toward the apical oxygen of the water molecule.

The pyrrolidine nitrogen atom coordinated with the copper ion acquires the *R* coordination. The benzyl group is turned away from the metal atom.

**3. Kinetic CH Acidity and Enantiospecific Effects in [(*S*)-BPAB–aa]$Cu^{II}$ Complexes.** The successful use of chiral reagents ((*S*)-BPAB or (*S*)-BPAAPh) for asymmetric synthesis and retroracemization of amino acids depends on the lability of the

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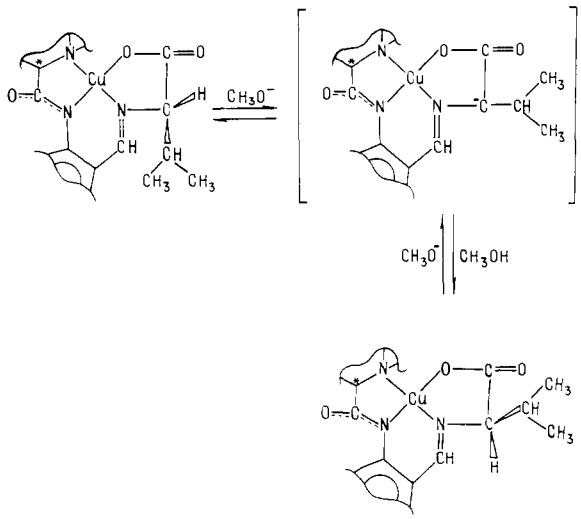
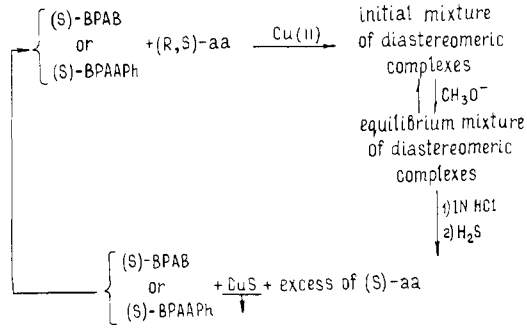
Scheme III



Scheme IV




$\alpha$-hydrogen of the amino acid fragment in the [(*S*)-BPAB-(BPAAPh)-aa]$Cu^{II}$ complexes. We have therefore investigated $CH_3O^-$-catalyzed epimerization of the valine fragment in [(*S*)-BPAB-(*S*)-Val]$Cu^{II}$ and [(*S*)-BPAB-(*R*)-Val]$Cu^{II}$.

Epimerization of these complexes at 25 °C in 0.01 N $CH_3ONa$ in anhydrous $CH_3OH$ follows first-order kinetics. The reaction rate was monitored spectropolarimetrically at $\lambda$ 578 nm. Figure 2 presents specific optical rotation of the complexes vs. time. This dependence shows that only one chiral fragment in the complex undergoes epimerization.

According to polarimetric evidence, the equilibrium mixture obtained, [(*S*)-BPAB-(*S*)-Val]$Cu^{II}$ as well as [(*S*)-BPAB-(*R*)-Val]$Cu^{II}$, contains a 53–55% enantiomeric excess (ee) of (*S*)-Val. Enantiomeric GLC analysis of valine quantitatively isolated upon decomposition of the equilibrium mixture gives a 59.6% ee of the (*S*)-Val. The CD spectrum calculated for a mixture containing 79.8% [(*S*)-BPAB-(*S*)-Val]$Cu^{II}$ and 20.2% [(*S*)-BPAB-(*R*)-Val]$Cu^{II}$ coincides with the experimentally observed CD spectrum of the equilibrium mixture of diastereomers.

By analogy with the behavior of other metal complexes with amino acids and their Schiff bases, it may be assumed that epimerization of the complexes follows a carbanion mechanism[8,10] which may be described by Scheme III.

