# Functionalized Amino Acid Complexation to a Cobalt(III) Complex of (2R,5R,8R,11R)-2,5,8,11-Tetraethyl-1,4,7,10-tetra-azacyclododecane. Crystal Structures of Complexes containing (R)- or (S)-Serine and (R)-α-Methylserine, and Release of Amino Acid from the Complexes†

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The complex [CoBr(H$_2$O)L]Br$_2$ (1) [L = (2R,5R,8R,11R)-2,5,8,11-tetraethyl-1,4,7,10-tetra-azacyclododecane] reacts with a racemic neutral amino acid having a hydroxymethyl group to give a pair of diastereomeric complexes. One of these crystallized preferentially as its appropriate salt. The less-soluble complex co-ordinated its (R)-amino acid. Structure determinations of (R)- or (S)-serinato (serO) and (R)-α-methylserinato (mseO) complexes, (3)—(5), showed that each hydroxyl group in the amino acid forms a hydrogen bond. The OH group of (R)-amino acids takes part in an intramolecular hydrogen bond to one of the secondary nitrogen atoms in L, and that of (S)-serO in (4) interacts with a cocrystallized water molecule and with an anion. Such different hydrogen-bonding formation results in different solubility between the diastereomers, and allows them to be isolated. Only a powdery solid was obtained for the complex co-ordinating (S)-mseO. Slightly racemized (R)- and (S)-ser and optically pure mse were obtained upon release from the corresponding complexes. Further, complex (1) was regenerated in good yield. The resolution expressed as the different solubilities between two salts in this series is ascribed to the effect of a three-point attachment.

The optically active complex *cis-SSSR*-aquabromo[(2R,5R,8R,11R)-2,5,8,11-tetraethyl-1,4,7,10-tetra-azacyclododecane]-cobalt(III) dibromide (1)[1] reacts with prochiral α-amino-α-methylmalonic acid (amm, 2-amino-2-methylpropanedioic acid) to give complex (2) as the sole product.[2,3] The structure determination of (2) showed that the pro-R carboxyl group is directly co-ordinated to the Co$^{III}$ and the un-co-ordinated pro-S group forms an intramolecular hydrogen bond with one of the N atoms in the macrocyclic ligand (L) (Scheme). Thus the prochiral centre of amm is recognized in (1) through a 'three-point attachment'[4] as found in several other cobalt(III) complexes containing optically active acyclic tetramines.[5,6] It seems that their mode of chiral recognition is applicable to chiral differentiation for an amino acid (aa) having residual functional group(s) capable of hydrogen bonding such as a hydroxymethyl group. In previous work[7,8] no distinct chiral selectivity was found for a neutral aa such as alanine (ala) and proline.

Chiral differentiation of α-amino acids has been of particular interest to many workers.[9] In co-ordination chemistry the importance of a three-point attachment for chiral recognition was noted as early as 1960. Dunlop *et al.*[10] reported the stereoselective interaction of amino acids and metal complexes. The structure determination of (+)-[Co{(S)-glu}(en)$_2$]ClO$_4$ (glu = glutamic acid, en = ethylenediamine), which was obtained from the reaction of (±)[Co(CO$_3$)(en)$_2$]ClO$_4$ and (S)-glu, was carried out by X-ray analysis. The characteristic feature of the complex is that the polar side-arm of the (S)-glu ion interacts with an N–H group of an en chelate ring. These authors emphasized, therefore, the importance of three-point bonding as a source of stereoselectivity in metal complexes. In 1968, racemic lysine or histidine was also resolved through K(−)$_{546}$[Co(edta)] (edta = ethylenediaminetetra-acetate) as the resolving reagent.[11] Liquid chromatography using a transition metal with an optically active phase or optically



L
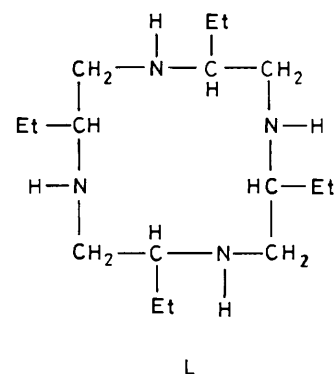
active solvent may also be achieved through the same principle.[12] Similarly the resolution of phenylalanine (phe) using (+)cis-[Co(NO$_2$)$_2$(en)$_2$]$^+$ as resolving agent shows that optically pure (S)-phe can be obtained *via* its salicylidene derivative.[13]

Here we describe another example of stereoselective complexation of racemic serine (ser) and α-methylserine (mse) to the optically active cyclen complex (1) and discuss their structures in relation to the separation of a diastereomeric pair, and include the isolation of aa from the corresponding complex (Scheme). The resolution of mse has been achieved.
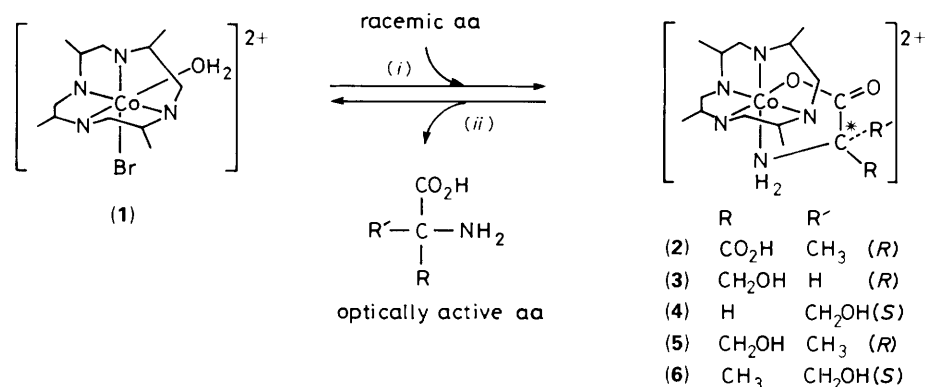
**Scheme.** (*i*) pH 8.0, room temperature; (*ii*) $Na_2CO_3$ then HBr

