Template Syntheses of Chiral Tetradentate Ligands derived from L-Amino Acids. Structural and Spectroscopic Characterization of the Free Ligands and of their Copper(II) Complexes †

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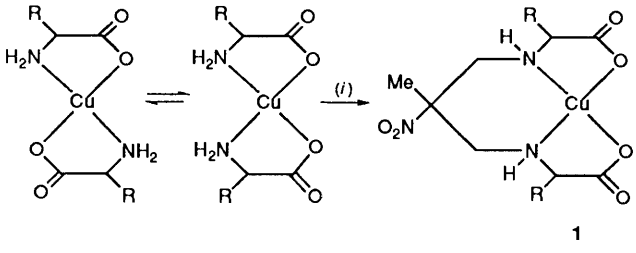
The copper(II)-directed condensation of amino acids with formaldehyde and nitroethane in basic methanol produces open-chain tetradentate ligands with a pendant nitro substituent in high yield. With optically pure L-amino acids full retention of configuration is achieved, and with racemic D/L-amino acids the condensation is fully selective, *viz.* only one out of three possible isomers is produced. These aspects are discussed based on ^1H and ^{13}C NMR data for the free ligands based on glycine, L-alanine, and D/L-alanine, and on the X-ray structures of the corresponding copper(II) template products, (5-methyl-5-nitro-3,7-diazanonanedioato)copper(II) **1a**, [(2*S*,8*S*)-2,5,8-trimethyl-5-nitro-3,7-diazanonanedioato]copper(II) hydrate **1b** and [(2*R*,8*S*)-5-methyl-5-nitro-3,7-diaza-nonanedioato)copper(II)] **1c** respectively. Complex **1a** crystallizes in the orthorhombic space group $P2_12_12_1$, $a = 6.197(1)$, $b = 12.772(1)$, $c = 13.717(1)$ Å, $Z = 4$; **1b** crystallizes in the monoclinic space group $P2_1$, $a = 9.532(2)$, $b = 6.371(1)$, $c = 11.832(2)$ Å, $\beta = 104.89(1)°$, $Z = 2$; **1c** crystallizes in the triclinic space group $P\bar{1}$, $a = 8.015(2)$, $b = 9.297(1)$, $c = 9.401(2)$ Å, $\alpha = 80.47(1)$, $\beta = 71.33(2)$, $\gamma = 79.78(2)°$, $Z = 2$. Preliminary solution spectroscopy of the copper(II) complexes indicates that the solution structures of a whole series of copper(II) condensation products with amino acids are similar to the reported X-ray structures, and all are similar to each other except for **1a** which in solution is predominantly dimeric.

Chiral transition-metal complexes are the subject of growing interest in areas such as biomimetic chemistry, stereoselective catalysis and racemate separation. L-Amino acids and their derivatives are readily available, versatile, and cheap building blocks in the synthesis of organic molecules, and they have been used in the synthesis of open-chain and macrocyclic polydentate chiral ligands.[1–3]

In recent years we have developed a preparative method based on the template condensation of complexes of Cu^{II} and Ni^{II} having *cis*-disposed primary amines, with formaldehyde and nitroethane, leading to open-chain and macrocyclic ligands in high yield.[4] Copper(II) complexes of L-amino acids are well known,[5] and seemed to be valuable substrates for the formaldehyde/nitroethane template reaction (Scheme 1). In this paper we present our results of these template reactions of bis complexes of copper(II) with glycine, L-alanine, D/L-alanine and L-phenylalanine, the structural and preliminary spectroscopic characterization of the resulting copper(II) complexes, and the isolation and spectroscopic characterization of the corresponding free ligands.



Scheme 1 (*i*) HCHO, $EtNO_2$, base

Experimental

Materials.—All reagents used were of analytical purity. Methoxy(phenyl)(trifluoromethyl)acetyl chloride $[\alpha]_D^{20} = -135.5$ (*R*), $+135.5°$ (*S*); 5.2 mol dm^{-3} CCl_4] was from JPS Chimie, Bevaix. Water used for spectroscopy was of MilliQuad quality.

Physical Methods.—UV–VIS–NIR spectra were recorded on a Cary 2300 instrument, CD spectra on a JASCO J-500 instrument and IR spectra (KBr pellets) with a Philips SP3 spectrometer. EPR spectra [dimethylformamide–water (1:2), 298 or 77K] were recorded on a Varian E9 spectrometer fitted with a Varian E101 microwave bridge, a Varian variable temperature control unit, a Bruker ER035 NMR Gaussmeter and a Marconi Instruments 2440 microwave counter. NMR spectra were measured on a Varian GEMINI 300 instrument at 75 (^{13}C) or 300 MHz (^1H) with dioxane or sodium 3-trimethylsilyltetradeuteriopropionate (tsp), respectively, as internal standards. Microanalyses were done by CIBA-GEIGY, Basel.

Complex Syntheses.—[Cu(mnpgly)] (mnpgly = 5-*methyl*-5-*nitro*-3,7-*diazanonanedioate*). The salt $Cu(NO_3)_2 \cdot 3H_2O$ (2.42 g, 10 mmol) and glycine (1.50 g, 20 mmol) in methanol (100 cm^3) were heated to 60 °C for 0.5 h. Then triethylamine (4.2 cm^3, 30

† *Supplementary data available:* see Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1991, Issue 1, pp. xviii–xxii.

Non-SI unit employed: G = 10^{-4} T.

mmol) and nitroethane (0.72 cm^3, 10 mmol) were added. Formaldehyde (37%, 1.5 cm^3, 20 mmol) in methanol (10 cm^3) was added under constant stirring over 0.5 h. After 1 h of constant stirring at 60 °C a purple precipitate was collected on a filter, redissolved in water, and crystallized. The crystals were collected, washed with a little ethanol and ether, and vacuum dried. Yield: 1.4 g (4.26 mmol, 42.6%) (Found: C, 30.8; H, 4.4; N, 13.4. Calc. for $C_8H_{13}CuN_3O_6$: C, 30.9; H, 4.2; N, 13.5%).

