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ASYMMETRIC SYNTHESIS AND RETRORACEMISATION OF AMINO ACIDS VIA COPPER(II) COMPLEXES WITH SCHIFF BASES BETWEEN CHIRAL 1-(N,N-DIMETHYLAMINOMETHYL)-2-FORMYLCYMANTRENE AND DIPEPTIDES

YU. N. BELOKON',* I. E. ZEL'TZER, N. M. LOIM, V. A. TSIRYAPKIN, G. G. ALEKSANDROV, D. N. KURSANOV, Z. N. PARNES, YU. T. STRUCHKOV and V. M. BELIKOV
Institute of Organoelement Compounds, U.S.S.R. Academy of Sciences, Moscow, U.S.S.R.

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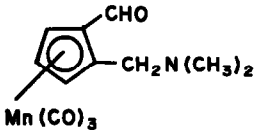
Abstract—1-(N,N-Dimethylaminomethyl)-2-formylcymantrene (AFCMT) has been resolved into enantiomers through an intermediate formation of diastereomeric complexes with (*S*)-Ala-(*S*)-Ala, (*S*)-Ala-Gly and Gly-(*S*)-Ala. By the X-ray anomalous dispersion method the absolute configuration of its enantiomers has been determined: $(-)_{436}$ AFCMT-(*S*), $(+)_{436}$ AFCMT-(*R*).

Alkylation of enantiomeric complexes (*R*)-and (*S*)-AFCMT-(GlyGly) Cu(II) with acetaldehyde gives, respectively, (*R*)-and (*S*)-Thr with an asymmetric yield of 92–98% and (*R*)- and (*S*)-allo-Thr with an asymmetric yield of 95–100%, only the N-terminal glycine being alkylated.

The AFCMT enantiomers were also employed for retroracemisation of (*R,S*)-Ala-(*R,S*)-Nva; in this case an excess of (*S*)-Ala and (*R*)-Nva is obtained for (*S*)-AFCMT. (*R*)- and (*S*)-AFCMT are not liable to racemisation in the course of the threonine synthesis and retroracemisation of depeptides and can be repeatedly employed for these transformations.

A pyridoxal-dependent enzyme serine transhydroxymethylase[1] may be regarded as a chiral carbonyl-containing reagent which effects the asymmetric synthesis of β-hydroxy-α-amino acids through condensation of aldehydes with glycine via an intermediate formation of a Schiff base of the latter with an aromatic aldehyde (pyridoxal). It was shown that the chiral environment of such a Schiff base on the active centre of the enzyme can be imitated in chiral stereochemically inert complexes of Co(III), where the ligands are Schiff bases of the amino acid and salicylaldehyde.[2] For the free amino acid to be isolated after the asymmetric transformation, the Co(III) complex must be destroyed, and its chirality conditioned by the spatial arrangement of the ligands about the Co(III) ion is irrevocably lost.[2] A replacement of salicylaldehyde with its chiral analogue would allow the chiral fragment of the complex to be preserved after isolation of the amino acid and, consequently, such a compound could be repeatedly employed for asymmetric transformations.

In the present work we report on the resolution of racemic 1-(N,N-dimethylaminomethyl)-2-formylcymantrene (AFCMT), the absolute configuration determination of its enantiomers, and also the employment of this compound for the asymmetric synthesis of threonine and retroracemisation of depeptides.



EXPERIMENTAL

Dipeptides (*S*)-Ala-(*S*)-Ala, Gly-(*S*)-Ala, Gly-Gly, (*R,S*)-Ala-(*R,S*)-Nva were purchased from "Reanal Budapest" and were used without further purification. (*S*)-Ala-Gly, Thr-Gly, Gly-Thr were synthethised according to the technique given.[3] The resulting dipeptides were chromatographically pure. Enantiomeric purity of the amino acids in the dipeptides was determened by glc after acid hydrolysis (6 N HCl, 105°, 24 hr Table 1).[4]

CD_3ONa was prepared by adding metallic Na into CD_3OD under argon with cooling. MeONa was prepared by adding metalic Na into absolute MeOH under argon with cooling.

Racemic AFCMT was synthesised from cymantrene according to the technique given,[5] m.p. 57–58° (from *n*-heptane).

^{1}H NMR spectra were recorded on "R-32" and "Perkin–Elmer H-90" spectrometers. IR spectra were recorded on a "UR-20"

Table 1. Enantiomeric purity of amino acids from initial dipeptides

Dipeptide	% of enantiomers			
	(S)-Ala	(R)-Ala	(S)-Nva	(R)-Nva
(S)-Ala-(S)-Ala	95.05	4.95	-	-
(S)-Ala-Gly	97.84	2.16	-	-
Gly-(S)-Ala	98.00	2.00	-	-
(R,S)-Ala-(R,S)-Nva	49.42	50.58	49.76	50.24

spectrometer. Electron spectra were recorded on a "SPECORD UV-VIS". ORD curves were recorded on a "Jasco ORD/UV-5" spectropolarimeter. CD curves were recorded on a "Jasco J-20". Specific rotation was determined on a Perkin–Elmer 241". Electrophoresis of the complexes was carried out in a 0.025M soln of $NaClO_4$ on a "Labor" instrument. Molecular weight of (*S*)-AFCMT-((*S*)-Ala-(*S*)-Ala)Cu(II) was determined ebullioscopically on a Soviet-made precision ebulliometer "∋ П-68".

Synthesis of AFCMT complexes with chiral dipeptides and resolution of AFCMT into enantiomers. Cu complexes of AFCMT with chiral dipeptides were synthesised by using a general technique exemplified for the case of (*S*)-AFCMT-((*S*)-Ala-(*S*)-Ala) Cu(II). To a soln of 0.240 g (1.5 mmole) of (*S*)-Ala-(*S*)-Ala in 15 ml of 0.1N MeONa in abs. MeOH, 0.2 g of molecular sieves ("Wolfen Zeosorb", 3 Å) and 0.435 g (1.5 mmole) of racemic AFCMT were added. The mixture was stirred in a stream of argon at room temp for 10 min in darkness, then 0.319 g (2 mmole) of anhyd $CuSO_4$ was added, and the mixture was stirred for another 15 min. The mixture was filtered, the filtrate was evaporated to *ca* 1 ml, and 15 ml of H_2O was added. The unreacted AFCMT enriched with (*R*)-enantiomer was extracted with benzene (3 × 20 ml), the benzene soln was evaporated, and the residue recrystallised from *n*-heptane. The yield of (*R*)-AFCMT was 0.132 g (0.457 mmole) (30.5%). $[\alpha]_{436}^{25} = +270$ ($CHCl_3$), $[\alpha]_{436}^{25} = -1240$ (0.1N HCl). Optical purity was 64%. The aqueous soln was evaporated to dryness *in vacuo* and the complex was desalted on a LH-20 Sephadex column (2 × 25 cm) eluted with 4:1 benzene/EtOH.