**Table 1.** Analytical and spectral data

| Complex | Yield (%) | Analysis* (%) | | | Visible absorption $10^3 v_{max.}/cm^{-1}$ ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$) | C.d. $10^3 v_{ext.}/cm^{-1}$ ($\Delta\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$) |
| | | C | H | N | | |
|---|---|---|---|---|---|---|
| (3) [Co{(R)-serO}L]Br[ClO$_4$] | 56 | 36.40 (36.40) | 6.80 (6.75) | 11.15 (11.15) | 20.4(173), 28.6(140) | 20.0(0.71), 22.3(0.31) |
| (5) [Co{(R)-mseO}L]Br[ClO$_4$]·0.5H$_2$O | 89 | 37.05 (36.95) | 6.90 (7.00) | 10.80 (10.75) | 20.2(256), 28.2(205) | 19.8(0.78), 22.2(−0.05), 27.4(0.44) |
| (6) [Co{(S)-mseO}L][ClO$_4$]$_2$·2H$_2$O | 55 | 34.65 (34.50) | 6.65 (6.95) | 9.85 (10.05) | 20.2(244), 28.2(196) | 19.4(0.62), 22.8(0.16), 28.2(0.45) |

* Calculated values are given in parentheses.

# Experimental

All materials used were of reagent grade. The ligand (L) and starting complex (1) were prepared by the method described previously.[1,14] The amino acidato complexes were synthesized according to ref. 7. The yields, analytical data, and spectral data are summarized in Table 1.

[Co{(R)-serO}L]Br[ClO$_4$] (3).—An aqueous solution of complex (1) (300 mg, 0.5 mmol) and racemic ser (53 mg, 0.5 mmol) was adjusted to pH 8.0 with 0.1 mol dm$^{-3}$ NaOH. After 1 h the solvent was evaporated to near dryness. The resulting precipitate containing the (R)-serO complex dibromide was filtered off. After addition of a slight excess of 1 mol dm$^{-3}$ NaClO$_4$ to an aqueous solution of the dibromide, single crystals of the bromide perchlorate were obtained. N.m.r. (D$_2$O), $^1$H, δ 0.96—1.04 (12 H, t, CH$_3$), 1.55—2.02 (8 H, m, CH$_3$CH$_2$), 2.84—3.65 (12 H, m, CH$_2$ and CH), 3.92 (1 H, t, CH in ser), and 4.06 (2 H, ABq, CH$_2$OH); $^{13}$C, δ 10.57, 11.27, 11.86, 11.98 (CH$_3$), 23.16, 23.21, 26.05, 27.47 (CH$_3$CH$_2$), 50.01, 52.73, 60.56, 61.21 (CH$_2$), 58.77, 59.39, 63.72, 69.25 (CH), 62.60 (CH$_2$OH), 70.34 (CHCH$_2$OH), and 184.46 p.p.m. (C=O).

When the ratio of the reagents was varied no improvement in the yield was obtained.

[Co{(S)-serO}L]Br[ClO$_4$]·H$_2$O (4).—To the above filtrate of the dibromide, NaClO$_4$ (50 mg) was added. The (S)-serO complex was separated by seeding of the pure sample, independently prepared using (S)-ser.[7] N.m.r. (D$_2$O): $^1$H, δ 0.97—1.04 (12 H, t, CH$_3$), 1.56—2.04 (8 H, m, CH$_3$CH$_2$), 2.78—3.65 (12 H, m, CH$_2$ and CH), 3.88 (1 H, t, CH in ser), and 4.05 (2 H, ABq, −CH$_2$OH); $^{13}$C, δ 10.57, 11.27, 11.86, 11.98 (CH$_3$), 23.16, 23.21, 26.05, 27.47 (CH$_3$CH$_2$), 50.01, 52.73, 60.56, 61.21 (CH$_2$), 58.77, 59.39, 63.72, 69.25 (CH), 62.60 (CH$_2$OH), 70.34 (CHCH$_2$OH), and 184.46 (C=O).

[Co{(R)-mseO}L]Br[ClO$_4$] (5).—An aqueous solution of complex (1) (2.40 g, 4 mmol) and racemic mse (0.48 g, 4 mmol) was adjusted to pH 8.5 with 0.1 mol dm$^{-3}$ NaOH. After 3 h the reaction mixture was concentrated to about 30 cm$^3$. To the resulting solution, 1 mol dm$^{-3}$ NaClO$_4$ (4 cm$^3$) was added with vigorous stirring. Prismatic crystals separated from the solution after 24 h. Additional solid could be obtained by evaporation of the reaction mixture (1.14 g). N.m.r. (D$_2$O): $^1$H, δ 0.96—1.04 (12 H, t, CH$_3$), 1.49 (3 H, s, CH$_3$ for mse), 1.51—2.05 (8 H, m, CH$_3$CH$_2$), 2.84—3.66 (12 H, m, CH$_2$ and CH), and 3.83 (2 H, ABq, CH$_2$OH) [Figure 1 (a)]; $^{13}$C, δ 10.21, 11.29, 11.83, 11.95 (CH$_3$), 22.76 (CH$_3$ for mse), 23.20, 23.25, 25.50, 27.45 (CH$_3$CH$_2$), 49.54, 52.93, 60.78, 61.18 (CH$_2$), 58.80, 63.70, 69.32, 70.31 (CH), 68.29 (CH$_2$OH), 65.19 (CCH$_2$OH), and 186.19 p.p.m. (C=O).

[Co{(S)-mseO}L][ClO$_4$]$_2$·2H$_2$O (6).—The separation of isomer (6) from (5) was easily carried out by filtration. Several recrystallizations from water–EtOH gave pure (6) as a powder. N.m.r. (D$_2$O): $^1$H, δ 0.93—1.06 (12 H, t, CH$_3$), 1.50 (3 H, s, CH$_3$ for mse), 1.53—2.05 (8 H, m, CH$_3$CH$_2$), 2.79—3.68 (12 H, m, CH$_2$ and CH), and 3.82 (2 H, ABq, CH$_2$OH); $^{13}$C, δ 10.29, 11.09, 11.93, 12.05 (CH$_3$), 22.89 (CH$_3$ for mse), 23.08, 23.30, 26.30, 26.96 (CH$_3$CH$_2$), 51.52, 56.32, 60.61, 62.07 (CH$_2$), 58.29, 64.15, 69.27, 70.28 (CH), 68.15 (CH$_2$OH), 65.37 (CCH$_2$OH), and 186.21 p.p.m. (C=O).