The rate constant of [(*S*)-BPAB-(*S*)-Val]$Cu^{II}$ and [(*S*)-BPAB-(*R*)-Val]$Cu^{II}$ epimerization under the action of 0.01 N $CH_3O^-$ is $9 \times 10^{-2}$ $M^{-1}$ $s^{-1}$ (assuming first-order dependence on $CH_3O^-$). Thus the kinetic CH acidity of Val in copper complexes of its Schiff base with (*S*)-BPAB 2 orders of magnitude higher than in copper complexes of its Schiff base with salicylaldehyde ($1 \times 10^{-3}$ $M^{-1}$ $s^{-1}$).[26]

Accordingly, in the presence of copper ions (*S*)-BPAB increases the CH acidity of an amino acid fragment and exhibits a capacity for distinguishing between amino acid enantiomers. These features of BPAB were employed for the retroracemization of several natural amino acids.

**4. Retroracemization of Amino Acids by (*S*)-BPAB or (*S*)-BPAAPh.** Interaction of 1 equiv of (*S*)-BPAB (or (*S*)-BPAAPh), 1 equiv of the racemic amino acid, and 1 equiv of Cu(II) in 0.1 N (0.5 N) solution of $CH_3ONa$ in anhydrous $CH_3OH$ results in amino acid retroracemization according to Scheme IV. The reaction is a one-pot process. The resulting enantiometrically enriched amino acid was obtained and the chiral reagent recovered without isolation of the intermediate diastereomeric complexes after neutralization of the reaction mixture and removal of $Cu^{2+}$ by $H_2S$. The results are presented in Table II.

Unfortunately, decomposition of copper complexes of amino acids by $H_2S$ is known to result in significant losses of the amino acids.[27] Also some losses occur because of the irreversible reagent adsorption on the surface of the molecular sieves used. Hence we believe that the much lower than 100% yields of the amino acids and recovered chiral reagents are mainly due to the losses during isolation rather than to side reactions involved in retroracemization. As the key stage of retroracemization is epimerization of diastereomeric complexes, the absence of side reactions may be confirmed also by the fact that the experimental CD curve of the equilibrium mixture derived from the epimerized [(*S*)-BPAB-(*S*)-Val]$Cu^{II}$ or [(*S*)-BPAB-(*R*)-Val]$Cu^{II}$ coincides with the calculated one. The retroracemization under the action of (*S*)-BPAB was performed so that even for Val, an amino acid with the lowest lability of the $\alpha$-hydrogen, the duration of the experiment sufficed for complete equilibrium to be reached. This is confirmed by the fact that the equilibrium ee of (*S*)-Val in epimerization of [(*S*)-BPAB-(*S*)-Val]$Cu^{II}$ and [(*S*)-BPAB-(*R*)-Val]$Cu^{II}$ coincides with that after retroracemization of Val under the action of (*S*)-BPAB.

Substitution of a methyl group for the aldimine hydrogen when passing from metal complexes of amino acid Schiff bases with salicylaldehyde to similar complexes based on *o*-hydroxyacetophenone brings about a considerable decrease in the kinetic CH acidity of the amino acid fragment of the complexes.[28] It seems likely that with (*S*)-BPAAPh the lability of the amino acid fragment $\alpha$-proton is also lower than in the case of (*S*)-BPAB. Therefore, the retroracemization under the effect of (*S*)-BPAAPh was carried out in more concentrated solutions of $CH_3ONa$ than that under the action of (*S*)-BPAB. Note that (*S*)-BPAAPh-induced retroracemization of (*R,S*)-Ala also proceeds to a complete equilibrium between the diastereomers: the enantiomeric excess of (*S*)-Ala is virtually independent of the experiment duration (Table II, runs 7 and 8).

The data in Table II point out that the efficiency of retroracemization increases with the size of the amino acid fragment side chain. Also (*S*)-BPAAPh is more effective reagent of retroracemization than *S*-BPAB (Table II, runs 1, 7, and 8).

(*S*)-BPAB and (*S*)-BPAAPh retrieved after retroracemization had the same specific optical rotation in $CHCl_3$ as the initial reagents. This means that the chiral reagents themselves undergo no racemization during the process and therefore may be used repeatedly.

**5. Partial Resolution of Racemic Amino Acids with (*S*)-BPAB.** The (*S*)-BPAB capacity for recognizing amino acid enantiomers may also be used for resolution of amino acids. The process takes place when the concentration of the base in the solution does not suffice for retroracemization and the racemic amino acid is in twofold molar excess over the chiral reagent.