[Cu{(*S,S*)-mnpala}]·H_2O [mnpala = (2S,8S)-2,5,8-*trimethyl*-5-*nitro*-3,7-*diazanonanedioate*]. The salt $Cu(NO_3)_2$·$3H_2O$ (4.84 g, 20 mmol) and L-alanine (3.5 g, 40 mmol) were stirred in methanol (200 cm^3) for 10 min at 50 °C, prior to the addition of triethylamine (8.7 cm^3, 60 mmol) and nitroethane (1.6 cm^3, 40 mmol). To the dark blue solution, formaldehyde (37%, 3.2 cm^3, 40 mmol) was added over 0.5 h. The reaction mixture was heated for 1 h and filtered while hot. The filtrate was sorbed onto a column of SP Sephadex C-25 (Na^+ form) resin, to separate some green charged side product from a single blue band which was eluted with methanol, and the resulting solution was evaporated at reduced pressure until the beginning of crystallization. The purple product was collected on a filter, washed with a little ethanol and then with diethyl ether, and dried in vacuum. Yield: 3.46 g (9.7 mmol, 48.5%) (Found: C, 33.6; H, 5.5; N, 11.8. Calc. for $C_{10}H_{17}CuN_3O_6$·H_2O: C, 33.7; H, 5.4; N, 11.8%).

[Cu{(*R,S*)-mnpala}]. To a solution of $Cu(NO_3)_2$·$3H_2O$ (7.75 g, 32 mmol) and D/L-alanine (5.70 g, 64 mmol) in methanol (200 cm^3), which was heated for 0.5 h to 60 °C, were added triethylamine (14.3 cm^3, 96 mmol) and nitroethane (2.3 cm^3, 32 mmol). Then formaldehyde (37%, 4.8 cm^3, 64 mmol) in methanol (20 cm^3) was added over 0.5 h and the solution heated to 60 °C for 1 h. The purple precipitate that formed was collected on a filter, washed with water,* and recrystallized from hot water. Yield: 6.8 g (19.1 mmol, 59.6%) (Found: C, 35.5; H, 5.0; N, 12.5. Calc. for $C_{10}H_{17}CuN_3O_6$: C, 35.4; H, 5.1; N, 12.4%).

The complex [Cu{(*S,S*)-mnpphe}]·H_2O [mnpphe = (2*S*,8*S*)-2,8-dibenzyl-5-methyl-5-nitro-3,7-diazanonanedioate] was prepared from L-phenylalanine (6.6 g, 40 mmol) as described for [Cu{(*S,S*)-mnpala}]·H_2O. Yield: 2.3 g (4.7 mmol, 23.4%) (Found: C, 52.2; H, 5.6; N, 8.8. Calc. for $C_{22}H_{25}CuN_3O_6$: C, 51.9; H, 5.6; N, 8.3%). The corresponding complexes of isobutyric acid, valine, leucine, isoleucine and 3-methylvaline were isolated as described in detail above. Small modifications were due to changes in the solubilities of the respective starting materials and products. All these compounds were characterized by their IR, UV–VIS and EPR spectra.

Ligand Syntheses.—To a solution of the copper(II) complex in HCl (1 mol dm^{-3}, 150 cm^3) ([Cu(mnpgly)], 0.986 g; [Cu{(*S,S*)-mnpala}]·H_2O, 1.070 g; [Cu{(*R,S*)-mnpala}], 1.020 g; 3.0 mmol each) was added a slight excess of $K_4[Fe(CN)_6]$ (0.81 g, 1.92 mmol) in HCl (1 mol dm^{-3}, 5 cm^3). The brown precipitate of $Cu_2[Fe(CN)_6]$ was removed by filtration and the filtrate sorbed onto an anion-exchange column (Dowex 1X2, Cl^- form) to remove excess of $[Fe(CN)_6]^{4-}$. The eluates in 1 mol dm^{-3} HCl were evaporated to dryness and the free ligands were separated from KCl by extraction into methanol and subsequent crystallization from solutions evaporated to near or complete dryness.† Yields of mnpgly·2HCl, (*S,S*)-mnpala·2HCl and (*R,S*)-mnpala·2.5HCl: 0.694 (2.0 mmol, 66.2%), 0.796 (2.16 mmol, 72.0%) and 0.859 g (2.22 mmol, 74.1%) {Found [mnpgly·2HCl, (*S,S*)-mnpala·2HCl and (*R,S*)-mnpala·2.5HCl]: C, 27.6, 32.6, 31.3; H, 5.8, 6.2, 5.9; N, 11.9, 11.1, 10.9. Calc. for $C_8H_{15}N_3O_6$·$1.5H_2O$·2HCl, $C_{10}H_{19}N_3O_6$·H_2O·2.5HCl and $C_{10}H_{19}N_3O_6$·H_2O·2.5HCl: C, 27.5, 32.6, 31.1; H, 5.8, 6.3, 6.1; N, 12.0, 11.4, 10.9%}.

Structure Determination.—Cell constants were determined by least-squares fits to the setting parameters of 25 independent reflections. Data were measured on an Enraf-Nonius CAD4-F diffractometer with the limit $2\theta_{max} = 50°$ with Mo-Kα radiation, $\lambda = 0.71\,069$ Å, graphite monochromator, and operating in the ω–1.33θ scan mode. Data were reduced and Lorentz, polarization, decomposition and absorption corrections were applied using the Enraf-Nonius structure determination package (SDP).[6] The structures were solved by heavy-atom methods and refined by full-matrix least-squares analysis with SHELX 76.[7] All non-hydrogen atoms were refined anisotropically. For hydrogen atoms x, y, z and U_{iso} were refined. Scattering factor values used for Cu were taken from ref. 8 and for other atoms were those supplied in SHELX 76. Non-hydrogen atom coordinates are listed in Tables 1–3 and bond lengths and angles in Table 4. The atomic nomenclature is defined in Figure 1.[9]

Additional material available from the Cambridge Crystallographic Data Centre comprises H-atom coordinates, thermal parameters and remaining bond lengths and angles.

Crystal data. [Cu(mnpgly)] **1a**, $C_8H_{13}CuN_3O_6$, M = 310.77, orthorhombic, space group $P2_12_12_1$, a = 6.197(1), b = 12.772(1), c = 13.717(1) Å, U = 1085.7 Å^3, D_c (Z = 4) = 1.901 g cm^{-3}, $F(000)$ = 636, μ(Mo-Kα) = 20.04 cm^{-1}. Specimen: blue needles, N = 1152, N_o = 1001, ranges of hkl 0–7, 0–15, 0–16, R = 0.023, R' = 0.025, residual extrema ±0.3 e Å^{-3}.