X-*Ray Data Collection and Processing.*—The crystal data and the experimental conditions are listed in Table 2. All the complexes are tetragonal, and contain the same number of molecules in the unit cell ($Z = 4$). The densities of these orange-red crystals were obtained by the flotation method in CCl$_4$–benzene. Rigaku AFC-4 four-circle automated diffractometer with graphite-monochromatized Mo-$K_\alpha$ radiation ($\lambda = 0.710\ 73$), using ω (2θ < 30°) and ω—2θ (2θ > 30°) scan modes, at scan rate 4.0° min$^{-1}$. Three standard reflections

**Table 2.** Crystal data (space group $P4_3$, $Z = 4$) and experimental conditions

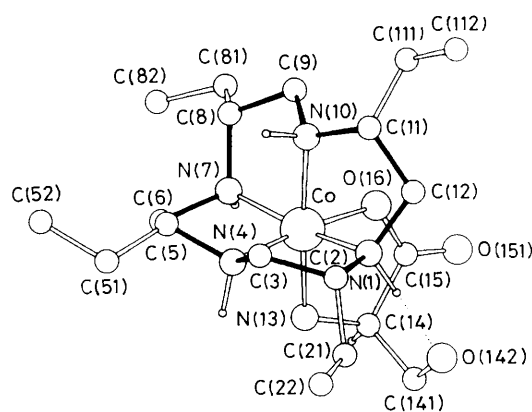| Complex | (3) | (4) | (5) |
|---|---|---|---|
| Formula | $C_{19}H_{42}BrClCoN_5O_7$ | $C_{19}H_{44}BrClCoN_5O_8$ | $C_{20}H_{44}BrClCoN_5O_7$ |
| $M$ | 626.86 | 644.87 | 640.88 |
| $a/Å$ | 14.283(5) | 14.327(2) | 14.168(4) |
| $c/Å$ | 13.378(6) | 13.318(2) | 13.834(6) |
| $U/Å^3$ | 2 736(5) | 2 737(5) | 2 777(2) |
| $D_m/Mg\ m^{-3}$ | 1.525 | 1.523 | 1.533 |
| $D_c/Mg\ m^{-3}$ | 1.526 | 1.521 | 1.535 |
| $F(000)$ | 1 304 | 1 344 | 1 336 |
| $\mu(Mo\text{-}K_\alpha)/mm^{-1}$ | 2.22 | 2.22 | 2.19 |
| Crystal dimensions/mm | 0.44 × 0.38 × 0.42 | 0.37 × 0.40 × 0.52 | 0.40 × 0.45 × 0.50 |
| No. of observed reflections [a] | 2 392 | 2 499 | 2 794 |
| No. of unique reflections | 2 145 | 2 421 | 2 494 |
| No. of unobserved reflections | 1 384 | 1 126 | 1 080 |
| No. of variables | 475 | 484 | 492 |
| $R^b$ | 0.094 | 0.073 | 0.060 |
| $R'^c$ | 0.098 | 0.079 | 0.064 |
| $\Delta/\sigma$ on final cycle | 0.29 | 0.12 | 0.11 |

[a] Criterion: $|F_o| > 3\sigma(|F_o|)$. [b] $R = \Sigma(|F_o| - |F_c|/\Sigma|F_o|)$. [c] $R' = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{\frac{1}{2}}$.
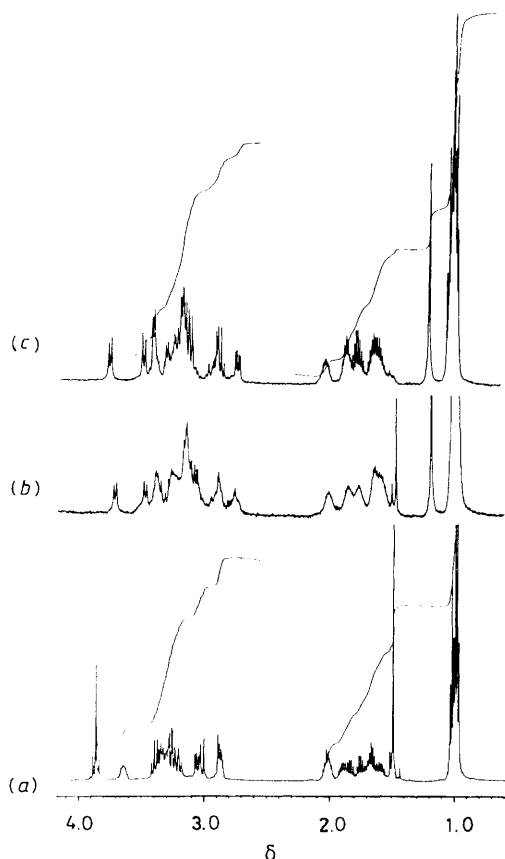


**Figure 1.** The release of α-mse from the (R)-mseO complex. Proton n.m.r. spectra of complex (5) in 0.1 mol dm⁻³ Na₂CO₃–D₂O solution; (a) in D₂O, (b) after 24 h at room temperature, and (c) after 72 h



**Figure 2.** Molecular structure of complex (3). Only the hydrogen atoms at the asymmetric nitrogens, and the chiral centre in aa, are attached for clarity

with all non-hydrogen atoms anisotropic and isotropic for all H atoms. The H atom attached to N(1) in complex (5) was located in a difference map; the others were placed in calculated positions. Unit weights were used for all reflections. The final difference maps showed no peaks higher than 0.8 e Å⁻³. Programs used and sources of scattering factor data are given in ref. 7. Calculations were performed on a FACOM M-780 computer of this Institute. The atomic parameters for the structures are given in Table 3. The ORTEP drawings are shown in Figures 2—4.