Interaction between 1 equiv of (*S*)-BPAB, 2 equiv of the racemic amino acid, 2 equiv of Cu(II), and $CH_3O^-$ yields a mixture from which, upon dilution with water, [(*S*)-BPAB-aa]$Cu^{II}$ may be extracted with chloroform.

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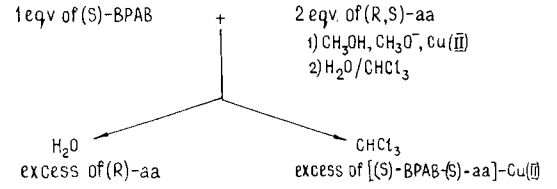
Scheme V




The amino acid exchange between the solution and the complex is extremely slow. For instance, the complex isolated from a $CH_3OH$ solution of [(*S*)-BPAB–(*S*)-Val]$Cu^{II}$ allowed to stand with tenfold excess of Gly–ONa at 25 °C for 2.5 h contains no glycine whatsoever. Amino acid exchange also does not accur in a two-phase $H_2O$–$CHCl_3$ system: after 26 h no exchange was observed between [(*S*)-BPAB–(*S*)-Val]$Cu^{II}$ solution in $CHCl_3$ and a thirtyfold excess of glycine in $H_2O$ (pH 8) even in the presence of phase-transfer catalysts.

GLC data on the enantiomeric and quantitative distribution of the amino acids in $CHCl_3$ (determined after decomposition of the complexes) and in water solutions are presented in Table III. They indicate that (*S*)-BPAB does cause resolution of the racemates. Absence of any losses of amino acids, comparison of the observed distribution of amino acids between $H_2O$ and $CHCl_3$ with that calculated from the data of enantiomeric analysis, as well as the distribution of Cu(II) between the two phases suggest the mechanism of resolution given in Scheme V.

In all the cases predominant formation of [(*S*)-BPAB–(*S*)-aa]$Cu^{II}$ is observed. Chiral recognition becomes more efficient in the series $n$-$C_3H_7$ < $CH_3$ < $C_6H_5CH_2$ < $(CH_3)_2CH$ < $CH_3$-CH(OH).

Since no amino acid exchange between the complex and the solution takes place, it appears that under these conditions the chiral recognition of amino acid enantiomers depends on the relative rate of formation of diastereomer complexes rather than on the difference between the free energies of the diastereomers.

**6. Asymmetric Synthesis of Threonine Using (*S*)-BPAB and (*S*)-BPAAPh.** The use of (*S*)-BPAB and (*S*)-BPAAPh has made it possible to carry out another type of asymmetric amino acid conversion, namely the asymmetric synthesis of threonine.

[(*S*)-BPAB–Gly]$Cu^{II}$ and [(*S*)-BPAAPh–Gly]$Cu^{II}$ under the action of a base ($CH_3ONa$ or $Et_3N$) in $CH_3OH$ at 25 °C (−5 °C) react with acetaldehyde to form a mixture of intermediate threonine complexes from which we isolated threonine of optical purity 60% and 97–100%, respectively, and the initial (*S*)-BPAB or (*S*)-BPAAPh in a 60–90% yield.

The optical purity of threonine did not depend on whether (*S*)-BPAB was "fresh" or previously recovered from the reaction mixture which means that proline fragment of (*S*)-BPAB conserves its enantiomeric purity.

The asymmetric and the chemical yields of threonine are given in Table IV. Both the enantioselectivity of the reaction and the threo/allo ratio of the isomers apparently depend on experimental conditions. A weak base ($Et_3N$ in $CH_3OH$) gives rise primarily to (*S*)-Thr (Table IV, runs 3 and 4), in agreement with the data on enantiospecific effects in the series [(*S*)-BPAB((*S*)-BPAAPh)–aa]$Cu^{II}$ (Tables II and III). However, under the action of a strong base ($CH_3ONa$) the principal product is (*R*)-Thr (Table IV, runs 5–10).

Substitution of a methyl group for the aldimine hydrogen (the use of (*S*)-BPAAPh) increases the ee of (R)-Thr to 97–100%.