[Cu{(*S,S*)-mnpala}]·H_2O **1b**, $C_{10}H_{19}CuN_3O_7$, M = 356.82, monoclinic, space group $P2_1$, a = 9.532(2), b = 6.371(1), c = 11.832(2) Å, β = 104.89(1)°, U = 694.4 Å^3, D_c (Z = 2) = 1.706 g cm^{-3}, $F(000)$ = 438, μ(Mo-Kα) = 15.77 cm^{-1}. Specimen: blue needles, N = 1416, N_o = 1237, ranges of hkl −11 to 11, 0–7, 0–14, R = 0.021, R' = 0.023, residual extrema ±0.25 e Å^{-3}. For the alternative configuration an R of 0.024 was obtained.

[Cu{(*R,S*)-mnpala}] **1c**, $C_{10}H_{17}CuN_3O_6$, M = 338.81, triclinic, space group $P\bar{1}$, a = 8.015(2), b = 9.297(1), c = 9.401(2) Å, α = 80.47(1), β = 71.33(2), γ = 79.78(2)°, U = 649.1 Å^3, D_c (Z = 2) = 1.733 g cm^{-3}, $F(000)$ = 350, μ(Mo-Kα) = 16.88 cm^{-1}. Specimen: blue prisms, N = 3742, N_o = 3415, ranges of hkl −11 to 11, −13 to 13, −13 to 13, R = 0.026, R' = 0.029, residual extrema ±0.5 e Å^{-3}.

For all the three crystal structures the criterion for observation was $I > 2.5\ \sigma(I)$. A weighting scheme $w = k/[\sigma^2(F_o) + gF_o^2]$ was employed with values of k, g of 0.36, 0.001 44 (**1a**), 0.80, 0.000 27 (**1b**) and 2.46, 0.000 22 (**1c**).

Results and Discussion

Owing to the large interest in L-amino acids as readily available and cheap chiral building blocks, a large number of condensation products with them is known. The reaction of uncomplexed L-amino acids with formaldehyde and nitroalkanes (Mannich condensation) produces substituted hexahydropyrimidines, known as possible antibactericides, in high yields.[10] This type of product, derived from our template ligands by an additional methyl linkage between the amines of the fused six-membered chelate ring, has been known to us for some time as an undesired side product,[4b,e] and it presumably is produced by condensation of the free ligand [lability of the copper(II) complexes] with excess of substrates. Also, Mannich-type reactions between formaldehyde, glycine, and a phenylhydrazone of an aryl aldehyde, in the presence or absence of metal ions, are well established.[11] The metal-directed

* A purple precipitate (1.6 g) was isolated from this phase by evaporation to dryness. Treatment with $K_4[Fe(CN)_6]$ (see below) produced some (*R,S*)-mnpala and some impurities but no other isomers of mnpala.

† These ligands usually were rather hygroscopic, and removal of residual HCl and KCl was difficult in some cases. With NMR spectroscopy it was shown, however, that the impurities were not of organic side products (for NMR data, see Results and Discussion).

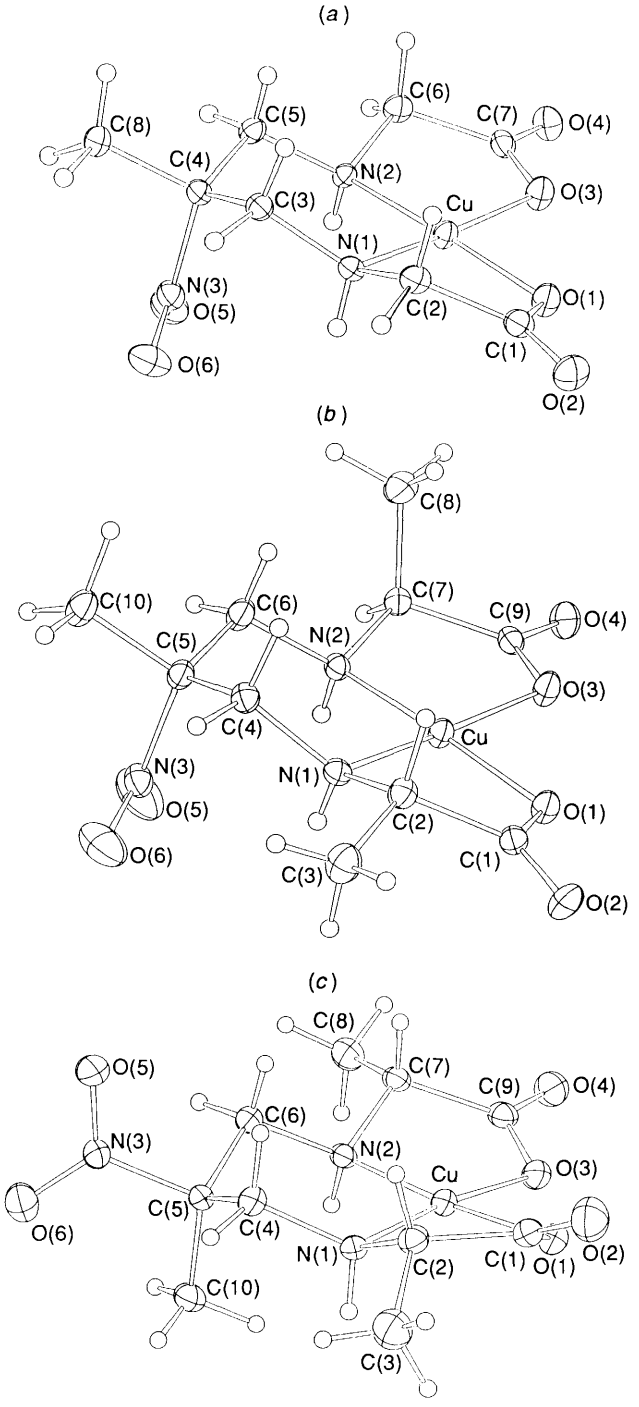


Fig. 1 ORTEP plots[9] of [Cu(mnpgly)] **1a** [Cu{(*S*,*S*)-mnpala}]·H_2O **1b** and [Cu{(*R*,*S*)-mnpala}] **1c**