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

*Release of Amino Acid from the Complexes and Regeneration of the Starting Complex.*—The procedure was carried out by the method described in ref. 7. A typical example is as follows. To an aqueous solution (20 cm³) of complex (5) (650 mg, 1 mmol), an equal amount of 0.2 mol dm⁻³ Na₂CO₃ solution was added and allowed to stand at room temperature for 72 h. Slow but complete exchange reaction occurs as shown in Figure 1. The resulting solution was poured on a column of SP-Sephadex C-25 cation exchanger. The amino acid which passed through the column without adsorption was collected, and the basic solution was acidified with acetic acid. The solution was poured

were monitored every 150 for each complex and showed no systematic decrease in intensity.

*Structure analysis and refinement.* All structures were solved by direct methods assuming space group $P4_3$ on the basis of experience and analysis of an analogue. The absolute configurations of the chiral centres in the ligand which were used as an internal reference for the asymmetric centres were found to be valid in all cases. Block-diagonal least-squares refinement

**Table 3.** Atomic co-ordinates ($\times 10^4$)

Complex (3)

| Atom | $x$ | $y$ | $z$ | Atom | $x$ | $y$ | $z$ |
|---|---|---|---|---|---|---|---|
| Co | 2 827(2) | 1 487(2) | 0 | C(81) | 2 144(18) | 252(15) | -2 596(22) |
| N(1) | 3 588(10) | 1 483(11) | 1 205(11) | C(82) | 1 539(20) | 813(20) | -3 343(20) |
| C(2) | 4 191(16) | 2 332(16) | 1 319(19) | C(111) | 4 873(14) | -563(17) | -79(23) |
| C(3) | 4 222(14) | 2 797(15) | 277(18) | (C112) | 5 654(24) | -807(23) | 584(33) |
| N(4) | 3 326(10) | 2 734(9) | -229(12) | N(13) | 1 671(10) | 1 987(9) | 605(13) |
| C(5) | 3 360(12) | 2 918(13) | -1 332(17) | C(14) | 1 142(14) | 1 263(15) | 1 194(18) |
| C(6) | 2 401(15) | 2 524(13) | -1 730(17) | C(15) | 1 590(15) | 285(13) | 969(16) |
| N(7) | 2 330(11) | 1 513(9) | -1 369(11) | O(16) | 2 272(9) | 296(8) | 343(10) |
| C(8) | 2 852(12) | 838(12) | -2 026(15) | C(141) | 1 106(19) | 1 441(17) | 2 267(22) |
| C(9) | 3 460(15) | 221(12) | -1 392(16) | O(142) | 2 068(15) | 1 355(15) | 2 643(13) |
| N(10) | 3 897(9) | 844(10) | -617(12) | O(151) | 1 269(11) | -392(9) | 1 366(12) |
| C(11) | 4 547(12) | 447(14) | 157(16) | Br | 1 679(2) | 4 303(1) | 564(3) |
| C(12) | 4 101(15) | 579(15) | 1 179(17) | Cl | 2 318(5) | 3 012(5) | -5 307(6) |
| C(21) | 3 753(15) | 2 959(15) | 2 110(17) | O(1) | 2 224(13) | 2 062(13) | -5 510(14) |
| C(22) | 4 369(18) | 3 783(18) | 2 374(24) | O(2) | 1 951(16) | 3 202(19) | -4 351(20) |
| C(51) | 3 469(18) | 3 962(14) | -1 534(18) | O(3) | 3 247(15) | 3 251(18) | -5 374(20) |
| C(52) | 3 587(19) | 4 180(16) | -2 639(21) | O(4) | 1 864(19) | 3 437(17) | -6 020(28) |

Complex (4)

| Atom | $x$ | $y$ | $z$ | Atom | $x$ | $y$ | $z$ |
|---|---|---|---|---|---|---|---|
| Co | 2 901(1) | 1 456(1) | 0 | C(82) | 1 420(14) | 851(14) | -3 281(13) |
| N(1) | 3 735(8) | 1 415(8) | 1 152(8) | C(111) | 4 847(12) | -648(12) | -184(15) |
| C(2) | 4 310(11) | 2 270(11) | 1 224(11) | C(112) | 5 621(14) | -990(13) | 472(16) |
| C(3) | 4 352(10) | 2 717(9) | 186(10) | N(13) | 1 782(7) | 1 960(8) | 682(8) |
| N(4) | 3 405(7) | 2 679(8) | -277(8) | C(14) | 1 540(11) | 1 321(13) | 1 497(13) |
| C(5) | 3 364(11) | 2 873(11) | -1 393(13) | C(15) | 1 744(10) | 315(11) | 1 130(13) |
| C(6) | 2 388(10) | 2 491(11) | -1 701(11) | O(16) | 2 339(5) | 289(6) | 383(8) |
| N(7) | 2 325(7) | 1 513(7) | -1 336(8) | C(141) | 639(13) | 1 427(17) | 1 925(17) |
| C(8) | 2 778(10) | 823(10) | -2 046(11) | O(142) | 453(10) | 2 367(10) | 2 213(12) |
| C(9) | 3 416(10) | 186(10) | -1 430(13) | O(151) | 1 438(7) | -362(9) | 1 562(9) |
| N(10) | 3 911(7) | 808(7) | -690(9) | Br | 1 706(1) | 4 274(1) | 478(2) |
| C(11) | 4 617(10) | 384(9) | 2(11) | Cl | 2 242(4) | 2 897(4) | 4 421(5) |
| C(12) | 4 293(12) | 564(12) | 1 091(11) | O(1) | 3 167(12) | 3 161(9) | 4 364(13) |
| C(21) | 3 887(12) | 2 916(12) | 2 036(12) | O(2) | 2 093(11) | 1 948(12) | 4 253(16) |
| C(22) | 4 501(12) | 3 768(15) | 2 258(16) | O(3) | 1 931(16) | 3 139(13) | 5 363(18) |
| C(51) | 3 482(10) | 3 924(13) | -1 639(12) | O(4) | 1 691(14) | 3 358(17) | 3 691(22) |
| C(52) | 3 558(13) | 4 116(14) | -2 746(14) | O(W) | 3 282(13) | 608(12) | 3 083(12) |
| C(81) | 2 050(11) | 249(14) | -2 611(13) | | | | |