The yield of (*S*)-AFCMT-((*S*)-Ala-(*S*)-Ala)Cu(II) was 0.675 mmole (45%). The yield of (*S*)-AFCMT-((*S*)-Ala-Gly) Cu(II) was 0.450 mmole (30%). The purity of the complexes was controlled by tlc on Silufol in a 3:2 EtOH/$CHCl_3$ system.

(*R*)-AFCMT-(Gly-(*S*)-Ala) Cu(II) was additionally purified on silca gel (40/100 μ) in EtOH, by collecting the fraction containing (*R*)-AFCMT-(Gly-(*S*)-Ala) Cu(II). The yield was 21%. The elemental analyses of the complexes are presented in Table 2.

Chiral AFCMT from the complex. To 0.5 mmole of the complex in 0.5 ml of EtOH and 10 ml of H_2O, 5 ml of 1N HCl and then immediately 1 ml of conc amm soln were added. AFCMT was extracted with $CHCl_3$ (3 × 20 ml). The yield of AFCMT was determined spectrophotometrically by the absorption of the AFCMT soln in $CHCl_3$ at 340 nm ($\epsilon = 1.84 \times 10^3$). The yield was 90%. The soln of AFCMT in $CHCl_3$ was evaporated and the oily residue was recrystallised once from 4–5 ml *n*-heptane. The yield was 0.52 g (0.18 mmole) (36%). (*S*)-AFCMT had $[\alpha]_{436}^{25} = -420$ ($CHCl_3$), $[\alpha]_{436}^{25} = +1940$ (1N HCl). Specific rotation in $CHCl_3$ and 1N HCl did not change upon recrystallisation, m.p. 78–80°. (*R*)-AFCMT had the same parameters as (*S*)-AFCMT, except for the opposite sign of rotation. ^1H NMR spectrum of (*R*)-, (*S*)-, (*R,S*)-AFCMT (solvent, CCl_4; chemical shifts in ppm with respect to HMDS): 2.6 (singlet, 6H, CH_3); 5.2 (multiplet, 2H, $H^{4,5}$); 5.76 (multiplet, H, H^3); 10.13 (singlet, H, HCO). Quartet of the system A B, CH_2 group $\delta = 3.49$ ppm and $\delta = 4.04$ ppm ($J_{AB} = 14$ Hz) IR spectrum of (*R*)-, (*S*)-, (*R,S*)-AFCMT ν cm^{-1}: 2030, 1960, 1930 (C=O); 1690 (CHO); 2790–3110 (C–H of cyclopentadiene ring); 2750, 2790 ($N(CH_3)_2$). Electron spectrum of (*R*)-, (*S*)-, (*R,S*)-AFCMT in $CHCl_3$: λ_{max} (ϵ) = 290, 340 nm (1.94×10^3; 1.84×10^3); $\lambda_{min} = 280$, 315 nm.

Synthesis of copper complexes of (R)- *and* (S)-*AFCMT with glycylglycine.* To 0.132 g (1 mmole) of glycylgylcine in 10 ml of 0.1N MeONa in abs. MeOH, 0.15 g of molecular sieves ("Wolfen Zeosorb, 3 Å) and 0.289 g of (*R*)- or (*S*)-AFCMT were added. The mixture was stirred in a stream of argon for 10 min, then 0.24 g (1.5 mmole) anhyd $CuSO_4$ was added, and the stirring was continued for another 1 hr. The mixture was filtered, the filtrate was evaporated to *ca* 1 ml, and the complex was desalted on a LH-20 Sephadex column (2 × 25 cm) with 4:1 benzene/EtOH as an eluent.

The yield of (*S*)-AFCMT-(GlyGly) Cu(II) was 0.6 mmol (60%). The yield of (*R*)-AFCMT-(GlyGly) Cu(II) was 0.62 mmol (62%). The data of the elemental analysis of the complexes are presented in Table 2.

Isolation of dipeptides and amino acids from complexes. The complexes were decomposed as described above, dipeptides were desalted on Dowex-50 (H^+ form) and hydrolysed with 6N HCl at 105° for 24 hr. The hydrolysate was evaporated *in vacuo* several times with addition of water and then desalted on Dowex-50 (H^+ form). Quantitative analysis of amino acids was carried out by glc.[4] The yield of the amino acids with respect to the internal standard was 80–90%. For the analysis, the dipeptides were additionally purified with charcoal. Quantitative analysis of the dipeptides was carried out on an amino acid analyser "AAA-881" (0.8 × 40 cm column with resin "aminex A-5", eluent, sodium citrate buffer pH = 4.25).

Determination of $(-)_{436}$ *AFCMT absolute configuration.* The X-ray investigation was conducted on an automatic 4-cycle diffractometer "Syntex-$P2_1$" (λMo, graphite monochromator, $2° \le 2\theta \le 46°$, $\theta/2\theta$-scan, 867 reflections with $F^2 \ge 2\sigma$). The structure was solved by the heavy atom method and refined by the least-square method in full-matrix anisotropic approximation. All calculations were carried out on a minicomputer "Eclipse S/200", using "Syntex-EXTL" programs. The final refinement gave R = 0.054, $R_w = 0.056$. The absolute configuration of $(-)_{436}$ AFCMT is *S*, as determined by the Hamilton test,[7] taking into account anomalous corrections for Mn and O atoms (for the inverted structure R = 0.060 and $R_w = 0.061$).

Crystals of $(-)_{436}$ AFCMT are orthorhombic, a = 7.501(3), b = 23.069(8), c = 7.654(3) Å, V = 1324.5(8) A^3; $d_{meas} = 1.44$; $d_{calc} = 1.45$ g·cm^{-3}, Z = 4, space group $P2_12_12_1$. Atomic coordinates and temperature factors are given in Table 3. Bond lengths and angles are given in Tables 4 and 5 respectively.

Alkylation of (R)- *and* (S)-*AFCMT-(GlyGly)Cu(II) complexes.* This was carried out according to the general technique. The experiment was conducted for 1 hr or for 4 hr. A typical 1 hr experiment was performed as follows.