chemistry reported here yields the new products **1** (Scheme 1) in high yield.*

The structures of [Cu(mnpgly)] and [Cu{(*R*,*S*)-mnpala}] and the structure and absolute configuration of [Cu{(*S*,*S*)-mnpala}]·H_2O have been confirmed by X-ray crystallography. Drawings of the complexes appear in Fig. 1. The capping reactions have produced tetradentate ligands which co-ordinate to the four equatorial sites of a copper(II) atom producing in each case a planar geometry which is slightly distorted (6.3–7.3°) in a tetrahedral fashion. In contrast to many comparable systems the copper(II) atom and the co-ordinated amines are displaced from the carboxylate plane by up to 0.75 (23°) and up to 0.63 Å, respectively. The capping has produced a six-membered chelate ring which, in each case, adopts a chair conformation. In [Cu{(*S*,*S*)-mnpala}]·H_2O the two alanine groups have the L configuration but the amine groups have opposite configurations. As a result, in one alanine the methyl group is axially disposed and in the other it is equatorially disposed. Similarly in [Cu(mnpgly)] the amine groups have opposite configurations. In [Cu{(*R*,*S*)-mnpala}] there is one L- and one D-ala. The amine groups have opposite configurations and both methyl groups are equatorial. In structures **1a** and **1b** there are weak axial interactions [2.595(3) and 2.703(3) Å, respectively] between the Cu atom and a co-ordinated O atom from an adjacent molecule. In structure **1c** there are two weak interactions, one to a co-ordinated O atom [2.728(1) Å] and one to a non-co-ordinated carboxyl O atom [2.578(1) Å]. The major difference in the structures is in the disposition of the nitro group; in [Cu(mnpgly)] and [Cu{(*S*,*S*)-mnpala}]·H_2O the nitro group lies *syn* to the amine H atoms but in [Cu{(*R*,*S*)-mnpala}] it lies *anti* to these H atoms. In all other respects the geometries of the complexes are nearly identical; the methyl groups of [Cu{(*S*,*S*)-mnpala}]·H_2O and [Cu{(*R*,*S*)-mnpala}] evidently exert little influence on the structure. The Cu–N bond lengths are longer than those in [Cu(L-alaO)$_2$] (alaO = alaninate),[5a] probably as a result of the additional constraints imposed by the cap. The in-plane Cu–O bond lengths are

Table 1 Positional parameters (× 10^4) for [Cu(mnpgly)]

Atom	*x*	*y*	*z*
Cu	4 577(1)	6 678(1)	10 282(1)
N(1)	5 246(6)	5 461(3)	11 119(2)
N(2)	5 564(7)	6 062(2)	9 027(2)
N(3)	8 793(6)	4 615(3)	9 964(3)
O(1)	3 771(5)	7 362(2)	11 479(2)
O(2)	3 376(6)	7 049(3)	13 074(2)
O(3)	3 613(5)	7 836(2)	9 498(2)
O(4)	3 588(5)	8 409(2)	7 967(2)
O(5)	9 543(6)	4 363(3)	10 759(3)
O(6)	9 803(5)	5 075(3)	9 333(2)
C(1)	3 684(7)	6 751(3)	12 240(3)
C(2)	3 921(7)	5 584(3)	12 000(3)
C(3)	5 174(7)	4 387(3)	10 705(3)
C(4)	6 443(6)	4 286(3)	9 761(3)
C(5)	5 543(8)	4 906(3)	8 907(3)
C(6)	4 385(8)	6 604(3)	8 245(3)
C(7)	3 857(7)	7 719(3)	8 564(3)
C(8)	6 561(8)	3 129(3)	9 466(3)

Table 2 Positional parameters (× 10^4) for [Cu{(*S*,*S*)-mnpala}]·H_2O

Atom	*x*	*y*	*z*
Cu	9 472(1)	5 000	9 005(1)
O(1)	9 751(3)	4 065(5)	10 590(2)
O(2)	8 772(3)	4 177(5)	12 098(2)
O(3)	11 407(3)	4 241(5)	8 990(2)
O(4)	12 914(3)	4 109(5)	7 844(2)
O(5)	6 808(4)	9 981(8)	7 829(3)
O(6)	7 482(4)	9 676(6)	6 257(3)
O(7)	6 886(5)	5 518(8)	3 512(4)
N(1)	7 543(3)	5 980(6)	9 138(3)
N(2)	9 233(3)	5 651(6)	7 330(3)
N(3)	7 007(4)	8 946(6)	7 022(3)
C(1)	8 692(4)	4 420(6)	11 046(3)
C(2)	7 243(3)	5 047(10)	10 218(3)
C(3)	6 279(5)	3 109(8)	9 983(4)
C(4)	6 291(4)	5 879(10)	8 080(4)
C(5)	6 589(4)	6 614(6)	6 951(3)
C(6)	7 758(4)	5 418(6)	6 548(3)
C(7)	10 356(4)	4 442(6)	6 932(3)
C(8)	10 702(5)	5 328(10)	5 853(4)
C(9)	11 689(4)	4 273(6)	7 990(3)
C(10)	5 158(5)	6 449(8)	5 988(4)

* A convenient quick test for a successful formaldehyde/nitroethane capping reaction is the appearance of ν_{asym} (s) and ν_{sym} (m) stretching frequencies at *ca.* 1550 and *ca.* 1350 cm^{-1}, respectively; see Table 6.

Table 3 Positional parameters ($\times 10^4$) for [Cu{(*R*,*S*)-mnpala}]

Atom	*x*	*y*	*z*
Cu	12 053(1)	383(1)	4 305(1)
O(1)	12 473(2)	121(1)	6 253(1)
O(2)	14 516(2)	642(2)	7 156(2)
O(3)	11 225(2)	−1 503(1)	4 691(1)
O(4)	10 908(2)	−3 280(1)	3 531(2)
O(5)	14 962(2)	3 501(2)	−543(2)
O(6)	12 554(2)	4 939(2)	−500(2)
N(1)	12 700(2)	2 391(1)	4 133(1)
N(2)	11 680(2)	435(1)	2 297(1)
N(3)	13 385(2)	3 887(1)	31(2)
C(1)	13 600(2)	927(2)	6 287(2)
C(2)	13 836(2)	2 316(2)	5 142(2)
C(3)	13 405(3)	3 674(2)	5 971(3)
C(4)	13 499(2)	3 115(2)	2 598(2)
C(5)	12 452(2)	2 986(2)	1 517(2)
C(6)	12 718(2)	1 420(2)	1 066(2)
C(7)	12 077(2)	−1 137(2)	1 984(2)
C(8)	11 403(3)	−1 447(2)	748(2)
C(9)	11 346(2)	−2 077(2)	3 492(2)
C(10)	10 522(2)	3 643(2)	2 044(2)