Complex (5)

| Atom | $x$ | $y$ | $z$ | Atom | $x$ | $y$ | $z$ |
|---|---|---|---|---|---|---|---|
| Co | 2 155(1) | 3 342(1) | 0 | C(82) | 3 601(10) | 4 314(10) | -3 152(10) |
| N(1) | 1 254(6) | 3 172(6) | 1 063(7) | C(111) | 80(9) | 5 363(9) | -6(12) |
| C(2) | 678(7) | 2 288(8) | 917(10) | C(112) | -776(13) | 5 575(13) | 634(17) |
| C(3) | 764(8) | 1 966(7) | -114(10) | N(13) | 3 284(6) | 2 837(6) | 648(7) |
| N(4) | 1 742(6) | 2 121(6) | -471(7) | C(14) | 3 671(7) | 3 480(7) | 1 417(8) |
| C(5) | 1 890(8) | 2 040(7) | -1 537(9) | C(15) | 3 255(8) | 4 462(7) | 1 187(7) |
| C(6) | 2 829(8) | 2 516(7) | -1 712(8) | O(16) | 2 632(5) | 4 502(4) | 516(6) |
| N(7) | 2 806(6) | 3 477(6) | -1 256(7) | C(141) | 3 393(9) | 3 159(8) | 2 407(10) |
| C(8) | 2 289(8) | 4 180(7) | -1 892(8) | O(142) | 2 440(7) | 3 359(8) | 2 637(8) |
| C(9) | 1 624(8) | 4 738(7) | -1 254(8) | C(143) | 4 764(9) | 3 493(10) | 1 398(10) |
| N(10) | 1 131(6) | 4 043(6) | -635(7) | O(151) | 3 571(7) | 5 164(5) | 1 611(6) |
| C(11) | 369(8) | 4 332(8) | 80(10) | Br | 3 362(1) | 529(1) | 344(1) |
| C(12) | 690(9) | 4 069(9) | 1 086(9) | Cl | 2 104(2) | 7 450(2) | -2 552(3) |
| C(21) | 975(10) | 1 519(9) | 1 665(11) | O(1) | 3 036(8) | 7 356(9) | -2 888(9) |
| C(22) | 672(11) | 1 741(11) | 2 682(12) | O(2) | 2 053(11) | 6 979(10) | -1 657(10) |
| C(51) | 1 866(10) | 1 031(9) | -1 934(12) | O(3) | 1 813(11) | 8 391(8) | -2 497(15) |
| C(52) | 1 057(14) | 706(11) | -2 398(21) | O(4) | 1 529(9) | 6 984(12) | 3 232(12) |
| C(81) | 2 989(9) | 4 828(8) | -2 423(10) | H(N1) | 158(10) | 319(10) | 171(11) |

on a Dowex 50-X8 column (30 × 300 mm, 200—400 mesh, $H^+$) and the column then washed until the effluent acid band had disappeared. Elution was effected with 2 mol dm$^{-3}$ $NH_4OH$, and the ninhydrin-positive fraction of the eluent was collected and subsequently concentrated to 15 cm$^3$. The optical purity of mse thus obtained was found to be almost 100% as shown in the h.p.l.c. chromatogram (Figure 5). The configuration of the rich enantiomer was assigned as $R$ using

an authentic sample of ($S$)-mse.[15] The concentrate was treated with 10 volumes of EtOH. After storage in the cold overnight, a white silky precipitate of ($R$)-mse was collected by filtration and recrystallized from water–EtOH–diethyl ether (57 mg, 48%), m.p. 243—245 °C (sublimes), $\alpha$ -6.1° (589 nm, $c$ 1.00, water) [lit.,[16] $\alpha$ -6.10 ($c$ 2.0), and -6.2° ($c$ 1.0, water)]. $^1$H N.m.r. ($D_2O$): $\delta$ 1.44 (3 H, s, $CH_3$) and 3.80 (2 H, ABq, $v_{AB}$ 121 Hz, $J_{AB}$ 12.0 Hz, $CH_2OH$) (Found: C, 40.25; H, 7.60; N, 11.80.
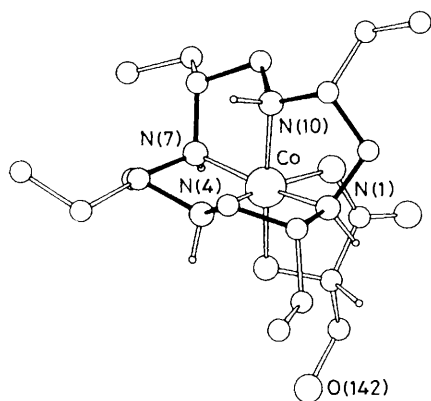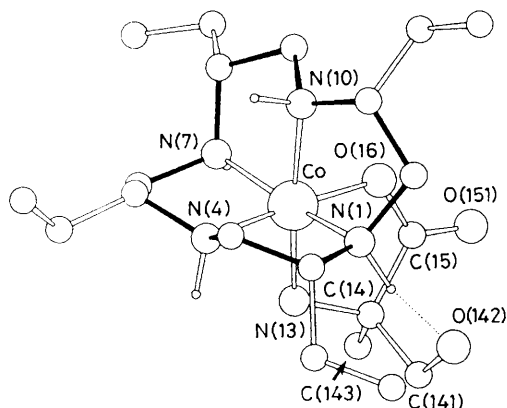
**Figure 3.** Molecular structure of complex (4)