To 0.018 g (0.0356 mmole) of the complex 9 ml of a 0.87% soln

Table 2. Elemental analyses of the complexes

Complex	% C		% H		% N		% Cu		% Mn	
	Found	Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found	Calc.
(S)-AFCMT-((S)-Ala-(S)-Ala)Cu(II)··C_2H_5OH	44.37	44.57	4.21	4.86	7.84	7.80	11.80	11.79	10.05	10.19
(S)-AFCMT-((S)-Ala-Gly)Cu(II)··H_2O·½C_2H_5OH	41.18	41.59	4.14	4.46	8.00	8.08	11.98	12.22	10.72	10.57
(R)-AFCMT-(Gly-(S)-Ala)Cu(II)··H_2O·½C_2H_5OH	41.98	41.59	4.38	4.46	8.46	8.08	12.21	12.22	10.53	10.57
(S)-AFCMT-(GlyGly)Cu(II)··H_2O·½C_2H_5OH	39.83	40.36	3.75	4.18	8.23	8.30	12.04	12.56	10.44	10.86
(R)-AFCMT-(GlyGly)Cu(II)··H_2O·C_2H_5OH	39.89	40.88	4.00	4.57	8.00	7.94	11.72	12.02	9.89	10.39

Table 3. Atomic coordinates (×10⁴, for Mn×10⁵) and anisotropic temperature factors (×10) $T = \exp[-\frac{1}{4}(B_{11}h^2a^{*2} + \cdots + 2B_{12}hka^*b^* + \cdots)]$

Atom	X	Y	Z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Mn	13802(22)	15261(7)	21341(21)	33(1)	36(1)	35(1)	-5(1)	1(1)	7(1)
O(1)	1258(23)	2507(5)	-277(18)	112(8)	99(7)	136(9)	-19(8)	-4(9)	83(7)
O(2)	3110(13)	2194(4)	4872(14)	79(7)	63(5)	93(7)	-18(5)	-20(6)	-21(5)
O(3)	4761(13)	1059(5)	732(16)	36(5)	122(8)	103(7)	1(5)	26(6)	-28(6)
O(4)	2411(13)	-76(4)	3231(10)	76(5)	49(4)	51(5)	34(4)	6(4)	7(4)
N	-2093(13)	1013(5)	6847(11)	40(5)	106(8)	12(4)	-8(6)	6(4)	1(5)
C(1)	1300(25)	2118(6)	681(19)	61(8)	68(8)	71(8)	-18(10)	-5(9)	20(7)
C(2)	2429(19)	1933(5)	3763(19)	52(7)	36(7)	65(8)	-20(6)	-9(7)	0(6)
C(3)	3500(20)	1255(6)	1248(17)	46(7)	62(7)	48(7)	-15(7)	5(7)	-11(6)
C(4)	509(14)	719(5)	3193(13)	26(5)	32(6)	17(6)	-6(5)	0(4)	-3(4)
C(5)	87(16)	727(5)	1385(14)	28(5)	28(6)	34(6)	2(5)	6(5)	-1(4)
C(6)	-1074(18)	1193(5)	1074(15)	30(7)	53(6)	27(6)	-5(6)	-5(6)	-1(5)
C(7)	-1403(15)	1471(4)	2737(14)	28(4)	33(4)	40(5)	1(6)	0(5)	-5(5)
C(8)	-444(15)	1179(5)	4042(13)	29(6)	36(6)	20(5)	-13(5)	-7(5)	12(5)
C(9)	1743(16)	324(5)	3991(14)	40(7)	34(6)	40(6)	6(5)	-4(6)	13(5)
C(10)	-618(16)	1305(5)	5963(14)	47(6)	43(6)	26(5)	11(5)	-9(5)	-9(5)
C(11)	-1931(18)	377(5)	6848(16)	83(9)	35(6)	57(7)	-17(6)	11(7)	7(6)
C(12)	-3795(19)	1237(6)	6233(16)	31(6)	136(11)	46(6)	3(8)	3(6)	9(7)

Table 4. Bond lengths d (Å)

Bond	d	Bond	d
Mn-C(1)	1.76(1)	C(4)-C(5)	1.42(2)
Mn-C(2)	1.75(1)	C(5)-C(6)	1.40(2)
Mn-C(3)	1.84(2)	C(6)-C(7)	1.45(2)
Mn-C(4)	2.13(1)	C(7)-C(8)	1.40(2)
Mn-C(5)	2.16(1)	C(8)-C(4)	1.43(2)
Mn-C(6)	2.15(1)	C(4)-C(9)	1.44(2)
Mn-C(7)	2.14(1)	C(9)-O(4)	1.20(1)
Mn-C(8)	2.16(1)	C(8)-O(10)	1.50(2)
C(1)-O(1)	1.16(2)	C(10)-N	1.46(2)
C(2)-O(2)	1.16(2)	N-C(11)	1.47(2)
C(3)-O(3)	1.12(2)	N-C(12)	1.46(2)

Table 5. Bond angles ω°)

Angle	ω	Angle	ω
C(1)MnC(2)	92.8(7)	C(6)C(7)C(8)	109(1)
C(1)MnC(3)	93.5(7)	C(7)C(8)C(9)	107(1)
C(1)MnCp*	122.7	C(8)C(4)C(5)	109(1)
C(2)MnC(3)	93.2(6)	C(8)C(4)C(9)	127(1)
C(2)MnCp*	124.7	C(5)C(4)C(9)	124(1)
C(3)MnCp*	121.6	C(4)C(9)O(4)	123(1)
MnC(1)O(1)	180(1)	C(4)C(8)C(10)	129(1)
MnC(2)O(2)	178(1)	C(7)C(8)C(10)	124(1)
MnC(3)O(3)	176(1)	C(10)NC(11)	113(1)
C(4)C(5)C(6)	108(1)	C(10)NC(12)	111(1)
C(5)C(6)C(7)	107(1)	C(11)NC(12)	115(1)
		C(8)C(10)N	115(1)

* Cp - centroid of cyclopentadienyl ring

Table 6. Enantiomeric composition of the mixture of threonines obtained in the condensation of (*R*)- or (*S*)-AFCMT-(GlyGly) Cu(II) with acetaldehyde in methanol (0.1N MeONa in CH_3OH), t = 25°, under argon

Configuration of AFCMT	Reaction time (h)	Thr/allo-Thr	Gly/Thr + allo-Thr	Asymmetric yield*), %	
				threonine	allo-threonine**)
S	1	2.42	1.9	92–98 S ***)	95–100 S ***
S	4	2.15	1.2	92 S	95–100 S
R	1	2.30	1.5	93 R	>99 R
R	4	2.30	1.2	96 R	>99 R

*) Enantiomeric GLC analysis[4].