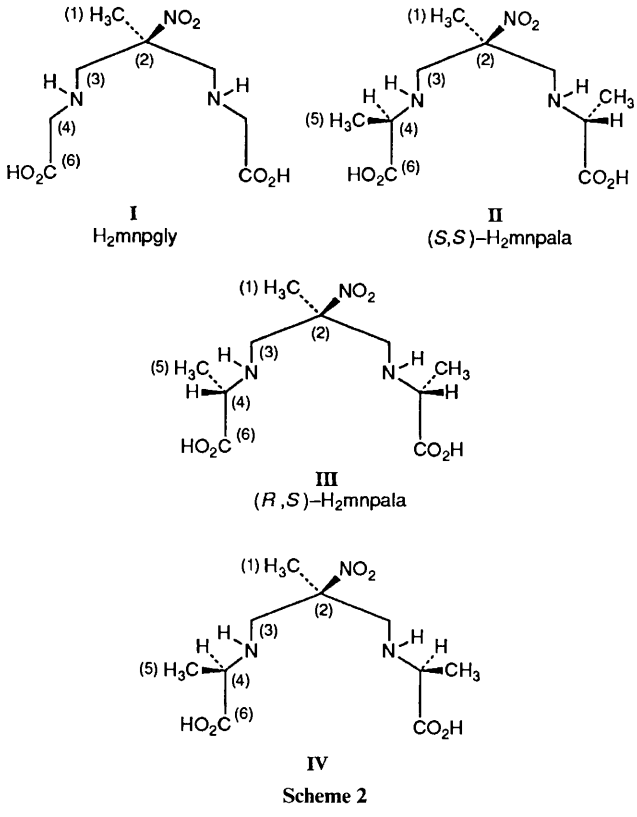
Table 4 Selected bond lengths (Å) and angles (°) for [Cu(mnpgly)] **1a**, [Cu{(*S*,*S*)-mnpala}]·H_2O **1b** and [Cu{(*R*,*S*)-mnpala}] **1c** (for atom numbering see Figure 1)

	1a	**1b**	**1c**
N(1)–Cu	1.977(3)	1.986(3)	1.992(1)
N(2)–Cu	1.988(3)	1.980(3)	1.995(1)
O(1)–Cu	1.926(3)	1.920(2)	1.935(1)
O(3)–Cu	1.923(3)	1.911(3)	1.923(1)
O(3′)–Cu	2.595(3)	2.703(2)	2.728(1)
O(2′)–Cu	—	—	2.578(1)
N(1)–Cu–N(2)	97.3(1)	98.2(1)	100.7(0)
N(1)–Cu–O(1)	85.1(1)	85.3(1)	84.5(0)
N(2)–Cu–O(3)	85.2(1)	84.7(1)	83.5(0)
O(1)–Cu–O(3)	92.7(1)	92.2(1)	91.6(0)
N(1)–Cu–O(3)	174.0(1)	174.6(1)	173.3(0)
N(2)–Cu–O(1)	175.6(1)	173.8(1)	174.2(0)

significantly shorter than those in that complex but the axial bonds are shorter than expected based on the suggested inverse correlation between equatorial and axial bonds.[5a,12] This is not unexpected because of the already discussed constraints imposed by the cap and because of the change from *trans* to *cis* configuration.

Sketches of the free ligands H_2mnpgly, (*S*,*S*)-H_2mnpala, and (*R*,*S*)-H_2mnpala appear in Scheme 2. In the absence of moisture these ligands are stable in the solid state. In neutral or basic aqueous solution, however, they decay rather quickly. Therefore, the extraction of the copper(II) ion had to involve a rather mild method in dilute acid. With the precipitation of copper(II) as the hexacyanoferrate in 1 mol dm^{-3} HCl acceptable yields and pure products were obtained. The instability of the ligands most probably is due to the nitro substituent, and similar problems were encountered with other condensation products based on the formaldehyde/nitroalkane template condensation. However, the instability does not extend to the corresponding metal complexes, and the nitro substituent clearly is an important centre of reactivity in these ligands and the corresponding metal complexes for their possible fixation to substrates (see below). Presently, we are testing a number of derivatization and coupling reactions for these nitro substituents.

* The fact that the isomer distribution of [Cu{(*R*,*S*)-mnpala}] was checked in the whole, not only in the recrystallized and purified fraction (see Experimental section), suggests that the selectivity is complete.



Scheme 2

One critical point was that some racemization of the L-amino acid moieties might occur during the template reaction, especially since L-amino acids are known to be accessible to metal ion-catalysed racemization, albeit only slowly and under quite rigorous conditions.[13] The optical purity of (*S*,*S*)-mnpala was confirmed by the X-ray structure of its parent copper(II) complex. To exclude accidental observation of the desired configuration (*e.g.* through conglomerate crystallization), NMR spectra of Mosher-acid derivatives of a number of metal-free ligands were recorded.[14] Because of the instability of the ligands, these derivatives usually contained some degradation products. However, in no case was any racemization observed.

The ^{13}C and ^1H NMR spectra of the free ligands appear in Figs. 2 and 3, respectively, and the corresponding parameters are listed in Table 5.. The chemical shifts and proton coupling constants are as expected for substituted aliphatic hydrocarbons. The ligands H_2mnpgly and (*R*,*S*)-H_2mnpala (Scheme 2) have a mirror plane, each, through the quaternary carbon atom 2. *S*,*S*-H_2mnpala is asymmetrical, *viz.* the carbon centres 3 and 3′, 4 and 4′, 5 and 5′ and 6 and 6′ are not symmetrically related. This is consistent with both the observed ^{13}C and ^1H NMR spectra. In (*R*,*S*)-H_2mnpala the quaternary carbon atom 2 is stereogenic but not chirotopic and therefore the compound is obviously achiral. In (*S*,*S*)-H_2mnpala the carbon atom 2 is chirotopic (and therefore chiral) but non-stereogenic. In this respect H_2mnpala is similar to the much discussed and studied 2,3,4-trihydroxyglutaric acid isomers.[15]