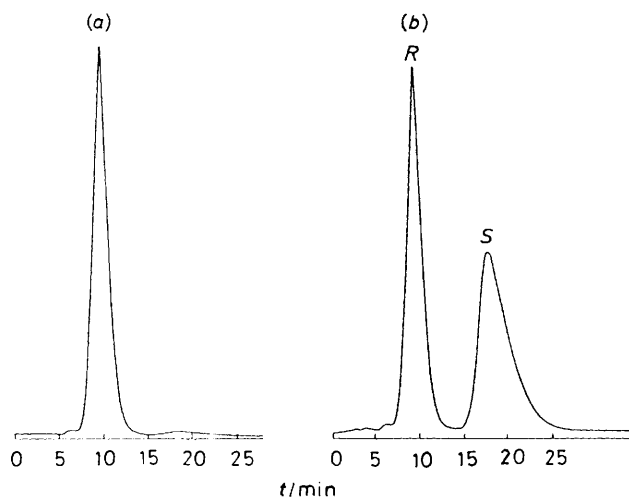
**Figure 4.** Molecular structure of complex (5)



**Figure 5.** H.p.l.c. of a sample of α-mse after release from complex (5): (a) sample and (b) DL-α-mse

Calc. for $C_4H_9NO_3$: C, 40.35; H, 7.60; N, 11.75%). Optical yields of the other aa were determined by h.p.l.c.: 80, 78, and 99% enantiomeric excess for (R)-ser, (S)-ser, and (S)-mse respectively.

*Chromatographic Experiments.*—The h.p.l.c. system consisted of a JASCO TWINCLE and UNIDEC-100-VI spectrophotometer. Column: Chiralpak WH (JASCO, 4.5 × 125 mm). Detection: 254 nm. Sensitivity: 0.32 area units full scale. Eluant: 0.5 mmol dm$^{-3}$ $CuSO_4$. Flow-rate: 1.0 cm$^3$ min$^{-1}$ (20 kg cm$^{-2}$). Chart speed: 5 mm min$^{-1}$. Room temperature.

*Recovery of the Starting Complex.*—The complex was recovered in the manner described in ref. 7. The complex on the Sephadex column was eluted with 0.1 mol dm$^{-3}$ $Na_2SO_4$. After desalting of the eluant followed by treatment with concentrated HBr, complex (1) separated out usually in good yield (490 mg, 82% for the above case). The crystal data for the recovered compound were consistent with those of (1). Regenerated (1) could be used repeatedly.

*Other Measurements.*—Electronic absorption spectra were obtained on a Hitachi 330 spectrophotometer, circular dichroism (c.d.) spectra on a JASCO J-20A spectropolarimeter. These measurements were made on aqueous solutions ca. 10$^{-3}$ mol dm$^{-3}$. Optical rotation was measured on a JASCO DIP 180 polarimeter. Proton and $^{13}C$ n.m.r. spectra were recorded on a JEOL GX-500 (500 MHz) spectrometer with sodium 3-trimethylsilylpropionic acid as an internal reference, and a JEOL GX-400 (100.5 MHz) with dioxane as an internal reference. The melting point was measured on a Mettler FP52 apparatus.

## Results and Discussion

*Separation and Characterization of Amino Acidato Complexes.*—The reaction of complex (1) with amino acids is exactly regioselective, and gives only a pair of diastereomers in all cases. One of these crystallizes preferentially as its appropriate salt. The (R)-serO complex was separated almost pure by filtration of the dibromide from the reaction mixture of the racemic serinato complexes. When $NaClO_4$ had been added to the initial racemic reaction mixture before the isolation of the (R)-serO complex dibromide the separation of the two diastereomers was less easy. On the other hand, the separation of (5) and (6), which differ in their anions, was easily achieved by filtration.

The respective bromide perchlorates in this series often give good single crystals for X-ray analysis. Treatment by gel filtration on a Sephadex column of such 'hetero-anion'* complexes resulted in two bands, of the dibromide and the diperchlorate, so that the complexes became 'homo-anion' species. Therefore, the purification of these complexes was carried out only by recrystallization in water, if necessary. The optical purity of the less-soluble diastereomer is usually so high that further recrystallization is unnecessary.

The visible absorption and c.d. spectra of the amino acidato complexes are summarized in Table 1. The absorption spectra are typical of an $N_5O$ chromophore as shown by the corresponding alaninato complexes, (7) and (8).[7] The c.d. curves show also analogous patterns to those of the diastereomeric pair of (7) and (8). Previous X-ray studies revealed that the aa in the complex ions co-ordinates in its cis-$\beta_1$ form without exception.[7] Since exact regioselective co-ordination occurred, this may be true of all the structures obtained here.

The $^1H$ n.m.r. patterns for these complexes consist of four different sets of signals for L and a single set of lines for the co-ordinated aa, as for the corresponding alaninato complexes and those of other amino acids.[7] In the $^{13}C$ n.m.r. spectra, 19 lines for serO complexes and 20 lines for mseO compounds were observed respectively. These mean that all the complexes have $C_1$ symmetry and the configurations of the macrocycle are maintained as in (1).

*Geometries of the Complexes.*—Figures 2—4 show the molecular structures of complexes (3)—(5) respectively. The

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* The terms 'hetero-anion' and 'homo-anion' indicate that the complexes contain two different kinds and only one kind of anion, respectively.