**) Accuracy of allothreonine optical purity determination is 5%.

***) Results of six experiments are in this range.

of freshly distilled acetaldehyde in abs. MeOH and 1 ml of 1N MeONa in MeOH (final concn 0.1M) were added under argon. The mixture was thermostatted at 25°, then 10 ml H_2O and 3 ml 1N HCl were added, and the acetaldehyde was extracted with ether (5 × 40 ml). Conc ammonia soln (0.8 ml) was added to the aqueous soln, and AFCMT was extracted with $CHCl_3$ (3 × 20 ml). The yield of AFCMT, as determined spectrophotometrically, was 85%. Dipeptides were desalted on Dowex-50 (H^+ form) and hydrolysed with 6N HCl at 105° for 24 hr. The enantiomeric and quantitative composition of the hydrolysate was determined by glc[4] (Table 6).

Deuterium exchange in the complexes. This was carried out in accordance with the general technique outlined below.

To 0.056 mmole of the complex, 10 ml of 0.1N CD_3ONa in CD_3OD was added under argon. The mixture was thermostatted at 25° for 4 hr, then 15 ml of H_2O, 3 ml of 1N HCl and 5 min afterwards, 0.8 ml of conc ammonia soln was added. AFCMT was extracted with $CHCl_3$. The yield of AFCMT, as determined spectrophotometrically, was 78%. Its specific rotation in $CHCl_3$ had not changed. The dipeptide was desalted on Dowex-50 (H^+ form) and hydrolysed with 6N HCl at 105° for 24 hr. The yield of Ala was 77% and that of Gly was 60%. The presence of deuterium was determined by the GC–MS method.

Mass spectra of amino acid N-TFA-O-iPr esters[4] were recorded on a combined gas chromatograph-mass spectrometer "AEIMS-1073" at 70 eV and source temp of 200°. Capillary columns LKB-Am-Ac at the temp of 100° were used. The jet separator temp was 150°.

Since the molecular ion intensity is low and the ion-molecular processes proceed with the formation of the (M + H) ion, approximate content of deuterium in the molecule was determined only for $M\text{–}OPr^{\oplus}$ ions. All intensities are given with respect to the $M_{(H,H)}$–OPr ion adopted to be 100%. For Ala and Gly isolated from the (*S*)-AFCMT-((*S*)-Ala-Gly) Cu(II) complex after treating it with 0.1N CD_3ONa in CD_3OD for 4 hr the [M–OPr + 1]/M–OPr ratio is close to that for non-deuterated Gly and Ala samples. On the contrary, glycine isolated from the (*R*)-AFCMT-(Gly-(*S*)-Ala) Cu(II) complex has the following distribution of the ions in the vicinity of the M–OPr ion: (M–OPr):(M–OPr + 1):(M–OPr + 2):(M–OPr + 3) = 1:1.8:7.5:0.5, which indicates a high degree of exchange of both α-hydrogens of the glycine for deuterium. For the Ala isolated from this complex the (M–OPr + 1)/M–OPr ratio is close to that for the non-deuterated Ala.

Retroracemisation of (R,S)-*Ala*-(R,S)-*Nva.* To 0.0188 g (0.1 mmole) of (*R,S*)-Ala-(*R,S*)-Nva; 0.289 g (0.1 mmole) of (*R*)- or (*S*)-AFCMT; 0.0182 g (0.1 mmole) of copper acetate and 0.15 g of molecular sieves ("Wolfen Zeosorb", 3 Å) 5 ml of abs. MeOH and 0.1 ml of 1N MeONa were added under argon. The mixture was stirred at 40° for 1 hr till complete dissolution of all the components, and then it was transferred under argon to 4.9 ml of 1N MeONa in abs. MeOH. The mixture was kept at room temp for (a) 1 hr, (b) 3 hr; then 20 ml of H_2O, 6 ml of 1N HCl and 0.5 ml of conc ammonia soln were added. AFCMT was extracted with $CHCl_3$ (3 × 20 ml). The yield of AFCMT, as determined spectrophotometrically, was 65%. The dipeptide was desalted on Dowex-50 (H^+ form) and hydrolysed with 6N HCl at 105° for 24 hr. The enantiomeric and quantitative composition was determined by glc.[4] The chemical yield of Ala was 68–100%, that of Nva was 80–100%. The percentage of Ala and Nva enantiomers is presented in Table 7.

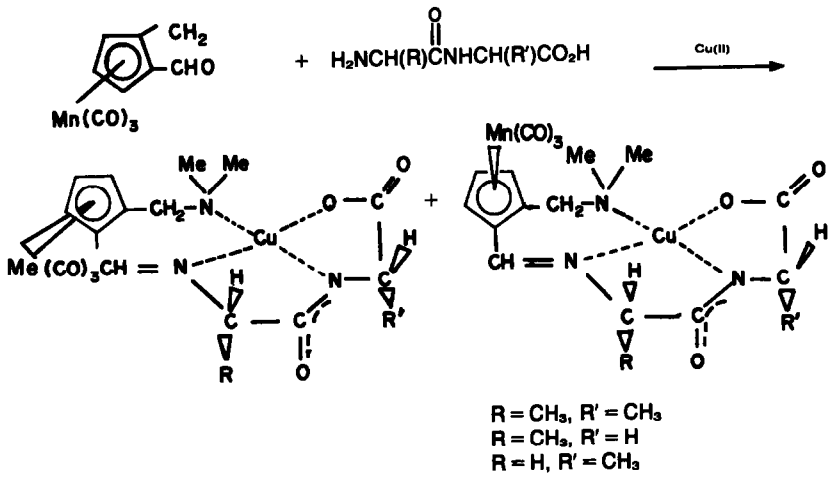
RESULTS AND DISCUSSION

To resolve racemic AFCMT into enantiomers we utilised the ability of bidentate aromatic aldehydes to form stable copper complexes with chiral dipeptides.[8] In the case of AFCMT the complexes must be diastereomeric (Scheme 1) and in principle can be resolved.