The template reaction with D/L-alanine might lead to either of three possible isomers, *viz.* a 1:1 mixture of [Cu{(*S*,*S*)-mnpala}] and [Cu{(*R*,*R*)-mnpala}] (see structure **II**), [Cu{(*R*,*S*)-mnpala}] with methyl groups 1 and 5 in *syn* (structure **III**) or *anti* (structure **IV**) disposition. The NMR data clearly indicate that only one of these three isomers is formed selectively.* The attack of the nitroethanate anion clearly is upon co-ordinated imines since the products of the template reaction described here are different from those of a similar reaction in the absence of copper(II),[10] and the stereoselectivity indicates that the attack of the nitroethanate anion is side-selective. In retrospect the observed stereoselectivity is not

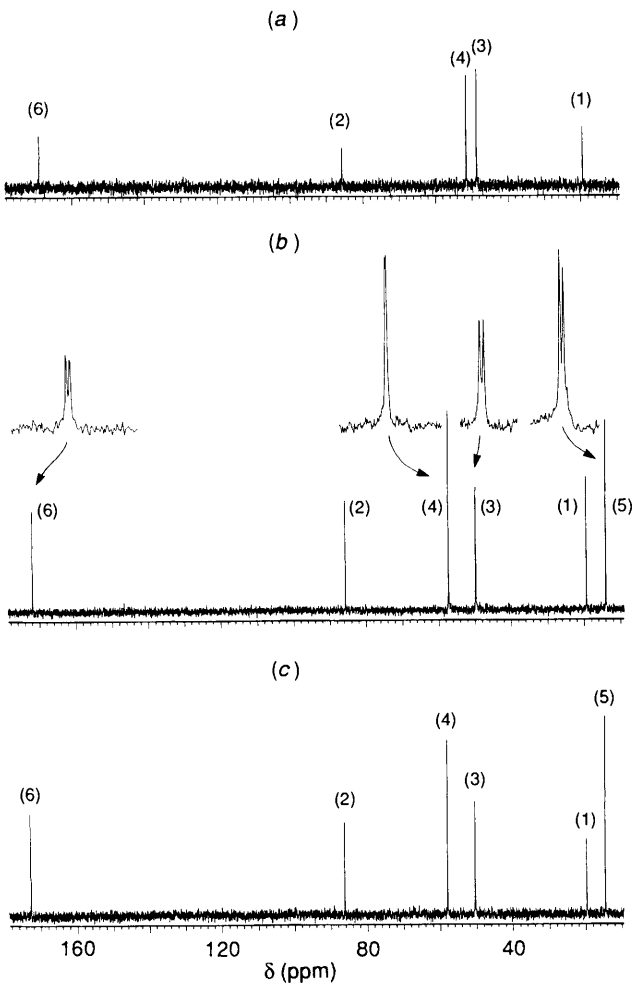


Fig. 2 75 MHz ^{13}C NMR spectra of H_2mnpgly (*a*), (*S,S*)-H_2mnpala (*b*) and (*R,S*)-H_2mnpala (*c*) (for atom numbering see Scheme 2)

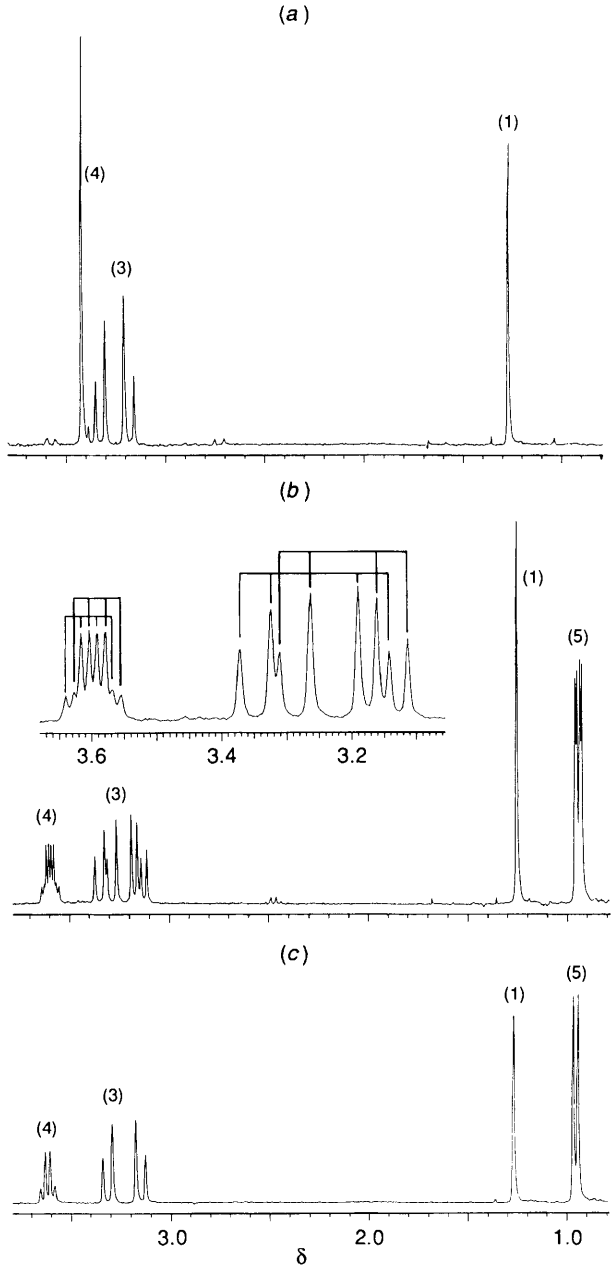


Fig. 3 300 MHz ^1H NMR spectra of H_2mnpgly (*a*), (*S,S*)-H_2mnpala (*b*) and (*R,S*)-H_2mnpala (*c*) (for atom numbering see Scheme 2)

really unexpected since the formaldehyde/nitroethane template condensation of diamines leading to macrocyclic products so far has never produced any ligands with the two nitro substituents in *syn* arrangement,[4] and this clearly is consistent with the selectivity observed here. Presently, we are extending the study of this selectivity to systems involving 1,2-diaminopropane, 1,2-diaminocyclohexane, *etc.*, where even more isomers might be produced.