**Table 4.** Bond lengths (Å) and angles (°) around the cobalt ion in complexes (3)—(5)

| | (3) | (4) | (5) |
|---|---|---|---|
| Co–N(1) | 1.944(15) | 1.946(11) | 1.962(10) |
| Co–N(4) | 1.943(14) | 1.931(11) | 1.939(9) |
| Co–N(7) | 1.964(15) | 1.964(11) | 1.976(9) |
| Co–N(10) | 1.967(14) | 1.951(11) | 1.965(9) |
| Co–N(13) | 1.972(14) | 1.980(11) | 1.968(9) |
| Co–O(16) | 1.932(12) | 1.926(9) | 1.915(7) |
| | | | |
| N(1)–Co–N(4) | 85.9(6) | 87.1(5) | 86.9(4) |
| N(1)–Co–N(7) | 167.1(6) | 166.9(5) | 167.0(4) |
| N(1)–Co–N(10) | 84.9(6) | 84.3(5) | 85.2(4) |
| N(1)–Co–N(13) | 97.4(6) | 98.5(5) | 98.2(4) |
| N(1)–Co–O(16) | 91.7(6) | 91.3(4) | 93.2(4) |
| N(4)–Co–N(7) | 88.2(6) | 86.9(4) | 86.1(4) |
| N(4)–Co–N(10) | 94.4(6) | 93.7(4) | 94.5(4) |
| N(4)–Co–N(13) | 92.3(6) | 93.4(5) | 94.3(4) |
| N(4)–Co–O(16) | 174.4(6) | 174.6(4) | 175.9(3) |
| N(7)–Co–N(10) | 84.1(7) | 84.5(5) | 84.4(4) |
| N(7)–Co–N(13) | 94.2(7) | 93.4(5) | 93.3(4) |
| N(7)–Co–O(16) | 95.1(6) | 95.7(4) | 94.6(4) |
| N(10)–Co–N(13) | 173.0(6) | 172.5(5) | 170.8(4) |
| N(10)–Co–O(16) | 90.4(6) | 91.2(4) | 89.6(3) |
| N(13)–Co–O(16) | 93.0(5) | 81.8(4) | 81.7(4) |

**Table 5.** Selected bond parameters of the 12-membered rings in complexes (3)—(5)

| | (3) | (4) | (5) |
|---|---|---|---|
| (a) Bond lengths (Å) | | | |
| N(1)–C(2) | 1.50(3) | 1.48(2) | 1.51(1) |
| N(1)–C(12) | 1.48(3) | 1.46(2) | 1.50(2) |
| C(2)–C(3) | 1.54(3) | 1.53(2) | 1.50(2) |
| C(3)–N(4) | 1.45(3) | 1.49(2) | 1.49(1) |
| N(4)–C(5) | 1.50(3) | 1.51(2) | 1.49(2) |
| C(5)–C(6) | 1.57(3) | 1.56(2) | 1.51(2) |
| C(6)–N(7) | 1.53(2) | 1.49(2) | 1.50(1) |
| N(7)–C(8) | 1.50(2) | 1.52(2) | 1.52(1) |
| C(8)–C(9) | 1.50(3) | 1.53(2) | 1.51(2) |
| C(9)–N(10) | 1.50(3) | 1.51(2) | 1.48(1) |
| N(10)–C(11) | 1.50(2) | 1.50(2) | 1.52(1) |
| C(11)–C(12) | 1.52(3) | 1.54(2) | 1.51(2) |
| | | | |
| (b) Bond angles (°) | | | |
| C(2)–N(1)–C(12) | 115.1(15) | 113.0(12) | 114.7(8) |
| N(1)–C(2)–C(3) | 105.8(18) | 108.1(11) | 109.6(10) |
| C(2)–C(3)–N(4) | 111.7(17) | 108.9(12) | 110.3(9) |
| C(3)–N(4)–C(5) | 114.9(15) | 115.7(10) | 116.6(9) |
| N(4)–C(5)–C(6) | 104.0(15) | 103.2(12) | 104.3(9) |
| C(5)–C(6)–N(7) | 106.8(16) | 107.5(12) | 108.6(9) |
| C(6)–N(7)–C(8) | 112.9(15) | 112.7(11) | 111.2(8) |
| N(7)–C(8)–C(9) | 109.4(16) | 108.1(12) | 107.7(9) |
| C(8)–C(9)–N(10) | 106.5(14) | 106.2(11) | 106.5(8) |
| C(9)–N(10)–C(11) | 120.7(14) | 118.8(10) | 122.2(8) |
| N(10)–C(11)–C(12) | 108.3(15) | 107.9(12) | 108.6(9) |
| N(1)–C(12)–C(11) | 109.6(17) | 110.8(12) | 110.4(10) |
| | | | |
| (c) Torsion angles (°) | | | |
| C(12)–N(1)–C(2)–C(3) | 104.9(19) | 100.4(14) | 102.1(11) |
| C(2)–N(1)–C(12)–C(11) | −77.1(21) | −82.9(15) | −74.5(12) |
| N(1)–C(2)–C(3)–N(4) | 37.8(22) | 42.4(15) | 37.8(12) |
| C(2)–C(3)–N(4)–C(5) | −163.6(17) | −165.6(12) | −166.9(9) |
| C(3)–N(4)–C(5)–C(6) | 163.9(16) | 163.3(11) | 162.9(9) |
| N(4)–C(5)–C(6)–N(7) | −53.8(18) | −52.8(14) | −51.9(11) |
| C(5)–C(6)–N(7)–C(8) | −82.4(18) | −83.1(14) | −80.0(10) |
| C(6)–N(7)–C(8)–C(9) | 130.7(16) | 131.5(12) | 134.5(9) |
| N(7)–C(8)–C(9)–N(10) | −42.0(19) | −41.8(14) | −46.3(10) |
| C(8)–C(9)–N(10)–C(11) | −179.3(15) | −177.9(11) | −177.3(9) |
| C(9)–N(10)–C(11)–C(12) | −116.1(18) | −120.5(13) | −118.7(11) |
| N(10)–C(11)–C(12)–N(1) | −36.1(21) | −28.2(16) | −34.6(12) |

geometries of the cyclen parts in all the complexes are essentially the same as those of the starting and other amino acidato complexes.[2,3,7,8,17] Thus a distorted octahedral and six-co-ordinate geometry occurs, where four N atoms of the macrocycle and N and O atoms of the amino acid are co-ordinated to the cobalt ion in a cis-$\beta_1$ form, as was aniticipated above. The cyclen ligand in each molecule bends about the line connecting N(1) and N(7), and the configurations of the asymmetric N atoms are SSSR.