The formation of such complexes proved to proceed enantiospecifically. Dipeptides containing an N-terminal *S*-amino acid ((*S*)-Ala-(*S*)-Ala, (*S*)-Ala-Gly) form complexes preferably with $(-)_{436}$AFCMT. AFCMT enriched with the enantiomer rotating $(+)_{436}$ in $CHCl_3$ can be easily removed from the mixture with benzene. Diastereomeric complexes enriched with a complex of $(-)_{436}$AFCMT are separated on silica gel in a system EtOH–$CHCl_3$ (3:2); in the case of (*S*)-Ala-(*S*)-Ala and

Table 7. Enantiomeric composition of amino acids obtained after the retroracemisation of (*R,S*)-Ala-(*R,S*)-Nva in 0.5N MeONa in MeOH in the presence of stoichiometric quantities of (*S*)- or (*R*)-AFCMT and copper acetate at room temperature in argon atmosphere

Configuration of AFCMT	Reaction time (h)	% of enantiomers			
		(S)-Ala	(R)-Ala	(S)-Nva	(R)-Nva
S	1	78.31	21.69	39.43	60.57
S	3	76.85	23.15	26.20	73.80
R	1	26.80	73.20	57.84	42.16



Scheme 1.

(*S*)-Ala-Gly the fraction containing a complex with $(+)_{436}$AFCMT is not stable and cannot be isolated. Decomposition of the remaining copper complex gives an enantiomer rotating (−) at 436 nm in $CHCl_3$. In the case of Gly-(*S*)-Ala both diastereomeric complexes are formed, which are separated on silica gel in EtOH, but the fraction containing the complex with $(-)_{436}$AFCMT is not stable and we have not been able to isolate it in pure form. Decomposition of the copper complex of Gly-(*S*)-Ala and $(+)_{436}$AFCMT gave an optically pure AFCMT enantiomer rotating (+) at 436 nm in $CHCl_3$. Recrystallisation of the enantiomers till constant specific rotation gives $(-)_{436}$ and $(+)_{436}$AFCMT which have the same elemental analyses, m.p. (79–80°), IR, ^{1}H NMR and electron spectra. ORD curves of these compounds are mirror images (Fig. 1).

The absolute configuration of the chiral AFCMT was determined by the X-ray anomalous dispersion method. The absolute configuration of $(-)_{436}$AFCMT has been established as (*S*)† and, hence, that of $(+)_{436}$AFCMT as (*R*).† The structure of the (*S*)-AFCMT with numbering of the atoms is shown in Fig. 2, the bond lengths and angles are given in Tables 4 and 5 respectively. The Mn atom is coordinated with η^5-$C_5H_3(COH)(CH_2NMe_2)$ ligand and three CO groups. Coordination of the Mn atom is octahedral and, accordingly, (O)CMnC(O) angles between CO groups are close to 90°. If one considers the Cp-ligand as occupying formally one site in the coordination polyhedron, the coordination may be regarded as distorted tetrahedral, and in accordance with a considerable bulkiness of the Cp-group the angles (O)C–Mn-centroid of the Cp-ring are increased to 121.6–124.7°. Complexes of the type $(\eta^5$-$C_5H_5)Mn(CO)_3$ have similar coordination geometry.[9] The aldehyde group C(9)O(4) has usual geometrical parameters (C(9)–O(4) 1.20(1) Å), the length of the bond C(4)–C(9) (1.44(1) Å) is only slightly smaller than that of the standard bond $C(sp^2)$–$C(sp^2)$[10] (1.48 Å). The C(4)C(9)O(2) plane makes with the plane of the Cp-ligand a dihedral angle of 6.9°. NMe_2-

†The nomenclature given in Ref. 6 was employed.

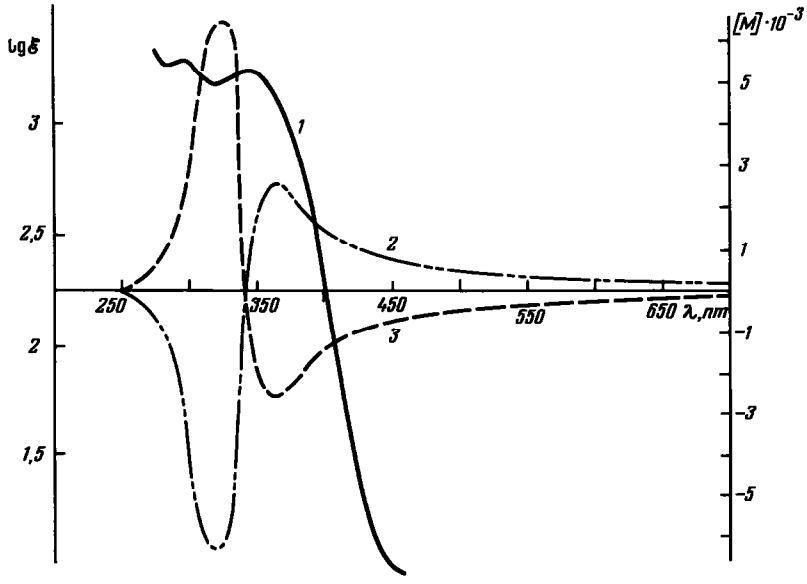


Fig. 1. Electronic spectrum of (*R*)-, (*S*)-, (*R,S*)-AFCMT in $CHCl_3$ (1), ORD of (*R*)-AFCMT in $CHCl_3$ (2), ORD of (*S*)-AFCMT in $CHCl_3$ (3).

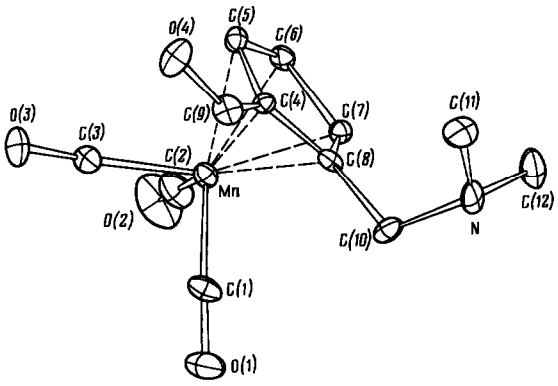


Fig. 2. Structure of (*S*)-AFCMT with numbering of atoms.

group is tilted away from the metal atom, the C(8)C(10)N plane is almost normal to the plane of the Cp-ligand (dihedral angle of 87.9°).

The interaction of (*S*)- and (*R*)-AFCMT with Gly-Gly and copper ions ($CuSO_4$) in absolute methanol in the presence of sodium methylate and molecular sieves leads to the formation of the complexes with the yield of 60%.