The results on epimerization of [(*S*)-BPAB–(*S*)-Thr]$Cu^{II}$ and [(*S*)-BPAB–(*R*)-Thr]$Cu^{II}$ under the action of $Et_3N$ in $CH_3OH$ in the presence of acetaldehyde (Table IV, runs 1 and 2) indicate that under these conditions (*R*)-Thr is converted to both (*S*)-Thr and (*R*)-allo-Thr, while (*S*)-Thr gives rise to (*R*)-Thr and (*R*)-allo-Thr. This can only happen provided that simultaneous C–C bond breaking and formation occurs in the threonine fragment. As the acetaldehyde condensation reaction with [(*S*)-BPAB–Gly]$Cu^{II}$ is more prolonged than the epimerization experiment (Table IV, runs 1–3), it may be safely assumed that the data concerning condensation in the presence of a weak base ($Et_3N$ in $CH_3OH$) closely reflect thermodynamic enantioselectivity in the series of threonine complexes, and the reaction may be described by Scheme VI. In order to explain the enantioselectivity of this reaction in the case of a strong base used ($CH_3ONa$) (Table IV, runs 5–10), we have to analyze the factors responsible for the enantioselective properties of the complexes being discussed.

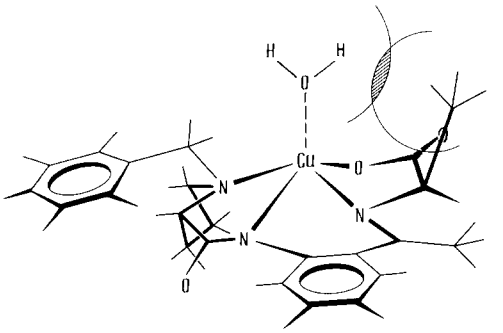
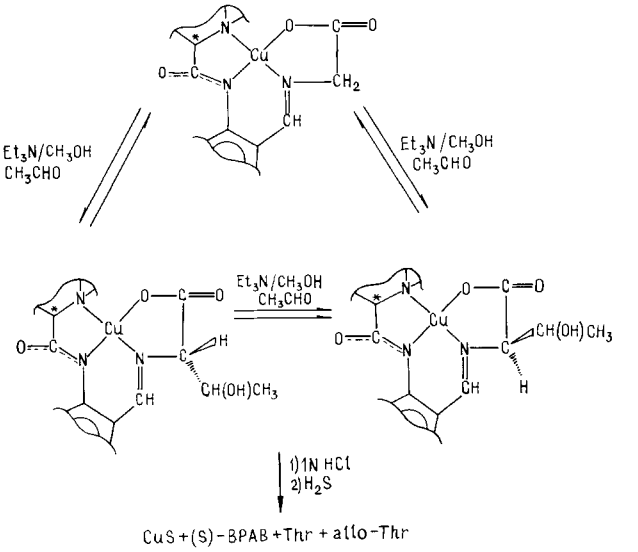


**Figure 3.** Schematic representation of nonbonding interaction between the amino acid chain and the apical water molecule in [(*S*)-BPAAPh–(*R*)-aa]$Cu^{II}$.