Bond parameters are listed in Tables 4—7. There are no particularly abnormal values compared with complex (1) and related complexes. Each aa ligand forms a five-membered ε or pseudo-ε chelate ring. Each hydroxyl group of (R)-aa in the complexes forms an internal hydrogen bond between one of the secondary amines [N(1)] in the ligand as given in Table 7. This is three-point attachment. On the other hand, the (S)-serO complex (4) does not have such an internal hydrogen bond, but both N(1) and CH$_2$OH interact with a water molecule co-crystallized. Thus the functional group in aa forms either an intra- or inter-molecular hydrogen bond depending on the steric requirement. The hydroxymethyl group in (R)-aa is favourably positioned to participate with part of L, but that of (S)-aa is different and interacts with a water molecule. Consequently, the (S)-aa complex is more soluble than the corresponding (R)-aa complex.

Thus, the difference in solubility between the diastereomers is caused by the different interactions between the residual functional group and the different numbers of water molecules in the two salts.

Compared with a diastereomeric pair based on ΔΛ isomerism,[18] there is little difference in strain energy between the present diastereomeric complexes.[19]

*Release of Amino Acid.*—The aa incorporated was easily released from the corresponding complex in weak basic solution as shown previously.[7] The intensities of the methyl and the methylene protons of the co-ordinated mse at δ 1.49 and 3.83 respectively gradually decrease to zero, while a new singlet and a quartet appear at δ 1.2 and at 3.6 respectively. The latter signals were assigned to free mse by comparison with an authentic sample. The first two signals had disappeared completely after 72 h at room temperature or 5 h at 50 °C.

A slight racemization occurred during dissociation of ser from the corresponding complex. Since mse has no hydrogen atom at the chiral centre, almost optically pure mse was isolated from complex (5) or (6) without racemization as shown in the chromatogram of the sample (Figure 5). In addition, the starting complex can be recovered in more than 80% yield without exception and used repeatedly.

In view of the optical resolution of aa, the most remarkable features of the present procedure using the stereochemically stable resolving agent (1) are: direct resolution of underivatized aa; under mild reaction conditions at room temperature; easy separation of the diastereomeric product mixture; complete release of aa without racemization although depending on a variety of amino acids; and easy regeneration of the asymmetric agent. Further, the reaction is carried out in aqueous solution without usage of organic solvents.

Since enantiomers differ only in their three-dimensional structure, the positions of a minimum of three groups must be identified to distinguish between members of an enantiomeric pair. The importance of the three-point interaction was first

**Table 6.** Selected bond parameters for the amino acidato five-membered ring of complexes (3)—(5)

| | (3) | (4) | (5) |
|---|---|---|---|
| (a) Bond lengths (Å) | | | |
| N(13)–C(14) | 1.50(3) | 1.46(2) | 1.50(1) |
| C(14)–C(15) | 1.57(3) | 1.55(2) | 1.54(1) |
| C(15)–O(16) | 1.28(2) | 1.31(2) | 1.28(1) |
| C(14)–C(141) | 1.46(4) | 1.42(3) | 1.50(2) |
| C(14)–C(143) | | | 1.55(2) |
| C(141)–O(142) | 1.47(3) | 1.43(3) | 1.42(2) |
| C(15)–O(151) | 1.19(2) | 1.21(2) | 1.24(1) |
| | | | |
| (b) Bond angles (°) | | | |
| Co–N(13)–C(14) | 112.8(11) | 107.7(9) | 113.5(6) |
| N(13)–C(14)–C(15) | 107.9(16) | 107.7(13) | 105.1(8) |
| C(14)–C(15)–O(16) | 115.1(16) | 112.9(13) | 116.8(9) |
| Co–O(16)–C(15) | 118.4(11) | 116.6(9) | 118.4(6) |
| | | | |
| (c) Torsion angles (°) | | | |
| O(16)–Co–N(13)–C(14) | 13.7(12) | 32.4(9) | 19.7(7) |
| Co–N(13)–C(14)–C(15) | −10.4(19) | −36.6(13) | −19.3(10) |
| N(13)–C(14)–C(15)–O(16) | −1.4(23) | 21.3(17) | 7.4(12) |
| C(14)–C(15)–O(16)–Co | 13.4(23) | 5.5(16) | 8.6(12) |
| N(13)–Co–O(16)–C(15) | −15.8(14) | −21.8(10) | −16.1(7) |

**Table 7.** Hydrogen-bond distances (Å)*

| Complex | (3) | (4) | (5) |
|---|---|---|---|
| Atom 1    Atom 2 | | | |
| N(1)–[H(N1)]–O(142) | 2.91(2)[I] | | 2.76(1)[I] |
| Angles (°) | 167(19) | | 163(13) |
| N(1) · · · O(W) | | 2.89(2)[I] | |
| N(4) · · · Br | 3.42(1)[II] | | 3.409(9)[II] |
| N(7) · · · O(151) | 2.81(2)[III] | 2.86(2)[V] | |
| N(10) · · · Br | 3.33(1)[IV] | 3.40(1)[IV] | 3.301(9)[VII] |
| N(13) · · · Br | 3.31(1)[I] | 3.33(1)[I] | 3.300(8)[I] |
| N(13) · · · O(142) | | | 3.09(1)[I] |
| O(142) · · · O(1) | 2.68(3)[II] | | 2.79(2)[III] |
| O(142) · · · O(4) | | 3.05(3)[I] | |
| O(142) · · · O(W) | | 2.94(2)[VI] | |
| O(2) · · · O(W) | | 3.00(3)[I] | |

* Roman numeral superscripts denote symmetry of atom 2: I $x, y, z$;
II $x, y, z + 1$; III $-y, x, z + \frac{3}{4}$; IV $1 - y, -x, z + \frac{3}{4}$; V $y, -x, z + \frac{3}{4}$;
VI $y, -x, z + \frac{1}{4}$; VII $y + 1, x, z + \frac{3}{4}$.

recognized for stereospecific enzyme reactions.[4] This feature is now recognized as being common even to non-enzymatic reactions. It provides a sufficient condition for chiral differentiation of the chiral centre in functionalized amino acids. Therefore, more precise molecular design of the asymmetric reagent is required for chiral recognition of a neutral aa without any functional side group.

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