A possible explanation for the observed side-selectivity is co-ordination of nitroethane to the copper(II) ion, at least in an intermediate or transition state. The expected product then would have the nitro substituent and alanine methyl groups in an *anti* arrangement (structure **III**), as is observed in the X-ray structure of the template condensation product [Fig. 1(*c*)]. Co-ordination of nitroethane to copper(II) might not really have been expected, since nitroethane is often used as an 'innocent' solvent, and co-ordination of uncharged organic nitro groups to metal ions has not attracted much interest so far. Co-ordination of the pendant nitro group in a structure of type **I** involves a conformational change of the fused six-membered chelate ring (chair to boat) and possibly a rotation of the nitro group. Based on a series of copper(II) complexes with macrocyclic ligands with different hole sizes and a pendant nitro group,[4c] it might have been expected that the copper(II) template products with β-amino acids tend to some co-ordination of the nitro group, since the comparable larger macrocycles have nitro–copper(II) interactions of 2.7 and 2.4 Å, this aspect is under further investigation.

Preliminary spectroscopic characterization included IR, UV/VIS, CD and EPR measurements. Infrared spectra of the 2-methyl-2-nitro bridged ligands and their copper(II) complexes have characteristic strong nitro bands in the region of 1550 and 1350 cm^{-1}. The spectral data are given in Table 6, and the EPR spectra of [Cu{(*S,S*)-mnpala}] and [Cu(mnpgly)] are presented in Fig. 4. The spectra of [Cu{(*S,S*)-mnpala}] and [Cu{(*S,S*)-mnpphe}] are qualitatively very similar to those of the parent bis(amino acid) complexes,[5a,16,17] and indicate approximately square-planar co-ordination around copper(II), qualitatively in good agreement with relatively large copper hyperfine splitting in the EPR spectra, and with resolved ligand hyperfine coupling, and consistent with the X-ray structures. The spectra of all the other complexes prepared qualitatively indicate very similar solution structures to that of [Cu{(*S,S*)-mnpala}]. The EPR spectrum of [Cu(mnpgly)] (Fig. 4) indicates the formation of a dimeric species. In solution there must be an equilibrium between a monomeric and a dimeric form, and the presence of minor amounts of the monomer is consistent with the EPR spectrum. Unfortunately, the monomer is less soluble in a range

Table 5 Carbon-13 [δ (ppm), internal dioxane or tsp] and ^{1}H NMR chemical shifts (δ, internal tsp) and proton coupling constants (*J*/Hz in parentheses) of H_2mnpgly, (*S,S*)-H_2mnpala and (*R,S*)-H_2mnpala (for atom numbering see Scheme 2)

^{13}C NMR

Atom	H_2mnpgly	(*S,S*)-H_2mnpala	(*R,S*)-H_2mnpala
C^1	19.498	19.407	19.367
C^2	85.771	85.725	85.804
C^3	48.711	49.872	49.978
$C^{3'}$	—	49.959	—
C^4	51.504	57.311	57.511
$C^{4'}$	—	57.352	—
C^5	—	13.939	14.010
$C^{5'}$	—	13.991	—
C^6	169.070	171.782	171.731
$C^{6'}$	—	171.819	—

^{1}H NMR

Atom	H_2mnpgly	(*S,S*)-H_2mnpala	(*R,S*)-H_2mnpala
H^1	1.27	1.25	1.27
H^3	3.19 (14.5)	3.14 (14.4)	3.15 (14.2)
$H^{3'}$	3.32 (14.5)	3.28 (14.4)	3.31 (14.2)
$H^{3''}$	—	3.17 (14.4)	—
$H^{3'''}$	—	3.34 (14.4)	—
H^4	3.43	3.59 (7.3)	3.61 (7.2)
$H^{4'}$	—	3.60 (7.3)	—
H^5	—	0.94 (7.3)	0.95 (7.2)
$H^{5'}$	—	0.95 (7.3)	—

Table 6 Spectroscopic data for the copper(II) complexes

Parameter	[Cu(mnpgly)]	[Cu{(*S,S*)-mnpala}]	[Cu{(*S,S*)-mnpphe}]
$\lambda_{max}{}^a$/cm^{-1}	16 193	16 736	16 884
$\lambda_{max}{}^b$/cm^{-1}	—	17 153 (−7345)	17 730 (−11 043)
EPR[c]			
g_{iso}		2.12	2.12
$g_\perp$		2.06	2.06
$g_\parallel$	*ca.* 2.2[d]	2.24	2.24
A_{iso}		79	77
$A_\perp$		22	20
$A_\parallel$	*ca.* 43[d,e]	194	192
$\nu_{asym}(NO_2)$[f]/cm^{-1}	1 550	1 545	1 550

[a] Electronic spectrum in water. [b] CD spectrum in water, with θ/° dm^3 mol^{-1}m^{-1} in parentheses. [c] In dimethylformamide–water (*ca.* 1:2); *A* in 10^4 cm^{-1}. [d] Preliminary qualitative analysis. [e] $D_\parallel$ (zero-field splitting) in 10^4 cm^{-1}. [f] IR spectrum.

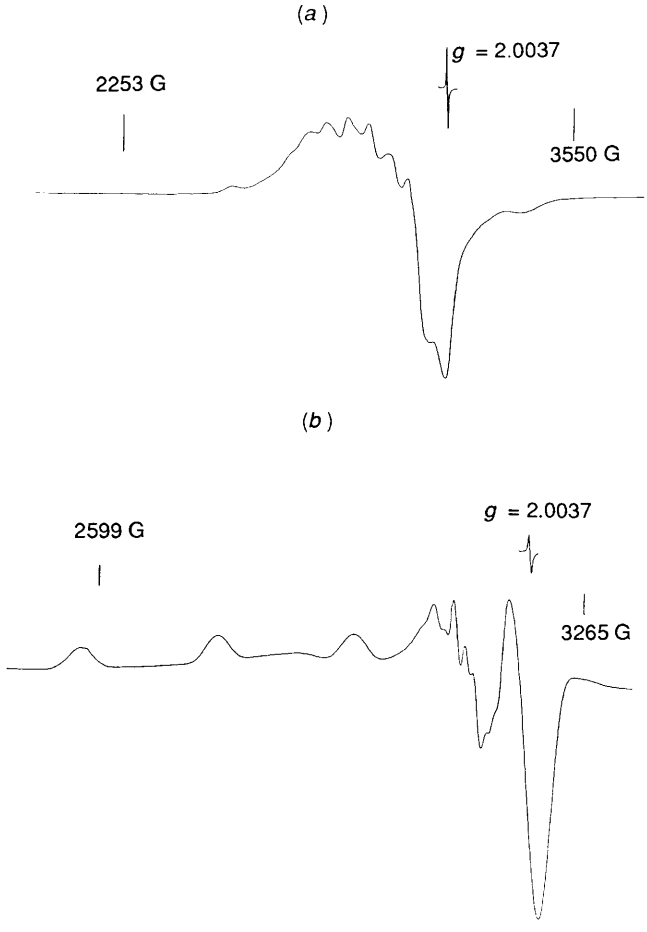


Fig. 4 Frozen-solution X-band EPR spectra of [Cu(mnpgly)] (*a*) and [Cu{(*S,S*)-mnpala}] (*b*)