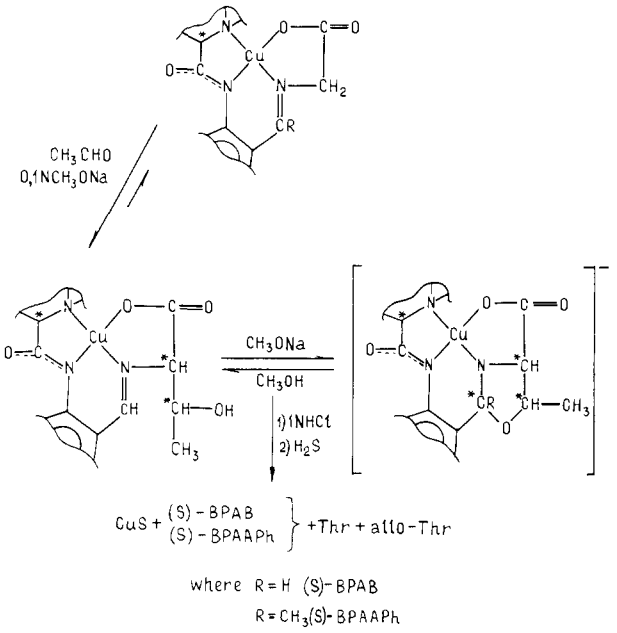
Scheme VI




## Discussion

In the distorted tetragonal-pyramid structure of [(*S*)-BPAAPh–Gly]$Cu^{II}$, the copper ion is a center of asymmetry. It is likely that this asymmetry is retained in solutions, the *N*-benzyl-(*S*)-proline fragment being responsible for the configuration of the complex. As we have already noted, the benzyl group in [(*S*)-BPAAPh–Gly]$Cu^{II}$ crystals does not shield the apical position in the coordination sphere of the Cu atom and does not prevent hydration. The resulting solvates may well exist sufficiently long in solutions. It is also not impossible that in the absence of solvation the phenyl group can occupy the position otherwise belonging to a water molecule. At any rate the pro-*R* and pro-*S* hydrogens of the glycine fragment have different steric surroundings. An alkyl group substitution for the glycine fragment pro-*R* hydrogen would cause energetically unfavorable steric interaction with the water molecule (or with the benzyl group fragment) in the apical position (see Figure 3). Such interaction would not occur if the pro-*S* hydrogen was substituted by a larger group. This may explain why both (*S*)-BPAB and (*S*)-BPAAPh from Schiff base complexes preferentially with (*S*)-aa. As for the better chiral recognition capacity of (*S*)-BPAAPh as compared to (*S*)-BPAB, it appears to arise from the fact that the amino acid substituent (*S*)-BPAAPh in complexes may be locked in its axial conformation due to interaction with the methyl ketimine group. In such a conformation the steric repulsion between the amino

Scheme VII




acid substituent and the apical water molecule would be increased.

This reasoning, however, does not account for the predominant formation of (*R*)-Thr rather than (*S*)-Thr when passing from a weak base ($Et_3N$) to a strong base ($CH_3ONa$) in acetaldehyde condensation with [(*S*)-BPAB–Gly]$Cu^{II}$ or [(*S*)-BPAAPh–Gly]$Cu^{II}$; the above-cited results on epimerization of [(*S*)-BPAB–(*S*)-Thr]$Cu^{II}$ and [(*S*)-BPAB–(*R*)-Thr]$Cu^{II}$ under the effect of $Et_3N$ imply that this effect is not due to the change from kinetic to thermodynamic control of the reaction.

We believe that high concentrations of $CH_3ONa$ effect intramolecular cyclization according to Scheme VII giving a negatively charged complex of substituted oxazolidine.

Scheme VII is supported by the following experimental evidence:

(1) The CD spectrum of the mixture of [(*S*)-BPAB–Gly]$Cu^{II}$ and $CH_3CHO$ in 0.1 N $CH_3ONa$ (Table IV, run 6) after 1 h (Figure 4) differs fundamentally from the initial spectrum of [(*S*)-BPAB–Gly]$Cu^{II}$ (Figure 1) and that of the mixture of diastereomeric complexes [(*S*)-BPAB–Thr]$Cu^{II}$ obtained upon neutralization of the above solution (Figure 4). The CD spectrum calcualted so as to allow for the enantiomeric composition of Thr and allo-Thr, as well as for the threo/allo ratio determined by GLC upon decomposition of the reaction mixture, corresponds to the spectrum of the neutralized reaction mixture (Figure 4). The electron and the IR spectra of the latter do not differ from the spectra of other [(*S*)-BPAB–aa]$Cu^{II}$ complexes. Therefore, the presence of the strong base is mandatory for the formation of a species whose structure is different from that of common [(*S*)-BPAB–aa]$Cu^{II}$ complexes. However, upon neutralization of the reaction mixture this species returns to the regular structure.