To prove the identity of the structure of all the synthesised complexes, we can put forward the following arguments:

(a) All the complexes after decomposition yielded the initial dipeptide in the molar ratio to AFCMT equal to 1:1.

(b) The elemental analyses of the complexes correspond, taking into account solvation molecules of H_2O and EtOH, to the calculated values (Experimental, Table 2).

(c) According to the data of the electrophoresis in a 0.025M soln of $NaClO_4$ all the complexes are not charged.

(d) For the (*S*)-AFCMT-((*S*)-Ala-(*S*)-Ala)Cu(II) complex, the molecular weight as determined ebullioscopically corresponds to the calculated figure.

(e) The electron spectra of the complexes are practically identical (Fig. 3). In the region of d–d transitions of copper they correspond to those expected for square complexes of Cu(II).[11]

(f) The CD spectra of (*S*)-and (*R*)-AFCMT-(GlyGly) Cu(II) have intensive Cotton effects in the region of d–d transitions of copper (Fig. 4), which can be realised only if AFCMT is coordinated with the copper ion.

(g) The ORD and CD curves of the complexes obtained from (*S*)- and (*R*)-AFCMT are almost mirror images (Figs. 3, 4).

(h) The IR spectra of the complexes show a band typical for C=N in metal complexes of Schiff bases of amino acids and dipeptides (1650 cm^{-1}),[12] the C=O band of the formyl group of AFCMT (1690 cm^{-1}) is absent. The frequencies of the CO groups bonded with Mn (1950, 2040 cm^{-1}) are preserved. The bands at 1590 cm^{-1} and 1610 cm^{-1} can be assigned to the carboxyl and ionised amide groups in the copper complexes of peptides.[12,13] The 2750 cm^{-1} and 2790 cm^{-1} bands which are present in the IR spectrum of AFCMT and characterise stretching C–H vibrations of non-coordinated $N(CH_3)_2$ groups,[14] disappear in the IR spectra of the complexes.

Thus, AFCMT with dipeptides forms Schiff bases which are tetradentate ligands in the complexes with Cu(II).

As has been stated above, the enantiospecificity of the formation of complexes from AFCMT and chiral dipeptides is very high. Comparison of the ORD curves of all the complexes obtained in the present work (Fig. 3) shows that the main contribution to the optical rotation of the complex is made by the chiral AFCMT rather than by the asymmetric carbon of the amino acid. The sign of the Cotton effect for the complexes is opposite to the sign of this effect for the chiral AFCMT, and the amplitude of the Cotton effect for any complex is one order of magnitude greater than for the initial AFCMT. This allows spectropolarimetrical monitoring of the appearance of the complex when a dipeptide. AFCMT and a copper salt are mixed in absolute methanol in the

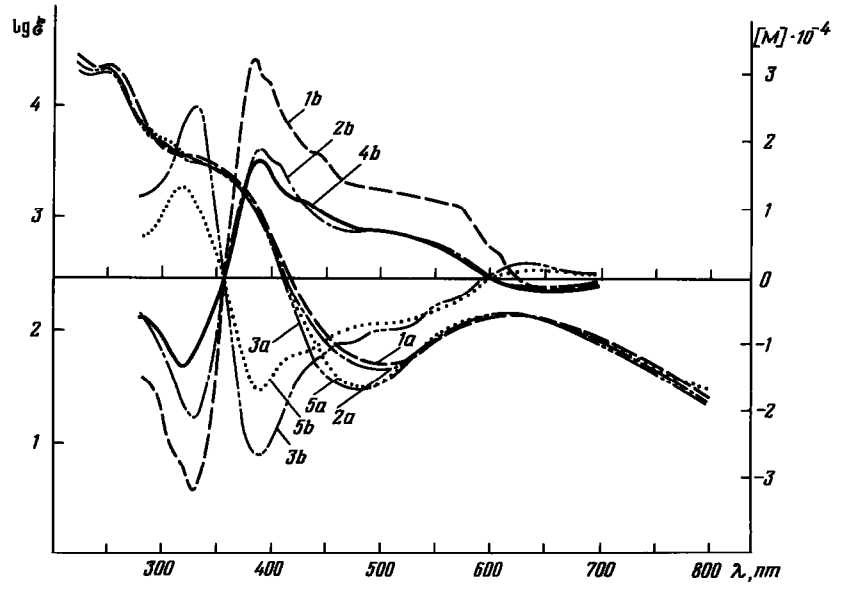


Fig. 3. Electronic spectra of complexes in 96% C_2H_5OH: (*S*)-AFMCT-((*S*)-Ala-(*S*)-Ala)Cu(II)(1a), (*S*)-AFCMT-((*S*)-Ala-Gly) Cu(II) (2a), (*R*)-AFCMT-(Gly-(*S*)-Ala) Cu(II) (3a), (*R*)-AFCMT-(GlyGly) Cu(II) (5a) and ORD curves of complexes in 96% C_2H_5OH: (*S*)AFCMT((*S*)-Ala-(*S*)Ala)Cu(II) (1b), (*S*)-AFCMT-((*S*)-Ala-Gly) Cu(II) (2b), (*R*)-AFCMT-(Gly-(*S*)-Ala) (Cu(II) (3b), (*S*)-AFCMT-(GlyGly) Cu(II) (4b), (*R*)-AFCMT-(GlyGly) Cu(II) (5b).

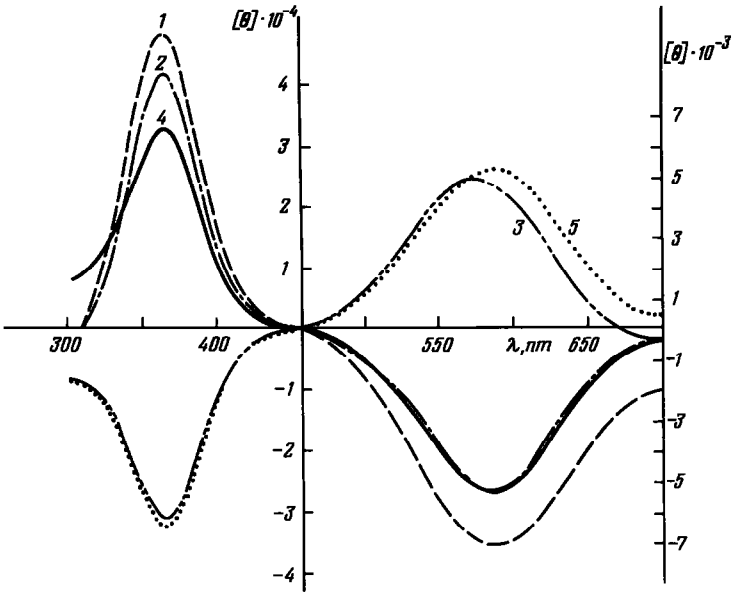


Fig. 4. CD spectra of complexes: (*S*)-AFCMT-((*S*)-Ala-(*S*)-Ala) Cu(II)—1, (*S*)-AFCMT-((*S*)-Ala-Gly) Cu(II)—2, (*R*)-AFCMT-(Gly-(*S*)-Ala) Cu(II)—3, (*S*)-AFCMT-(GlyGly) Cu(II)—4, (*R*)-AFCMT-(GlyGly) Cu(II)—5.