of solvents, and only crystals of it have been isolated so far. The dimer might have a structure similar to the ones observed for copper(II) complexes with DL-tartrate[18] and *N,N'*-dipicolinoyl-1,3-propanediamine,[19] and this is consistent with a preliminary analysis of the EPR spectrum. A more rigorous study of this dimer is in progress.

One of our present areas of interest involves the design and synthesis of chiral transition-metal complexes for racemate separation by stereoselective ligand exchange,[20] and the requirements for the chiral matrix complexes involve ready availability, high symmetry, and the possibility of their fixing to supports. Our template reaction has been tested on a number of optically pure substrates such as 1,2-diaminocyclohexane, 2-aminomethylpyrrolidine, and a range of α- and β-amino acids.[4e] The resulting tetradentate chiral and optically pure ligands and their transition-metal complexes with bidentate substrates lead to only a few diastereoisomers.* The ligand backbone is very similar to the products from organic reactions based on peptide condensations (four steps, relatively high yielding)[1-3] but the template condensation product has a unique possibility for derivatization: the nitro substituent of the fused six-membered chelate ring may be used for coupling of the ligands and their metal complexes to supports.

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* This statement is based on some preliminary molecular mechanics calculations and experimental results with cobalt(III) complexes of 1,9-diamino-3,7-diazanonane and some chiral derivatives that suggest that the β configuration may be produced selectively.[14]

References

1 T. R. Wagler and C. J. Burrows, *Tetrahedron Lett.*, 1988, **29**, 5091; T. R. Wagler, Y. Fang and C. J. Burrows, *J. Org. Chem.*, 1989, **54**, 1584.
2 T. Murakami and C. Koichi, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 3675.
3 S. Kitagawa, T. Murakami and M. Hatano, *Inorg. Chem.*, 1975, **14**, 2347.
4 (*a*) P. Comba, T. W. Hambley and G. A. Lawrance, *Helv. Chim. Acta*, 1985, **68**, 2332; (*b*) P. Comba, N. F. Curtis, G. A. Lawrance, A. M. Sargeson, B. W. Skelton and A. H. White, *Inorg. Chem.*, 1986, **25**, 4260; (*c*) P. Comba, N. F. Curtis, G. A. Lawrance, M. A. O'Leary,

B. W. Skelton and A. H. White, *J. Chem. Soc., Dalton Trans.*, 1988, 2145; (*d*) P. Comba, G. A. Lawrance, T. M. Manning, A. Markiewicz, K. S. Murray, M. A. O'Leary, B. W. Skelton and A. H. White, *Aust. J. Chem.*, 1990, **43**, 69; (*e*) P. Comba, L. L. Martin, K. Várnagy and L. Zipper, unpublished work.
5 (*a*) M. A. Hitchman, L. Kwan, L. M. Engelhardt and A. H. White, *J. Chem. Soc., Dalton Trans.*, 1987, 457; (*b*) *Metal Ions in Biological Systems*, ed. H. Sigel, Marcel Dekker, Inc., New York and Basel, 1979, vol. 9.
6 Enraf-Nonius Structure Determination Package, Enraf-Nonius, Delft, 1985.
7 SHELX 76, G. M. Sheldrick, University of Cambridge, 1976.
8 *International Tables for X-Ray Crystallography*, Kynoch Press, Birmingham, 1974, vol. 4.
9 ORTEP, C. K. Johnson, Report 3794, U.S. Atomic Energy Commission, 1965.
10 H. J. Roth and K. Ergenzinger, *Arch. Pharm. (Weinheim, Ger.)*, 1978, **31**, 492.
11 S.-B. Teo, S.-G. Teoh, T. W. Hambley and M. R. Snow, *J. Chem. Soc., Dalton Trans.*, 1986, 553.
12 J. Gažo, I. B. Bersuker, J. Garaj, M. Kabesová, J. Kohout, H. Langfelderova, M. Melnik, M. Serátor and F. Valach, *Coord. Chem. Rev.*, 1976, **19**, 253; B. J. Hathaway and P. G. Hodgson, *J. Inorg. Nucl. Chem.*, 1973, **35**, 4071.
13 G. G. Smith, A. Khatib and G. S. Reddy, *J. Am. Chem. Soc.*, 1983, **105**, 293.
14 P. Comba and K. Várnagy, unpublished work.
15 F. M. Jaeger, *Spatial Arrangements of Atomic Systems and Optical Activity*, McGraw-Hill, New York, 1930; J. K. O'Loane, *Chem. Rev.*, 1980, **80**, 41; K. Mislow and J. Siegel, *J. Am. Chem. Soc.*, 1984, **106**, 3319.
16 C. J. Hawkins and C. L. Wong, *Aust. J. Chem.*, 1970, **23**, 2237.
17 T. Szabó-Plánka, A. Rockenbauer and M. Györ, *J. Chem. Res.*, 1988, (*S*) 180; T. Szabó-Plánka, A. Rockenbaur, M. Györ and F. Gaizer, *J. Coord. Chem.*, 1988, **17**, 69.
18 N. D. Chasteen and R. L. Belford, *Inorg. Chem.*, 1970, **9**, 169.
19 Y. Kajikawa, K. Mukai, K. Ishizu and H. Ojima, *Chem. Lett.*, 1981, 801; Y. Kajikawa, T. Sakurai, N. Azuma, S. Kohno, S. Tsuboyama, K. Kobayashi, K. Mukai and K. Ishizu, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 1454.
20 P. Comba, A. Hörmann, L. L. Martin and L. Zipper, *Helv. Chim. Acta*, 1990, **73**, 874.

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