(2) With increasing strength of the base, the threo/allo ratio increases (see Table IV, runs 5–10), as is the case with the synthesis of threonine from glycine copper complexes and acetaldehyde.[29] The formation of oxazolidine rings in the latter

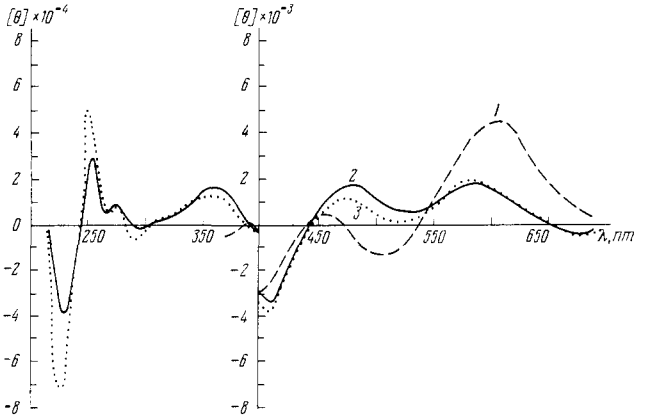



**Figure 4.** CD spectra in 96% $CH_3OH$: (1) reaction mixture, [(*S*)-BPAB–Gly]$Cu^{II}$ and $CH_3CHO$, in 0.1 N $CH_3ONa$ at 25 °C (after 1 h); (2) diastereomeric complexes isolated from the reaction mixture after its neutralization; (3) calculated spectrum of the mixture of the diastereomeric complexes (based on the GLC enantiomeric amino acid analysis data).

instance was demonstrated by X-ray diffraction analysis.[30]

(3) It is interesting to note that the reported enantioselectivity in Λ-[$Co(en)_2$–Gly]$^{2+}$ condensation with acetaldehyde[6] (prevailing of Λ-[$Co(en)_2$–(*S*)-Thr]$^{2+}$) is also at variance with the greater stability of Λ-[$Co(en)_2$–(*R*)-aa]$^{2+}$ for complexes with other amino acids.[8] This discrepancy was explained earlier by the formation of oxazolidine rings during the synthesis of threonine.[31] Complexes containing such an intermediate structure should exhibit stereoselective effects different from those featured by complexes of amino acids with a primary amino group. This analogy may be regarded as supporting the formation of similar cyclic structures in the synthesis of threonine from [(*S*)-BPAB–Gly]$Cu^{II}$ and [(*S*)-BPAAPh–Gly]$Cu^{II}$.

A more detailed analysis of the enantioselective and enantiospecific effects exhibited by the complexes derived from aa and BPAB or BPAAPh has to await results of strain energy minimization calculations which are currently in progress.

**Registry No.** (*S*)-Pro, 147-85-3; (*S*)-BPAB, 82704-14-1; (*S*)-BPAAPh, 82704-15-2; [(*S*)-BPAB-Gly]$Cu^{II}$, 83542-56-7; [(*S*)-BPAB-(*S*)-Val]$Cu^{II}$, 83528-05-6; [(*S*)-BPAB-(*R*)-Val]$Cu^{II}$, 83572-18-3; [(*S*)-BPAB-(*S*)-Thr]$Cu^{II}$, 83601-91-6; [(*S*)-BPAB-(*R*)-Thr]$Cu^{II}$, 83528-06-7; [(*S*)-BPAAPA-Gly]$Cu^{II}$, 83528-07-8; (*R,S*)-Ala, 302-72-7; (*R,S*)-Nva, 760-78-1; (*R,S*)-Phe, 150-30-1; (*R,S*)-Val, 516-06-3; (*R,S*)-Thr, 80-68-2; (*R*)-Ala, 338-69-2; (*S*)-Ala, 56-41-7; (*R*)-Nva, 2013-12-9; (*S*)-Nva, 6600-40-4; (*R*)-Phe, 673-06-3; (*S*)-Phe, 63-91-2; (*R*)-Val, 640-68-6; (*S*)-Val, 72-18-4; (*R*)-Thr, 632-20-2; (*S*)-Thr, 72-19-5; (*R*)-*allo*-Thr, 24830-94-2; (*S*)-*allo*-Thr, 28954-12-3; (*R,S*)-*allo*-Thr, 144-98-9; *N*-benzyl-(*S*)-proline, 31795-93-4; benzyl chloride, 100-44-7; *N,O*-dibenzylproline, 83528-04-5; *o*-aminobenzaldehyde, 529-23-7; *o*-aminoacetophenone, 551-93-9.

**Supplementary Material Available:** Tables of final fractional coordinates and thermal parameters and ORTEP drawing with all the bond distances (4 pages). Ordering information is given on any current masthead page.

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