presence of sodium methylate. One hr after the mixing of racemic AFCMT, $CuSO_4$ and Gly-(*S*)-Ala, mixture reveals optical rotation, which corresponds to 20% of a pure copper complex of (*R*)-AFCMT with Gly-(*S*)-Ala. In 2 hr, the optical rotation of the mixture diminishes by a factor of 5, which indicates the formation of a second diastereomer. Mixing of racemic AFCMT, $CuSO_4$ and (*S*)-Ala-(*S*)-Ala leads within 1 hr to optical rotation corresponding to 27% of a pure copper complex of (*S*)-AFCMT with (*S*)-Ala-(*S*)-Ala. Molecular rotation of the mixture does not change during next 67 hr. At the same time (*R*)-AFCMT does not interact with (*S*)-Ala-Gly for 3 hr at 40°, while (*S*)-AFCMT easily forms a copper complex with (*S*)-Ala-Gly at room temp.

Thus, it is shown that in such complexes even a sterically undemanding amino acid as (*S*)-Ala is sufficient for recognising AFCMT enantiomers.

The formation of the AFCMT complexes with chiral dipeptides being highly enantiospecific, it may be expected that monoalkylation of the amino acid fragments of the (*R*)- or (*S*)-AFCMT-(GlyGly)Cu(II) would allow yield a high enantiomeric excess of one of the resulting dipeptide enantiomers. By analogy with metallic complexes of salicylidene dipeptides it can be foreseen that the N-terminal glycine fragment will have an enhanced CH-acidity[15] and undergo alkylation.

The proof of the lability of the α-proton of the N-terminal glycine in copper complexes of diglycine with (*R*)- and (*S*)-AFCMT is furnished by the data on the deuterium exchange in the (*S*)-AFCMT-((*S*)-AlaGly) Cu(II) and (*R*)-AFCMT-(Gly-(*S*)-Ala)Cu(II) complexes in 0.1N CD_3ONa in CD_3OD. In the copper complex of (*S*)-AFCMT with (*S*)-AlaGly α-hydrogen is not exchanged for deuterium in 0.1N CD_3ONa at 25° during 4 hr either in glycine or in alanine; meanwhile under the same conditions (0.1N CD_3ONa, 25°) in the copper complex of (*R*)-AFCMT with Gly-(*S*)-Ala after 4 hr the α-hydrogens of glycine turn out to be almost fully exchanged for deuterium. Consequently, it may be supposed that in the copper complexes of diglycine and (*R*)- and (*S*)-AFCMT α-hydrogen of the N-terminal glycine is labile, while that of the C-terminal glycine is not.

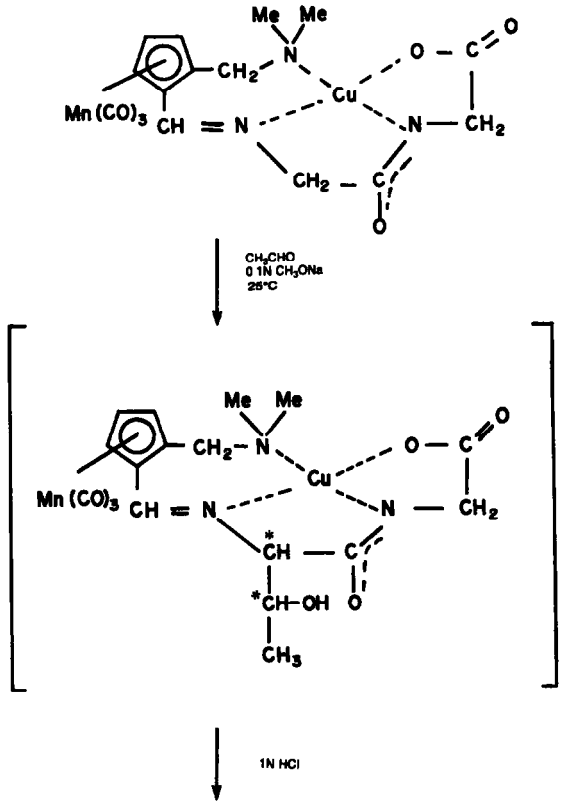
(*S*)- or (*R*)-AFCMT-(GlyGly)Cu(II) interacts with a 50-fold excess of the acetaldehyde in 0.1N MeONa at 25°, giving a new set of complexes which after decomposition by the usual technique (Experimental) give two dipeptides. These dipeptides are not the inital GlyGly, and their hydrolysis gives a mixture of diastereometric threonines (thero/allo *ca* 2) and glycine in the 1:1 ratio. Chromatographic behavior of one of the dipeptides is identical to that of a specially synthesised Thr-Gly. The copper complex of GlyGly under these conditions does not react with acetaldehyde.

The data obtained fit into the following scheme of the interaction of the (*R*)- and (*S*)-AFCMT-(GlyGly) Cu(II) complexes with acetaldehyde (Scheme 2).

The chemical yield of threonines practically does not change during 1–4 hr and is 80% for the N-terminal glycine. If the initial AFCMT is chiral, then chiral threonines are formed in the course of the reaction. The results are summarised in Table 6.

On completion of the alkylation, a corresponding AFCMT enantiomer was removed from the mixture in a 85% yield by extracting with $CHCl_3$. The ^1H NMR, IR and electron spectra of the AFCMT from the mixture were identical to the ^1H NMR, IR and electron spectra of the initial AFCMT. The interaction of the isolated (*S*)- or (*R*)-AFCMT with GlyGly and Cu(II) gave a complex whose ORD curve in 96% EtOH is identical to the ORD curve of the initial complex. This complex was alkylated with acetaldehyde under the same conditions. The asymmetric yield of threonine did not change. Thus, the AFCMT enantiomers can be repeatedly employed as reagents for the asymmetric synthesis of threonine and threonine-containing dipeptides from glycylglycine.

As can be seen from the data presented in Table 6, by using chiral AFCMT it is possible to obtain a 92–98% enantiomeric excess of threonine. Each of the experiments, the results of which are presented in Table 6, started with the isolation of chiral AFCMT. The enan-



Scheme 2.

tiomeric purity of the initial AFCMT determines how great the asymmetric yield of the resulting threonine will be. Unfortunately, polarimetric analysis of the optical purity of the AFCMT does not allow detecting the admixture of 1–2% of another enantiomer. Therefore we can only state that 98% is the maximum asymmetric yield of threonine, attained in the present work. A possibility that the yield may be increased by additional purification of AFCMT and modification of the reaction conditions cannot be excluded.

Examination of possible conformations of copper complexes of (*S*)-AFCMT with chiral dipeptides using Dreiding models shows that the conformation of the system is energetically most favourable when the "basket" of $Mn(CO)_3$ looks away from the copper ion. Such conformation for (*S*)-AFCMT-((*S*)-Ala-(*R*)-Ala) Cu(II) is shown in Fig. 5. Both the 7-membered and two 5-membered chelate rings are strongly distorted. The Me group of the N-terminal alanine has an essentially perpendicular orientation to the plane of the aldimine group, and its interaction with the aldimine hydrogen is minimal. It is easy to see that the Me group of the N-terminal alanine in the pseudo-equatorial position ((*R*)-Ala) would create additional steric interactions with the aldimine hydrogen. This explains why the interaction of (*S*)-AFCMT-(GlyGly) Cu(II) with acetaldehyde gives excess of the *S*-form of threonines and why (*S*)-AFCMT forms complexes preferably with (*S*)-Ala-(*S*)-Ala and (*S*)-Ala-Gly. Reasoning in the same manner, one can explain preferable formation of (*R*)-Thr from (*R*)-AFCMT-(GlyGly) Cu(II).

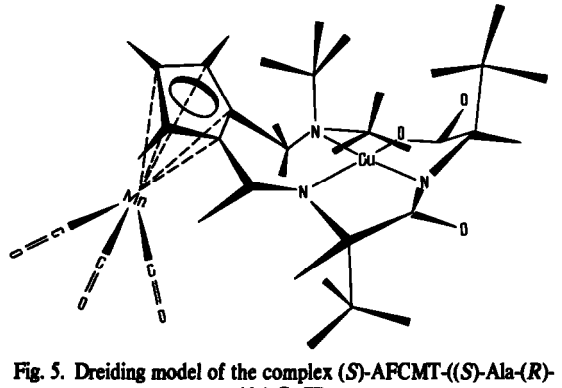
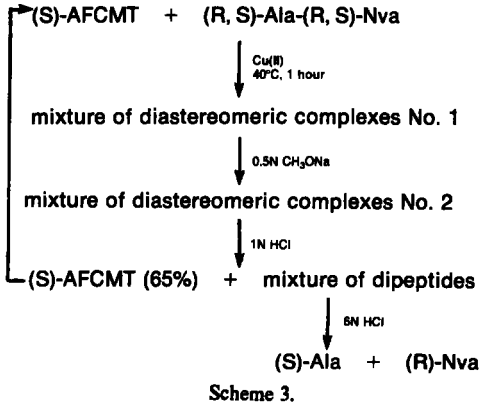


Fig. 5. Dreiding model of the complex (*S*)-AFCMT-((*S*)-Ala-(*R*)-Ala) Cu(II).

Stereospecific formation of the complexes allows one to suppose that in the interaction of a racemic dipeptide, with chiral AFCMT in the presence of copper ions and sodium methylate in methanol would lead to a mixture of diastereomeric complexes. (Scheme 3, mixture of diastereomeric complexes No. 1), and these complexes would have different free energies. Due to the lability of the α-proton of the N-terminal amino acid one could expect a shift of the equilibrium towards a more stable diastereomer, i.e. after the decomposition of the mixture one would obtain enantiomeric excess of one form of the N-terminal amino acid of the dipeptide.

Using enantiomers of AFCMT, we have succeeded in carrying out retroracemisation of the dipeptide (*R,S*)-Ala-(*R,S*)-Nva according to Scheme 3. The retroracemisation of (*R,S*)-Ala-(*R,S*)-Nva was conducted in 0.5N MeONa in MeOH at room temperature in argon atmosphere in the presence of the stoichiometric quantity of copper acetate and the corresponding AFCMT enantiomer. After decomposition of the mixture (Scheme 3, mixture of diastereomeric complexes No. 2) with 1N HCl, a mixture of dipeptides was isolated, which, after acid hydrolysis (6N HCl, 105°, 24 hr) was analysed by the glc method (Table 7).[4]



Scheme 3.

Dipeptides are separated from the mixture quantitatively. As can be seen from Table 7, both the N-terminal and C-terminal amino acids are retroracemisation. A 5-fold increase of the MeONa concentration in MeOH, compared with the alkylation conditions of the copper complexes of (*R*)- and (*S*)-AFCMT with diglycine, leads to labilisation of the α-proton of the C-terminal amino acid.[16] As expected, for the (*S*)- and (*R*)-AFCMT, the preferable configuration of the N-terminal fragment of the dipeptide is *S* and *R* respectively. For the C-terminal fragment, however, the enantiospecificity reverses, and

for (*S*)-AFCMT the preferable configuration of the C-terminal amino acid is *R*, while for (*R*)-AFCMT such preferable configuration is *S*. Evidently, distortion of the chelate ring formed by the C-terminal fragment of the dipeptide is also essential. For the complexes from (*S*)-AFCMT *R*-configuration of the amino acid fragment is favourable, since in this case the alkyl substituent is in the axial position, and its steric non-bonding interaction with the CO of the coordinated amide group is minimal (Fig. 5).

After decomposition of the mixture with 1N HCl, a corresponding AFCMT enantiomer having the same specific rotation in $CHCl_3$ as the initial AFCMT was obtained in the 65% yield. Consequently, by using AFCMT enantiomers, it is possible to effect retroracemisation of dipeptides. The AFCMT enantiomers are not liable to racemisation in the course of the threonine synthesis and retroracemisation of dipeptides.

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